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Laboratory Real-Time Biomarkers for
Immune Related Adverse Events in Immunotherapies of
Patients with Metastasized Malignant Melanoma

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Die dieser Arbeit zugrundeliegenden Labordaten wurden ohne meine Mitarbeit vom Zentrallabor der Uniklinik Köln ermittelt.

Sämtliche Laborwerte wurden von mir zusammengetragen und ausgewertet.

Die dieser Arbeit zugrundeliegenden klinischen Verläufe wurden durch das ärztliche und patienten-betreuende Personal des Zentrums für Integrierte Onkologie Köln-Bonn (CIO) in der Uniklinik Köln erhoben.

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Glossary

General

AE	–	adverse event
AEC	–	absolute eosinophil count
AJCC	–	American Joint Committee on Cancer
CIO	–	Center for Integrated Oncology
CoT	–	course(s) of therapy
CRP	–	c-reactive protein
irAE	–	immune related adverse event
LC	–	leucocyte count
LDH	–	lactate dehydrogenase
MHC	–	major histocompatibility complex
NA	–	not available (missing data)
NPV	–	negative predictive value
OS	–	overall survival
PFS	–	progression free survival
PPV	–	positive predictive value
REC	–	relative eosinophil count
StD	–	standard deviation
SEN	–	sensitivity
SPE	–	specificity
TCR	–	T cell receptor
TME	–	tumor microenvironment
TN	–	true negative
TP	–	true positive
VIF	–	variance inflation factor

Laboratory anomalies

In combination with a laboratory parameter (AEC, REC, LC, LDH, CRP) as described in Section 2.2

HS	– “half to single”	– interval between half and upper reference value
SD	– “single to double”	– interval between upper reference value and its twofold
DT	– “double to triple”	– interval between two- and threefold upper reference value
E	– “elevation”	– single elevation above upper reference value
T	– “triple”	– elevation above threefold of upper reference value

1. Introduction

The treatment of metastatic malignant melanoma remains one of the most important topics within modern oncology. For many years there has been almost no progress in the treatment of metastatic melanoma as traditional chemotherapy has long been shown incapable of improving survival rates (Eigentler et al. 2003). With the introduction of targeted therapy and immunotherapy in several tumor entities, these innovations have brought new perspectives especially to the therapy of American Joint Committee on Cancer (AJCC) stage IV melanoma. However, with those new approaches new challenges arose: Whereas in targeted therapy the development of resistant tumor cells towards the inhibitors is the main concern (Mai et al. 2015), the major issue in immunotherapy is a new variety of immune-related adverse events (irAEs), the pathogenesis of which is closely linked to the very effect mechanisms of the agents (Inno et al. 2017).

Early recognition of these irAEs plays an essential role in controlling them and thus preventing severe complications including death (Weber et al. 2016). While much research has been conducted concerning treatment, only few authors focused on early recognition of irAEs. This study aims to uncover one or multiple biomarkers that function as early warning signals of upcoming irAEs in patients with metastasized or unresectable melanoma at the Center for Integrated Oncology (CIO) in Cologne.

1.1. Epidemiology of the malignant melanoma

Before delving into the therapy of metastasized melanoma, the present trends of epidemiology in Germany and other countries will be presented. This is necessary to comprehend its proportions.

In 2012, melanoma ranked fifth among the most common new cancer cases in Germany (Robert Koch Institut (Publ.) et al. 2015) and sixth within developed countries (Erdmann et al. 2013). Melanoma is also the third most common cause for brain metastasis (Sampson et al. 1998), indicating a poor prognosis of 4-5 months of survival at the point of diagnosis (Fife et al. 2004; Gibney et al. 2012).

The lasting trend towards sun tanning with UV light exposure remains the major factor to drive the increase of melanoma incidence in the last decades in the German population (Leitlinienprogramm Onkologie 2016) as well as worldwide (Erdmann et al. 2013). The additional reluctance especially of the young to take protective measures, such as using sunscreen or wearing long sleeved clothes or a hat, induce a possible, further

aggravating effect on incidence levels (Görig et al. 2017). It can be expected that melanoma will remain an increasingly frequent diagnosis for dermatologists to deal with, which grants necessity for intensive and continuous research on this topic.

Despite the efforts of governments and professional societies (see for example Cancer Council Australia 2016; Deutsche Krebshilfe & Deutsche Krebsgesellschaft (Publ.) 2015; European Association of Dermato Oncology 2017; G-BA 2008), the rates of melanoma classified T4 at the initial diagnosis have not changed particularly in Germany. Since 2008, they remain at 8% for women and 10% for men. This most important prognostic factor of tumor classification at the time of diagnosis (Balch et al. 2001) leads to the slight but steady increase of the absolute fatality count due to metastasized melanoma since 1998 (Robert Koch Institut (Publ.) et al. 2012, 2013, 2015).

1.2. Treatment options of metastasized melanoma

As shown, dermatooncologists will have to face a growing number of patients affected by unresectable or metastasized melanoma. This section will give a short overview on the most important treatment options for these patients in order to provide a good understanding of the role of immunotherapy in modern dermatooncology.

1.2.1. Surgery

As suggested in the German S3-Guideline for diagnostics, therapy and aftercare, clinicians should always consider the excision of the tumor if R0 resection can be reached. This counts for stage IV melanoma as well, given that complete excision is almost the only treatment that can provide definitive cure (Leitlinienprogramm Onkologie 2016). Wevers et al. (2013), however, state that patients who can be treated in this manner are rare among those with metastasized melanoma. This relates in particular to metastases of the brain, which were shown to correlate with the worst outcome compared to pulmonary and intestinal metastases (Wevers et al. 2013). These unresectable stages of melanoma therefore clearly demonstrate the limits of surgical therapy.

1.2.2. Radiotherapy

Radiotherapy as one of the pillars of therapy in modern oncology can be used to treat the tumor where surgery cannot reach it. It is a good option especially for brain or spinal metastases in a palliative setting of metastasized melanoma therapy (Leitlinienprogramm Onkologie 2016). It also shows good response in satellite and distant metastases (Chadha et al. 1990; Overgaard et al. 1986) and has proven effective in

local tumor control, e.g. after lymph node dissection (Burmeister et al. 2012; Creagan et al. 1978). Its ubiquitous reach, however, comes at the cost of sometimes severe damage to the collateral tissue, several sensitive organs and the immune system (Radvansky et al. 2013).

With the uprise of immunotherapy, the abscopal effect of radiotherapy recently gained importance: It describes the effect of localized radiation leading to a systemic antitumor immune response, which in the past 50 years was rare and most frequently observed with immunogenic tumors (Hu et al. 2017). With immunotherapy, reports of the abscopal effect have become more frequent and a synergistic effect is continuously being discussed (Franceschini et al. 2016).

1.2.3. Chemotherapy

Chemotherapy used to be the traditional therapeutic approach to treat stage IV melanoma. After extensive literature review, the German S3-Guideline concludes that no extension of survival could be proven for any of the available chemotherapeutics. The most frequently used substance is dacarbazine (DTIC) (Leitlinienprogramm Onkologie 2016), with temozolomid and fotemustin having equal response rates (Avril et al. 2004; Middleton et al. 2000; Patel et al. 2011).

With the introduction of signal transduction inhibitors and immune checkpoint blockers, chemotherapy takes a subordinate role. It is recommended in case these modern therapies lead to tumor progression (Leitlinienprogramm Onkologie 2016).

1.2.4. Signal transduction inhibitors

The first BRAF inhibitor, vemurafenib, of this rather new therapy was first approved in 2011 in the USA (FDA 2011) and in 2012 in the EU (EMA 2012). The most important substances are effective only in a subset of 35-50% of patients with melanoma, bearing a mutation in the BRAF pathway relevant for its carcinogenesis (Cancer Genome Atlas Network 2015). There are also inhibitors available for the rare c-KIT mutation, which are effective in the small proportion of patients that have this kind of mutation (Carvajal et al. 2011; Guo et al. 2011).

Treatment with the BRAF inhibitors dabrafenib or vemurafenib alone has proven very effective (Hauschild et al. 2012; McArthur et al. 2014), even more so in combination with a MEK-inhibitor like trametinib or cobimetinib: These combinations caused response rates between 64-69% in randomized clinical trials (Larkin et al. 2014; Long et al. 2015; Robert et al. 2015a).

As this combination could prolong progression free survival (PFS), the development of tumor resistance against these agents in the course of treatment is common and in general no durable response can be reached (Mai et al. 2015).

1.2.5. Immunotherapy

The introduction of the immune checkpoint inhibitors ipilimumab, an anti-CTLA-4 antibody approved in the EU in 2011 (EMA 2011), and the anti-PD-1 antibodies pembrolizumab and nivolumab, approved in 2015 (EMA 2015a, 2015b), brought significant improvement to the therapy of metastasized melanoma for the first time in many years. This relates to response rates, PFS and overall survival (OS) as well as high grade adverse events (AEs) compared to chemotherapy (Robert et al. 2015c, 2015b).

Considering therapeutic success, ipilimumab has shown durable response with a plateau in survival reached after 3 years (Maio et al. 2015; Schadendorf et al. 2015).

Anti-PD-1 antibodies, however, were shown to induce better response and survival rates with decreasing rates of AEs (Larkin et al. 2015; Schachter et al. 2017) and are therefore preferred over monotherapy with ipilimumab (Leitlinienprogramm Onkologie 2016).

The newer concept of combining ipilimumab with nivolumab, approved in the EU in 2016, further enhanced response rates and survival, yet raising the occurrence of high grade irAEs to 55%, which led to discontinuation of therapy in almost 30% of patients in a randomized phase 3 study. This was more than three times the AE rate of nivolumab and two times the rate of ipilimumab in the same study (Larkin et al. 2015).

These findings clearly indicate that further research is needed to gain better understanding of this special set of irAEs in order to improve their detection and management. This is necessary to avoid therapy discontinuation and impairment of the patient's quality of life. In sequence, a brief overview will show the effect mechanisms of immunotherapeutic agents and the current knowledge on how the pathogenesis of irAEs is linked to them.

1.3. Immune checkpoints and the side effects of their inhibition

The irAEs are different to AEs of chemotherapy and directly linked to the effect mechanisms of immunotherapy (Inno et al. 2017). This section will give a brief overview on tumor immunogenicity and the two immune checkpoints targeted in immunotherapy to give an understanding on how and why irAEs emerge. Because this is a vast topic in the field of immunology with a detailed elaboration reaching far beyond the scope of this dissertation, there is an exclusive focus on the general mechanisms involved in the effect

of the anti-CTLA-4 antibody ipilimumab and the anti-PD1-antibodies nivolumab and pembrolizumab, all of which are frequently used in the CIO Cologne.

1.3.1. Cancerogenesis and T cells

The immune system in general and T cellular immunity in particular play a vital role in engaging foreign elements in the human body. This counts as well for preventing a cancer from growing. The mechanisms a cancer utilizes to escape the immune system are not yet fully understood. Schreiber et al. (2011) postulate a cancer immunoediting hypothesis that consists of the following three phases, as depicted in Figure 1:

- *Elimination*: The immune system recognizes and destroys existing tumor cells.
- *Equilibrium*: Few tumor cells escape destruction by the immune system, dormant and unable to proliferate. This phase can last over decades until additional mutation eventually leads to the escape phase.
- *Escape*: Tumor cells escape immunologic control, now capable of growing and spreading throughout the host. Schreiber et al. (2011) therein highlight the loss of tumor antigen expression and the tumor induced immunosuppressive state as main contributors.

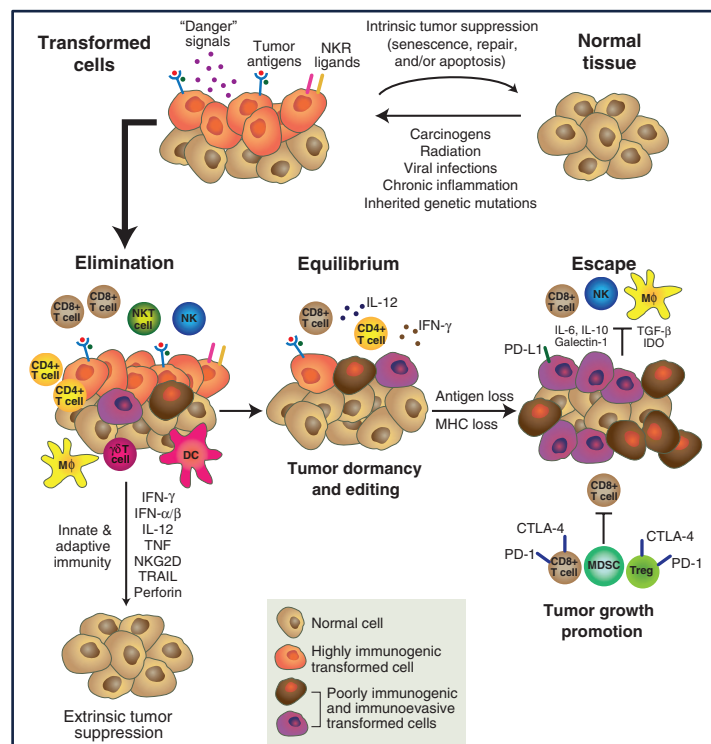


Figure 1: Cancer immunoediting (Schreiber et al. 2011, p. 1567)

The latter of those two ways of immunoediting, the induced immunosuppression, is particularly interesting to target in immunotherapy. Especially so if the immunosuppressive

state is achieved by manipulating the response of T cells, which play a major role in the immune response to tumors (Suarez-Almazor et al. 2017).

T cell mediated immunity involves multiple steps including clonal selection of antigen-specific cells, activation and proliferation, infiltration of the respective tissue, engagement of targeted cells, and mediation of further immune response through cytokines - with each step being controlled by a fine balance of up- and downregulating signals provided by immune checkpoints (Pardoll 2012). These immune checkpoints are essential to prevent autoimmunity, maintain self-tolerance and avoid collateral tissue damage (Pardoll 2012).

As a tumor exploits these inhibitory immune checkpoints to downregulate and escape its respective immune response, the blockade of the respective checkpoints mediated by antibodies has shown to improve antitumoral immune response (Ribas 2015).

For immunotherapy, antibodies targeting the pathways of CTLA-4 and PD-1 do just that. They have therefore become very important for the therapy of metastasized melanoma and in the next sections, some of their functionalities will be described.

1.3.2. The CTLA-4 pathway

The 'cytotoxic T-lymphocyte-associated protein 4' (CTLA-4, also known as CD152) is a membrane protein receptor localized on CD8⁺ T effector cells. It is part of a physiologically well-balanced feedback loop involving the T cell co-stimulating receptor CD28, which influences T cell activation after a cognate antigen has been presented to the T cell receptor (TCR) (Rudd et al. 2009; Schwartz 1992).

Both receptors CTLA-4 and CD28 share the same ligands CD80 (also known as B7.1) and CD86 (also known as B7.2), with CTLA-4 having a higher overall affinity to both ligands (Grohmann et al. 2002). When CD28 connects to one of its ligands after occurrence of antigen recognition, it promotes T cell activation signaling induced by the TCR (Pardoll 2012).

Depending on the intensity of these signals, CTLA-4 – which until then remained sequestered in intracellular vesicles – is transported to the cell surface to reduce T cell activation (Chikuma 2017; Egen et al. 2002). This is shown in Figure 2. The main function is the avoidance of an overreaction of the immune system in terms of autoimmunity. It does so by sending inhibitory signals within the T cell (Parry et al. 2005; Schneider et al. 2006) and actively removing CD80 and CD86 from the antigen presenting cell's membrane. This reduces activation of its counterpart CD28 by depriving it from its ligands (Qureshi et al. 2011).

Additionally, CTLA-4 effects $CD4^+$ T cells by downregulating helper T cell activity and upregulating immunosuppressive activity of T_{reg} cells (Lenschow et al. 1996; Wing et al. 2008), enabling a broad inhibition of immune responses. The vast influence of CTLA-4 on moderating immunologic responses was illustrated in CTLA-4 knockout mice that experienced lethal grades of immune hyper activation (Tivol et al. 1995; Waterhouse et al. 1995).

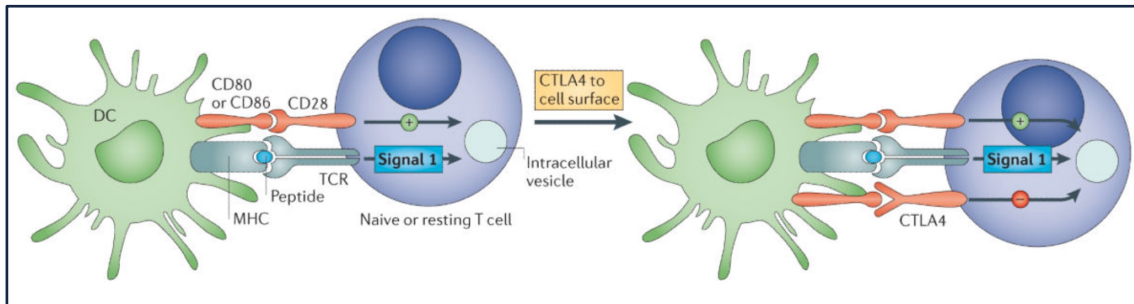


Figure 2: The CTLA-4 pathway (Pardoll 2012, p. 279)

1.3.3. The PD-1 pathway

Similar to CTLA-4, the T cell membrane protein receptor 'programmed cell death protein 1' (PD-1, also known as CD279) plays an important role in limiting T cell activity and preventing autoimmunity (Freeman et al. 2000; Nishimura et al. 2001). With the matching antigen contacting the TCR, PD-1 expression begins (Ishida et al. 1992). After T cell migration it acts directly in the respective tissue of the tumor (Blank et al. 2004; Dong et al. 2002). This is shown in Figure 3.

The expression of PD-1 is induced at the activation state of a T cell (Ishida et al. 1992) inhibiting T cell activation associated kinases (Freeman et al. 2000) on contact with its ligands. These ligands, which are induced by inflammatory cytokines (Keir et al. 2008), are PD-L1 (also known as B7-H1 and CD274) and PD-L2 (also known as B7-DC and CD273) (Dong et al. 1999; Latchman et al. 2001). PD-1 can also be found on T_{reg} cells, where it promotes their proliferation on contact to abovementioned ligands (Francisco et al. 2009). It is additionally located on B lymphocytes, reducing antibody production, and natural killer cells, which PD-1 activity inhibits (Fanoni et al. 2011; Terme et al. 2011). The respective checkpoint inhibition would therefore enhance both cellular and humoral immune activity (Velu et al. 2009).

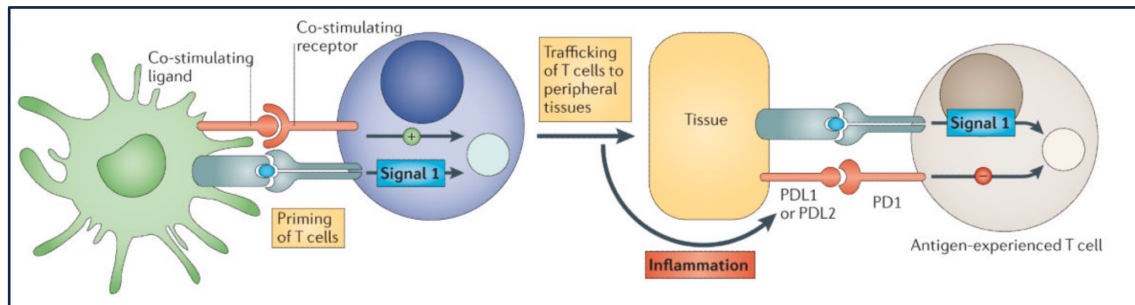


Figure 3: The PD-1 pathway (Pardoll 2012, p. 279)

Chronic antigen exposure in chronic infections or tumor disease can lead to increased PD-1 expression. This leads to a stagnation of needed immune response that PD-1 blockade can partially reactivate (Barber et al. 2006).

In melanoma especially the presence of PD-L1 on the surface of tumor cells was shown to influence the effectivity of PD-1 inhibition: Strong presence of PD-L1 suggested strong immunosuppressive activity through the PD-1 pathway, thus correctly indicating higher effectivity of PD-1 inhibitors in patients with high PD-L1 concentrations in tumor tissue (Abdel-Rahman 2016).

1.3.4. Immune related adverse events

Knowing about the pathways of PD-1 and CTLA-4 enables basic understanding of how a tumor can utilize those pathways and how blocking them can induce antitumor immune response. It also demonstrates how depriving the immune system of one or more of its downregulating checkpoints via specific antibodies can lead to a vast variety of immune related adverse events that ultimately are manifestations of acute autoimmunity.

Because of similar effect mechanisms of PD-1 and CTLA-4 antibodies, irAEs in general manifest themselves quite similar across the different immunotherapies. Due to the up-regulation of a broad spectrum of immune responses, every organ can be affected by irAEs. They are frequent and often severe, sometimes even fatal (Chen et al. 2015; Michot et al. 2016).

To date, there exists a large and growing number of publications on the different irAEs, their onset timing, pathogenesis and management (see for example Champiat et al. 2016; Iglesias 2017; Stucci et al. 2017; Suarez-Almazor et al. 2017; Tarhini 2013). The authors propose differentiated approaches depending on symptoms, severity and affected organ system. To properly reflect on all of these approaches would extend far beyond the scope of this dissertation. Thus, there is a focus on general epidemiology and pathogenesis as well as basic approaches concerning irAE management.

Epidemiology

Despite the advantages of immunotherapy concerning therapy outcome, irAEs remain a considerable downside. This is mainly due to their frequency: irAEs of any grade occur in up to 90% of patients with anti-CTLA-4 therapy (Hodi et al. 2010), 70% of patients with anti-PD-1 or anti-PD-L1 treatment (Brahmer et al. 2012; Topalian et al. 2012) and 96.8% of combination therapy (Callahan et al. 2017). IrAEs of grades 1 or 2 mostly affect the skin and the bowel, whereas severe irAEs are mainly prevalent in the digestive tract (Topalian et al. 2014; Weber et al. 2013). Severe irAEs occurred in 40.4-55% of patients receiving combination therapy (Callahan et al. 2017; Postow et al. 2015; Wolchok et al. 2013), as opposed to 16-34.9% in monotherapy with anti-PD-1 (Weber et al. 2017; Wolchok et al. 2013) and 24-27% in monotherapy with anti-CTLA-4 antibodies, respectively (Postow et al. 2015; Wolchok et al. 2013). The occurrence of irAEs sometimes lead to a discontinuation of treatment (Michot et al. 2016).

IrAE onset generally takes place within 3-6 months of anti-CTLA-4 therapy (Topalian et al. 2014; Weber et al. 2013) or anti-PD-1 therapy (Topalian et al. 2014; Weber et al. 2017), while late toxicity is uncommon (Callahan et al. 2017). Dose dependency of irAEs has been observed with anti-CTLA-4 but not with anti-PD-1 treatment (Maker et al. 2006; Topalian et al. 2014; Wolchok et al. 2010).

Generally, irAE profiles of anti-CTLA-4 and anti-PD-1/PD-L1 treatments are very similar although those of the latter are less frequent and severe (Cousin et al. 2016). There are, however, some differences besides the onset frequencies in different organ systems to be affected. For example, irAEs deriving from anti-CTLA-4 treatment mostly affect the skin (44% of cases), mainly papular rashes and pruritus, and the gastrointestinal tract (35%) predominantly in the term of colitis (Bertrand et al. 2015). In anti-PD-1 therapy, the most common toxicity is fatigue/asthenia (16-34%) followed by loss of appetite (5-19%), rash (16%) and diarrhea (14%) (Larkin et al. 2015; Weber et al. 2015, 2017). Overall, immunotherapy can affect every organ system including the endocrine, with hypophysitis and thyroiditis being the most common (Iglesias 2017). Immunotherapy also sometimes leads to exacerbations of pre-existing autoimmune diseases such as vitiligo, rosacea or alopecia (Bertrand et al. 2015).

While irAEs in general were more frequent in combination therapy compared to anti-CTLA-4 therapy and more frequent in the latter than in anti-PD-1 therapy, in some cases exceptions of this trend were reported. For example, Sjögren's syndrome seems to be more frequent in anti-PD-1 treatment (Topalian et al. 2012), thereby suggesting

that the differences between each immunotherapy concerning irAEs might not be limited to frequency and intensity alone.

Pathogenesis

Not much is known about the pathogenesis of irAEs other than it being a result of the general increase in immunologic activity, leading to antitumor and autoimmune responses, as described in Section 1.3 (Stucci et al. 2017; Ueda et al. 2003).

Several authors describe phenomena linked to the onset of one group of irAEs or the other thereby taking an individual approach for each group of irAEs. Some examples will be presented in sequence:

Biopsies of irAEs affecting the skin showed edema and occasionally perivascular lymphocytic infiltrates (Attia et al. 2005). Immunohistochemical analyses identified CD4⁺ and melan-A-specific CD8⁺ T cells close to melanocytes (Weber et al. 2012), which was interpreted as the effect of anti-CTLA-4 antibody induced immune response directly against melanocytes and linked to vitiligo (Tarhini 2013). Gastrointestinal irAEs, as another example, have been associated with an expansion of Th17 cells and serum IL-17 elevation (Callahan et al. 2011) and Iglesias (Iglesias 2017) reviewed individual pathogenetic theories for many endocrinopathic irAEs.

Although reviewing available theories about the pathogenesis of irAEs would go beyond the scope of this study, it becomes clear that despite CTLA-4 and PD-1 blockade leading to a general increase of immunologic response, the aspects that ultimately cause the onset of each individual irAE seem to be less universal.

Treatment

When reviewing the different recommendations on irAE management in literature, an individual approach for each affected organ system, while mostly independent of the respective immunotherapy, is being suggested. Again, elaborating on all different sets of irAEs would exceed the scope of this thesis. However, all suggestions basically follow the same principles of organ specific treatment in the sense of symptomatic treatment in mild cases. In more severe cases, they are augmented with immunosuppression and eventual therapy discontinuation, thereby following a more causal therapy approach (see e.g. Champiat et al. 2016; Iglesias 2017; Stucci et al. 2017; Suarez-Almazor et al. 2017; Tarhini 2013).

Outlined using the review of Stucci et al. (2017) as example, the causal intervention is very similar in each group of irAEs: For irAEs grade ≥ 2 , a delay of the next dose of

immunotherapy is suggested. If the symptoms persist, a systemic corticoid should be administered. In case of an irAE grade ≥ 3 , a permanent discontinuation of immunotherapy is suggested combined with a higher dose of the systemic corticoid and a close in-ward follow-up. In case the irAE worsens or persists, the administration of another immunosuppressant like infliximab is recommended, which mostly resolves the irAE.

The principles of the organ specific treatment will be explained looking at the examples of immune related rash, pneumonitis and colitis as proposed by Stucci et al. (2017). Causal aspects in all cases are as described above and will be left out here.

A maculopapular rash, for example, can be treated supportively from grade 1 with antihistamines, topical steroids, or a combination of both.

Concerning the irAE pneumonitis, grade 1 should only be monitored, whereas in grades 2-4 the consideration of a biopsy is recommended to rule out differential diagnoses that might contraindicate a steroid intervention.

If the irAE is a colitis, in grade 1 the supportive care would include oral fluids and antimotility agents. In grade ≥ 3 , a lower gastrointestinal endoscopy is recommended to verify the diagnosis, comparably to as it is recommended with pneumonitis.

Such organ specific approach balancing symptom control and causal treatment completes the algorithm of irAE treatment in general. To obtain more detailed information on irAE treatment, please refer to Stucci et al. (2017) or one of the other abovementioned publications.

1.4. Biomarkers in immunotherapy

The previous sections shed light on the significance of irAEs in immunotherapy. Yet, many patients do not respond to immunotherapy. Furthermore, some reports exist on cases of hyperprogression, an accelerated progression phenomenon (Champrat et al. 2017), which emphasizes the necessity of risk-benefit assessment prior to therapy. This section focusses on biomarkers described in literature for both outcome and risk of irAEs.

1.4.1. Biomarkers for outcome

While it lies in the nature of targeted therapy that identifying a specific mutation in the tumor cells yields a valid biomarker for therapy response, it is not that simple for immunotherapies. Given the complexity of the immune system itself, few or even a single biomarker capable of making valid predictions on therapy outcome are unlikely – a large

number of different biomarkers with interactions reflecting those of the physiologic immune system seem far more probable. Axelrod et al. (2017) postulate four general immunologic conditions for a successful immune response to immunotherapy:

- The ability of T cells to infiltrate tumor microenvironment.
- The ability of T cells to be activated by immune checkpoint inhibitors.
- The capability of neoantigens to be presented to, and recognized by, T cells.
- The capability of T cells to effectively mount a cytotoxic response.

There are several areas of biomarkers being investigated in the context of immune checkpoint inhibitors that involve these four conditions. Although this study focuses particularly on biomarkers in the peripheral blood, other areas will be introduced as well in order to provide a proper overview on the topic.

Melanoma genomics

The most important genetic melanoma subtypes BRAF (35-50% prevalence), NRAS (10-25% prevalence) and NF1 (14% prevalence) (Cancer Genome Atlas Network 2015) have shown different potential as biomarkers for therapy outcome in immunotherapy. While the BRAF mutation seems to have no impact on tumor response (Shahabi et al. 2012; Sznol et al. 2014), NF1 mutations were described to be associated with higher response rates to anti-PD-1 treatment (Johnson et al. 2016b). Although generally associated with inferior prognosis, NRAS mutations may be associated with higher response rates to ipilimumab and anti-PD-1 therapy (Johnson et al. 2015, 2016c).

Tumor microenvironment

The tumor microenvironment (TME) includes surrounding blood vessels, immune cells, fibroblasts and the extracellular matrix, which communicate with the tumor cells and influence its growth (Axelrod et al. 2017). Given the main effect of the CTLA-4 pathway being activated in lymphoid tissue during T cell priming as described in Section 1.3.2, TME is more intensively researched in the context of anti-PD-1 treatment.

Especially immune cells in the TME caught the attention of researchers. For example it has been shown that higher CD8⁺ T cell density at the tumor margin as opposed to the tumor center is associated with higher response rates to immunotherapy (Daud et al. 2016; Tumeh et al. 2014). However, the immunophenotype seems to influence response rates as well: In the study of Daud et al. (2016), patients with > 20% CTLA-4^{hi} PD-1^{hi} of the CD8⁺ tumor infiltrating lymphocytes showed a significantly longer PFS (31.6 months) compared to those with a share of < 20% (9.6 months) in anti-PD-1 treatment.

The expression of immune checkpoints in T cells of the TME as biomarkers for outcome are also discussed in literature. Van Allen et al. (2015), for example, show a significant association of CTLA-4 and PD-L2 expression in melanoma patients with higher response rates to ipilimumab.

The PD-L1 expression as a biomarker for anti-PD-1 blockade in tumor cells is controversially discussed in literature and the results yet remain inconclusive – despite the seemingly obvious theoretical connection between the presence of checkpoint activators on tumor cells and the success of its blockade. This is due to several reasons that cannot all be accounted for in this study's scope, eventually leading to a lack of comparability between the findings. For example, there were different thresholds used to define PD-L1-positive cells in different studies and different binding antigens utilized in immunohistochemistry. For further reading, Axelrod et al. (2017) provide a more detailed review on this topic.

Tumor cell signaling

As reviewed in Section 1.3, tumors learn to evade the immune system in the course of their development. Oncogenic cell signaling pathways are an important aspect in the immunosuppression induced by a cancer and thus also in the topic of immune checkpoint inhibition.

Alterations in the Ras-MAPK signaling, for example, were shown to be associated with lower tumor infiltrating lymphocytes in triple negative breast cancer (Loi et al. 2016). This implies the utilization of the corresponding MEK inhibitors, which also play an important role in prolonging the response in targeted therapy of the melanoma (see Section 1.2.4) in combination with PD-L1/PD-1 inhibition. This led to improved response rates in mouse models (Ebert et al. 2016; Loi et al. 2016).

Another example is PTEN, a tumor suppressant lipid phosphatase that dampens the activity of the PI3K pathway. PI3K is responsible for several cellular processes among which are the promotion of proliferation and survival. According to Peng et al. (2016), the loss of PTEN seems associated with worse response to anti-PD-1 therapy in a mouse model, likely due to the mediation of immunosuppressive cytokines. Treatment of affected mice with a selective PI3K β inhibitor led to improved response rates of both anti-PD-1 and anti-CTLA-4 treatment.

Given the vast amount of possible mutational and transcriptional alterations, their value as practical biomarkers will probably remain inferior to their value for the theoretical understanding of tumor-immune interactions.

Mutational burden and neoantigens

Using whole exon sequencing, it has been shown that a high mutational burden is associated with clinical benefit in anti-CTLA-4 (Snyder et al. 2014) and anti-PD-1 treatment (Le et al. 2015). This is possibly due to the high rate of neoantigens induced by the high mutation rates, thereby increasing the chance for the immune system to recognize the tumor and mount a response. Concurring, patients with low intra-tumoral heterogeneity of neoantigens and a large amount of clonal neoantigens showed improved OS in an anti-CTLA-4 treatment study (McGranahan et al. 2016).

These results could be confirmed using less expensive next generation sequencing anti-PD-1 and anti-PD-L1 treatment (Johnson et al. 2016b).

Antigen presentation

The expression of major histocompatibility complex (MHC) II, but not of MHC I, was shown to be associated with improved response rates and OS in anti-PD-1 therapy (Johnson et al. 2016a, 2017). It may therefore prove to be a viable biomarker to be considered when deciding between the different immunotherapies.

Other defects of antigen presentation have also shown to be associated with anti-PD-1 therapeutic resistance. Those are pre-existing or acquired mutations in JAK1 or JAK2, ultimately leading to antigen presentation defects, loss of PD-L1 expression and therapeutic resistance (Shin et al. 2017; Zaretsky et al. 2016). Another example is the loss of β -2 microglobuline, necessary in the assembly of MHC I. Its lack was also associated with anti-PD-1 resistance (Zaretsky et al. 2016).

Cytotoxic T cell response

A final step of an antitumor immune response is the cytotoxic T cell response. Therein perforin and granzyme transcripts were high particularly in patients who responded to, and long-term survivors of, ipilimumab (Allen et al. 2015).

As a more general promotor not only for cytotoxic T cells, IFN- γ plays an important role as well. For anti-CTLA-4 therapy, the loss of the IFN- γ pathway appears associated with therapeutic resistance (Gao et al. 2016), whereas Herbst et al. (2014) postulate higher response rates in anti-PD-1 therapy to be associated with higher pretreatment expression of IFN- γ and IFN- γ inducible genes.

Clinical biomarkers

Clinical characteristics as biomarkers for response to immunotherapy represent a more practical alternative to those reviewed in the last subsections, because they usually are either obvious and require no further testing or are raised as part of routine diagnostic. For example, patients who received therapy prior to the respective immunotherapy had inferior response rates to anti-PD-1 treatment in a large phase-I study ($n = 655$) (Ribas et al. 2016).

Other researchers published studies about the association of tumor burden and localization with response to immunotherapy and found that, for example, high tumor burden can be associated with a lack of clinical response even despite immune response being present and measurable in terms of induced CD8⁺ proliferation (Huang et al. 2017). Other authors emphasize the predictive value of distribution of metastases, especially the presence of liver metastases being associated with inferior response to anti-PD-1 therapy (Tumeh et al. 2017). Weide et al. (2016) find the absence of metastases other than soft-tissue/lung to be associated with favorable OS.

A completely different biomarker that seems associated with anti-PD-L1 response involves intestinal microbiota. Sivan et al. (2015) identified the presence of bifidobacterium to promote antitumoral response and enhance response to anti-PD-L1 treatment in mice. This biomarker has the additional advantage of the possible application as a therapeutic intervention in melanoma treatment and immunotherapy enhancement.

Especially interesting in the scope of this study are irAEs as biomarker for clinical response. It seems consequential that irAEs being a sign of an immunotherapy induced immune response would correlate with clinical antitumor response. In fact, studies have shown not only an association of irAE occurrence with antitumor response during anti-PD-1 treatment (Judd et al. 2017), but also a dependence on irAE frequency. Patients suffering from ≥ 3 irAEs had a significantly longer OS compared to those who had one or no irAE ($p < 0.001$) (Freeman-Keller et al. 2016). These findings suggest a strong correlation between the occurrence of irAEs and clinical response.

Peripheral blood biomarkers

Biomarkers for antitumor response to immunotherapy in the peripheral blood represent an easily accessible option, especially when possessing predictive value in longitudinal monitoring. Thereby, assessments of early therapy response are additionally enabled that could help to decide about alterations in the therapy regime.

LDH has been established as a prognostic biomarker for general melanoma progression. Consequently, higher levels were also associated with worse outcome compared to

lower levels both in anti-CTLA-4 and anti-PD-1 treatment (Diem et al. 2016; Martens et al. 2016a). For this, Weide et al. (2016) propose a threshold value of the 2.5-fold elevation at baseline, which will also be utilized in this study. In anti-PD-1 treatment, Diem et al. (2016) additionally suggest that an LDH mean decrease during treatment seems to be associated with better response compared to patients experiencing an LDH mean increase.

Other blood markers were described to be associated with therapy response as well. Among them is a relative lymphocyte count of $> 10.5\%$ that correlates with a 1-year survival rate of 40.8%, compared to counts $< 10.5\%$, in anti-CTLA-4 treatment (Martens et al. 2016a). Martens et al. also found other markers such as low absolute and relative eosinophil count to correlate with favorable outcome. Weide et al. (2016) state that a relative eosinophil count below 1.5% and a relative lymphocyte count $\geq 17.5\%$ are linked to superior OS. In another study, Martens et al. (2016b) propose an increase of absolute lymphocyte count and shares of $CD4^+$ and $CD8^+$ T cells during therapy as an indicator of favorable survival. Most of these parameters are being measured regularly during therapy follow-up and are therefore generally easily accessible for the attending dermatooncologist.

A more specific biomarker of the peripheral blood is circulating tumor DNA. A study of Lee et al. (2017) suggests strong correlation between the absence of measurable circulating tumor DNA and response to anti-PD-1 treatment. This correlation to superior response rates includes patients with tumor DNA that is not measurable in the peripheral blood at baseline (72% clinical response) as well as those who reached undetectable levels within the first 12 weeks of therapy (77%) compared to those who did not (6%).

It can be concluded that there are various biomarkers available and more are being researched for therapy outcome of immunotherapy, most of which require additional tests and only involve an assessment at baseline. Only clinical biomarkers and those of the peripheral blood are widely and easily accessible and can therefore be assessed during the course of treatment.

1.4.2. Biomarkers for adverse events

Compared to biomarkers for response to immunotherapy, biomarkers for irAEs have been less thoroughly investigated (Hopkins et al. 2017). There are, however, some noteworthy findings that will be reported in this section.

An increase of irAE occurrence likelihood depending on the presence of prior autoimmune disorders has been reported. Yet, this increase relates mostly to low grade irAEs

and was found to be no contraindication for anti-CTLA-4 or anti-PD-1 treatment (Johnson et al. 2016d; Menzies et al. 2017), thereby presenting itself as a viable baseline indicator of low grade irAEs.

Another baseline antecedent for irAEs was found by Daly et al. (2017), they used analysis of CT imagery to correlate body composition parameters with ipilimumab toxicities. The authors found sarcopenia and low muscle attenuation to be associated with high grade irAEs. As discussed in the previous section, Roy et al. (2017) state an association of microbiota with antitumor and immunological activity to be connected to irAEs as well. Thus, another biomarker has been added that, although mainly researched in mice, may be utilized as an additional approach for treatment.

Other authors name various further aspects to be linked to irAE occurrence, such as tumor infiltration and location, viral infections like HIV or hepatitis, or medication with agents that are known for autoimmune toxicities of their own; namely antiarrhythmics, antibiotics, anticonvulsants or antipsychotics (Champiat et al. 2016; Manson et al. 2016).

Concerning parameters of the peripheral blood, there has also been progress in research. In anti-CTLA-4 treatment, Fong et al. (2016) and Oh et al. (2017) suggest T cell diversification in CD4⁺ and CD8⁺ within the first two weeks to be associated with irAE occurrence. They found patients with irAEs to have a higher grade of CD4⁺ / CD8⁺ diversification during therapy, thus introducing an indicator of interaction between patient and therapy. Although measurements of CD4⁺ and CD8⁺ usually do not count as laboratory routine parameters in immunotherapy, this biomarker is comparably easily accessible. Similar holds true for increased levels of circulating IL-17 at baseline, which seems to be associated with gastrointestinal toxicity (Hopkins et al. 2017; Tarhini 2013). Schindler et al. (2014) researched the immunologically related absolute and relative eosinophil counts at baseline, four and seven weeks after anti-CTLA-4 therapy start for their correlation with irAEs and OS. They found associations of absolute and relative eosinophil continuous values with irAE occurrence at week four and seven, but not at baseline. Additionally, the respective changes from baseline to week four and from baseline to week seven reached statistical significance in their correlation with irAE occurrence.

Concluding, there are much fewer antecedents known to predict the outcome than the occurrence of irAEs. Most of them, much like predictors of therapy response, are baseline biomarkers and can therefore not be used as red flags for irAE occurrence.

1.4.3. Research gap

Immune checkpoint inhibitors are a new and promising option for cancer therapy, not only for the malignant melanoma. As such, they are subject to a vivid field of research with frequent new publications and approaches for every aspect of therapy. Most authors, however, focus on the aspect of therapy response. But as this form of therapy comes of age and more is known about its efficacy, severe “[...] adverse events highlight the urgent need to develop suitable biomarkers for patient risk-benefit management” (Axelrod et al. 2017, p. 2).

To date, such biomarkers are mostly limited to assessment at baseline and therefore rather vague in their predictive value concerning irAE onset. The only approaches towards a biomarker that can be used *during* therapy, as opposed to before, concern early T cell differentiation, circulating IL-17, and relative as well as absolute eosinophil count, as reviewed in the previous section. They have not yet been researched for both anti-PD-1 and anti-CTLA-4 treatment. An assessment of more blood parameters has been conducted by Khoja et al. (2016a) – however, those were again measured at baseline and no reliable antecedent was found for irAEs among several blood count parameters for anti-CTLA-4 treatment.

It is still unknown whether there are any reliable biomarkers warning in real time against an upcoming irAE – and which they might be. Although such a biomarker would not necessarily contribute to a risk-benefit assessment before an immunotherapy, it could very well help the dermatooncologist with therapy management and the patient with life quality: Early recognition and treatment are considered the most important aspects of preventing irAEs to become severe.

1.5. Objectives of this study

“Critical to the successful management of select AEs is early recognition”

– (Weber et al. 2017, p. 790)

The primary objective of this study is to give clinicians a new and easily available tool for irAE surveillance in immunotherapy and to contribute to closing the research gap described in the previous section. This was pursued by analyzing several possible antecedents concerning their individual and combined predictive values using a multilevel logistic regression approach augmented by descriptive methods. This section will provide an overview on which main antecedents were investigated. In sequence, this study’s goals will be defined.

1.5.1. Red flags for adverse events

Biomarkers that can be used to predict any or severe irAEs are scarce in literature. Even harder to find are those that can be used as a real time red flag against an upcoming irAE, hence parameters that must be measurable on a regular basis, such as those in the peripheral blood. Those that were published followed the logic of the irAE pathogenesis to be a result of general inflammation due to immunotherapy. They were inflammation parameters like T cell differentiation, circulating IL-17 or eosinophil granulocytes, as reviewed in Section 1.4.

In this study, those laboratory parameters that are measured as a routine in every cycle of therapy and reflect immunologic activity were investigated for their ability to predict upcoming irAEs. In the data available, these parameters were relative and absolute eosinophil count (REC & AEC) as well as leucocyte count (LC), grouped as the leucocyte group¹, C-reactive protein (CRP), and lactate dehydrogenase (LDH). There were several threshold values defined for biomarkers in each parameter, which will be explained in Section 2.2.

1.5.2. Demographics as a risk factor for adverse events

In addition to the possible predictive power of laboratory parameters, two other variables were available and of interest for the purpose of this study: Gender and age at the beginning of the course of therapy (CoT). As shown in Section 1.4, the scarce knowledge on risk factors for irAEs expands to these demographics as well. When looking at other immunogenic diseases, however, some have shown to be associated with a certain age or gender: Bechterew's disease typically afflicts young males, more elderly patients suffer from arteritis temporalis and especially the female get Basedow's disease (Renz-Polster et al. 2013). Additionally, Khoja et al. (2016b) state that, among others, female gender as well as toxicity during anti-CTLA-4 treatment is associated with better PFS. If it was assumed that irAEs are associated with better outcome, as Judd et al. (2017) suggest, the association of female gender with better PFS theoretically might be in fact an association of female gender with irAEs.

For these reasons, a possible risk of irAE depending on gender and age will be added to the final regression models.

¹ The reasons for this grouping are due to requirements of the method and will be explained in Section 2.3.2

2. Methods

This study is a monocentral, retrospective, longitudinal study to investigate temporal relations primarily between laboratory parameters and the occurrence of irAEs in immunotherapies of the metastatic melanoma. Existing data of the University Hospital of Cologne were used of patients with metastasized or unresectable malignant melanoma who received immunotherapy as treatment.

Predominantly five routine laboratory tests with various threshold values were analyzed concerning possible heralding of upcoming therapy related AEs. In the following sections, the process of sampling will be described, the relevant parameters explained and developed, and the selected methods of regression and supplementary analysis derived and illustrated.

2.1. Sampling

Eligible patients had metastasized, unresectable melanoma and received at least one dose of any of the following immunotherapies:

- Ipilimumab: 3 mg / kg every 3 weeks for 4 doses
- Pembrolizumab: 2 mg / kg every 3 weeks
- Nivolumab: 3 mg / kg every 2 weeks
- Combination therapy: 1 mg nivolumab and 3 mg ipilimumab / kg every 3 weeks for 4 doses, subsequently 3 mg nivolumab / kg every 2 weeks

The different treatment groups will further be referred to by their target receptors as PD-1 treatment group (pembrolizumab / nivolumab), CTLA-4 treatment group (ipilimumab) and combination therapy group. Data of patients receiving one of the two PD-1 antibodies were pooled in this study because of the same effect mechanism. All therapies were conducted as long as patients continued to benefit from them.

To maximize efficacy, not individual patients but individual Courses of Therapy (CoT) were investigated, i.e. the timeframe from the first until the last administration of one of the abovementioned agents. By that method, CoT could be harnessed of patients who had received various immunotherapies: If one patient had a first successful therapy leading into a prolonged therapy-free period of more than six months followed by progression and another CoT with the same drug, they were as well separated into two different CoT. This was done twice in this study.

Major exclusion criterion was an uncompleted first cycle of therapy for any other reason than death or AEs. There were no limitations concerning the number or kind of previous treatments.

2.2. Parameters

The parameters for the study were collected from the hospital information system of the University Hospital of Cologne. Every target parameter was collected at the beginning of each cycle of therapy, including baseline. The advice of the Ethics Committee of the University of Cologne has been implemented and approval followed in November 2016 under the sign 16-239.

2.2.1. Timeframe for data collection

The day of the first dose of immunotherapy was defined as baseline. A cycle was defined as the timespan from one dose to the next. The last day of the last cycle after the last dose was chosen according to the documented dates of patient visits and the standard length of cycles of therapy (21 days, except nivolumab: 14 days). Deviations from the standard length were tolerated from half to double of the standard length. This was chosen in order to be able to document any irAEs that occurred after the last dose and might have caused therapy discontinuation. If the last cycle did not fit the abovementioned requirements (e.g., no information given after the last dose), it was not taken into consideration and the last cycle was considered the one before the last dose.

If at the date of treatment administration no laboratory tests were documented (e.g., in case of a common cold leading to a delay of treatment administration by one week, but tests were conducted on the day of planned treatment), it was matched with the closest documented tests before the therapy. Up to half of the average cycle length time difference was tolerated. If there were no laboratory results documented matching these requirements, they were marked as not available (NA).

This study's focus on irAEs in a longitudinal design made adaptations necessary concerning follow-up because the common definition of follow-up from the first dose to the last visit could not be applied here. For example, a patient of the CTLA-4 treatment group, whose last visit took place a year after the first dose, has a follow-up of one year when following the common definition. For the abovementioned requirements of this study, however, the timespan that irAEs would be documented in on a sufficiently regular basis is naturally limited to the duration of the four cycles of therapy. A similar problem arises

if a therapy break lasted until the end of data collection. This is why follow-up was defined as the timespan from the first dose to the end of the last cycle as described above.

2.2.2. Laboratory results

All laboratory results were obtained from the central laboratory of the University Hospital in Cologne and were retrospectively compiled for each cycle of therapy. The tests were conducted at the day of the first dose of immunotherapy for baseline and afterwards every day of planned immunotherapy administration.

Standard parameters were chosen that were routinely sampled at the beginning of each cycle of immunotherapy, in particular such parameters that may be associated with the occurrence of irAEs in the experience of attending dermatooncologists. They had to be routine tests not only because of the retrospective setup but also to maximize the potential benefit of this study. In case a suitable biomarker was detected, clinicians ideally should become aware of it merely by looking at their routine diagnostics without the need to use extra tests, which might not be available for financial or other constraints. The laboratory parameters chosen were c-reactive protein (CRP), leucocytes (LC), relative eosinophil count (REC), absolute eosinophil count (AEC) and lactate dehydrogenase (LDH) in blood.

To recognize whether a laboratory parameter was a suitable marker for irAEs, threshold values were defined for every laboratory parameter to be considered an anomaly. For that the relevant upper reference value of the Institute of Clinical Chemistry of the University Hospital of Cologne was used. The upper reference values were defined as follows:

- CRP: 5 mg/l
- LDH: 250 U/l
- LC: 11.3 x1E9/l
- REC: 7.6%
- AEC: 59 x1E7/l

Based on these thresholds, several markers were defined consisting of one-sided thresholds and intervals. One of the thresholds for each parameter was chosen to be the above-mentioned upper reference value. They will further be referred to as “E” (Elevation), noted after the respective parameter (for example: CRP E for CRP > 5 mg/l).

For REC and LDH, an additional respective threshold was defined based on the findings of Weide et al. (2016): The authors found four predictors that, if apparent at baseline, would indicate a favorable OS. Among them were $\geq 1.5\%$ REC and ≤ 2.5 -fold elevation

of LDH. These thresholds were adopted and will further be referred to as “W” (Weide) after the respective parameter.

Additionally, several intervals were defined for each parameter that, based on the above-mentioned upper reference value, would

- a) reach from half the upper reference value to a single elevation (HS).
- b) include the single elevation reaching up to double of the upper reference value (SD).
- c) include the double elevation and reach up to triple of the upper reference value (DT).

As the last threshold, the threefold of the reference value was added, which will further be referred to as “T” (Triple).

In the following table, all definitions of one-sided and interval thresholds are listed:

Relative eosinophil count

REC W:	≥ 1.5%
REC E:	> 7.6%
REC HS:	> 3.8 – 7.6%
REC SD:	> 7.6 – 15.2%
REC DT:	> 15.2 – 22.8%
REC T:	> 22.8%

Lactate dehydrogenase

LDH W:	> 625 U/l
LDH E:	> 250 U/l
LDH HS:	> 125 – 250 U/l
LDH SD:	> 250 – 500 U/l
LDH DT:	> 500 – 750 U/l
LDH T:	> 750 U/l

Absolute eosinophil count

AEC E:	> 59 x1E7/l
AEC HS:	> 29.5 – 59 x1E7/l
AEC SD:	> 59 – 118 x1E7/l
AEC DT:	> 118 – 177 x1E7/l
AEC T:	> 177 x1E7/l

Leucocytes

LC E:	> 11.3 x1E9/l
LC HS:	> 5.65 – 11.3 x1E9/l
LC SD:	> 11.3 – 22.6 x1E9/l
LC DT:	> 22.6 – 33.9 x1E9/l
LC T:	> 33.9 x1E9/l

C-reactive protein

CRP E:	> 5 mg/l
CRP HS ² :	> 3 – 5 mg/l
CRP SD:	> 5 – 10 mg/l
CRP DT:	> 10 – 15 mg/l
CRP T:	> 15 mg/l

² Because in most cases the lowest CRP value measurable by the laboratory was 3 mg/l, it was not expedient to define CRP HS as 2.5 – 5 mg/l and an exceptional adaption of the interval was made to enable measurements below the HS interval.

For each of these thresholds, dichotomous dummy variables were created for each measurement. They were set “True” if the condition defined by the respective one-sided or interval threshold was met. In addition to that, either the measurement had to be taken at baseline, and therefore had to have no preceding measurement, or the measurement of the preceding cycle had to be below this threshold or interval. When these conditions are not met, the dummy variable’s value for the respective cycle is set to “False”. This way, every “True” value represents the very first of a possible series of measurements matching the respective threshold or interval of a parameter. This will further be referred to as laboratory anomaly. An illustration of this principle using an exemplary course of CRP values can be reviewed in Figure 4.

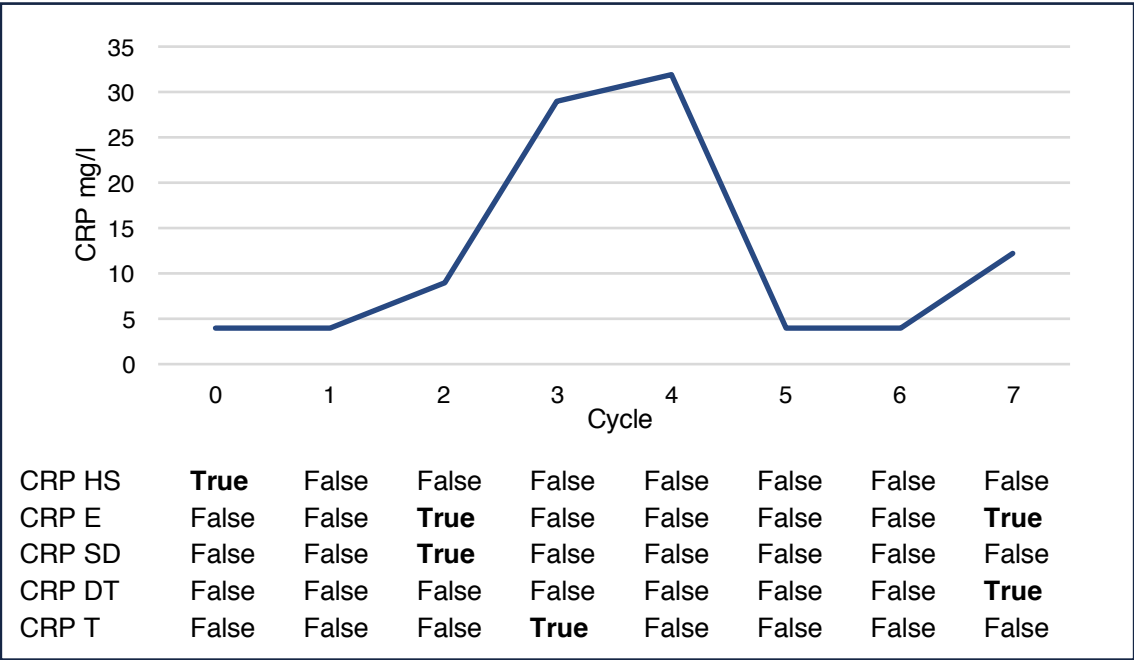


Figure 4: Laboratory anomalies constructed from an exemplary course of CRP
The requirement of CRP HS in this example is met only at baseline. Hence, only then its value is “True”. In the fifth cycle it is “False”, although the value is between 3 and 5 mg/l because the previous value was above 5 mg/l. CRP E conditions are met twice in the second and the last cycle. CPR SD is “True” in the second cycle only because between the sixth and the last cycle there was no measurement with a value from 5 to 10 mg/l. It is the same reason for which CRP DT is only “True” in the last cycle and not in the second or third, too. A first value above 15 mg/l is only given in the third cycle. Hence, only then is CRP T “True”.

The utilization of such dummy variables was considered superior compared to analyzing the actual values of the parameters: In many cases when a laboratory value rose in the context of an irAE, it stayed elevated for several cycles after the irAE onset and sometimes resolved long after or before the irAE. With these dummy variables it was possible to enable statistical comparability to actual onsets of irAEs for validation. Additionally, these possible biomarkers were suitable to stand out in clinical practice.

Owed to this method, laboratory anomalies occurring at baseline are of a different nature as compared to later occurrence: At baseline it cannot be determined whether the parameter was elevated long before or whether this elevation is acute, because there is no earlier measurement available. Additionally, this anomaly cannot be caused by direct interaction of the immune system with the respective immunotherapy, whereas anomalies during therapy might. Thus, possible predictive values of laboratory anomalies differ depending on their onset at baseline or during therapy. For this reason, all main analyses were conducted on three different groups of baseline considerations: The complete dataset including baseline measurements and subsets in which baseline was either excluded or exclusively analyzed.

2.2.3. Adverse events

Data on AEs were extracted from the routine documentations by physicians during doctor-patient conversations and assessments at the CIO in Cologne. They were categorized as follows: fatigue, pruritus, neuritis, alopecia, dermatitis, thyroiditis, hepatitis, colitis, pneumonitis, hypophysitis, nephritis, arthritis, pancreatitis, myalgia, angioedema, stomatitis, encephalitis, lupus-like appearance and unspecific infectious appearance.

Based on the information given in the documentations, only AEs that were probably immunotherapy-related were included. This was considered to be the case if ...

- there had been an assessment of the AE documented concluding that it was therapy-related.
- the attending physician noted his opinion of a likely therapy-relation.
- the AE occurred shortly after a dose and was a common irAE according to guideline (Leitlinienprogramm Onkologie 2016).
- the AE was a common irAE without a likely alternative diagnosis.

Additionally, irAE grades were categorized in accordance with the CTCAE v4.0 (U.S. Department of Health and Human Services 2010), modified to suit the study design:

Grade 1: Mild - Clinical or diagnostic observations only, intervention not needed.

Grade 2: Moderate - Minimal, local or noninvasive intervention sufficient.

Grade 3: Severe - Hospitalization or prolongation of hospitalization necessary.

The original grades 3 and 4 had to be combined because retrospectively it was hard to differentiate whether a condition was life-threatening, hence CTCAE grade 4, or not. Thus, all life-threatening irAEs were integrated into grade 3. Because no death occurred due to therapy, there was no need for an analogue of CTCAE grade 5.

However, for the purpose of this study, there is a lack of differentiation within grade 2. For example: Whenever there is any non-invasive treatment indicated, the irAE would be classified as grade 2. This holds true for the moderate pruritus that is intense enough to prescribe antihistamines as well as for the potentially lethal encephalitis that was detected early and could be controlled with infusions of corticosteroids. To solve this issue, another attribute was added to the grades indicating the necessity of corticosteroid-treatment at any point during the course of the irAE.

The presence and grade of every irAE was classified for each cycle of therapy. However, especially in cases of low grade, irAEs follow-up was not always complete; for example, the presence of pruritus would not have been specifically documented for every cycle despite prevailing for months. Therefore, these gaps were closed if, in the context of the documentation, one prolonging irAE was considered more likely than two onsets of the same irAE shortly after each other.

Analogously to the dummy variables describing the onset of laboratory anomalies as described in Section 2.2.2, there was a dummy variable for the onset of each irAE. The default value of these dichotomous variables was “False” but was set “True” to mark the irAE onset in every cycle in which an irAE was first described. If several cycles after the offset of an irAE the same symptoms returned, it was possible that there was more than one onset of the same irAE in one CoT. Additionally, the highest grade reached in the course of the respective irAE was added to the dummy variable as well as information on whether corticosteroids were necessary. This way, it became possible to differentiate the irAE onsets by their severity. Statistically analyzing the laboratory anomalies separately for every grade would go beyond the scope of this thesis and likely not yield relevant results. Therefore, the main regression analyses were limited to two groups of irAEs having the highest clinical relevance: Any irAE and irAE with steroid intervention. This way, it could be analyzed if there were any respective antecedents for any and severe irAEs – and if so, which they were. Due to its probable requirement of intervention and intensive care, it is especially the latter that needs to be recognized and treated as early as possible (Weber et al. 2016).

To reach this goal, the 18 dichotomous irAE dummy variables were condensed into the two variables of any and severe irAE onsets. For example, a “True” value in the severe irAE variable would mark the cycle of onset of any irAE requiring treatment with steroids. This way, it became possible to directly analyze statistical relationships between the onset of laboratory anomalies and irAE onsets in the subsequent cycle of therapy. The approach is illustrated exemplary in Figure 5.

Cycle	1	2	3	4	5	6	7	8
Mild pruritus								
Severe colitis								
Severe hypophysitis								
Mild thyroiditis								
Any irAE	False	True	True	True	True	False	False	False
Steroid irAE	False	True	False	False	True	False	False	False



 irAE not documented
  irAE documented

Figure 5: Exemplary demonstration of irAE dummy variable construction

The severe hypophysitis is first documented in the second cycle and lasts until the last cycle. Because it is severe and hence needs treatment with steroids, both dummy variables' values in the second cycle are "True". The mild pruritus, only treated with antihistamines, begins in the third cycle. Because it needs no steroid intervention, only the any irAE dummy variable's value is "True" in this cycle. The same counts for the mild thyroiditis, which begins in the fourth cycle and is treated with Levothyroxin. The severe colitis, which begins in the fifth cycle and requires steroid intervention, causes both dummy variables' values to be "True" in the fifth cycle. In every other cycle, no irAE onset occurs, hence both variables' values are "False".

2.3. Regression analyses

The main methods used in this study to statistically investigate relationships between the abovementioned laboratory anomalies and the onset of irAEs were multilevel and ordinary logistic regression models. A total of 159 regressions were conducted on the six different subsets of the dataset. This section will explain the choices of methods made and provide detailed insight into how the analyses were conducted. Finally, an additional, descriptive method will be introduced, which will help to better relate the value of the regressions' results to clinical practice.

2.3.1. Choice of methods

This section will explain the reasons that led to the choice of multilevel and ordinary logistic regression as the main statistical methods of this thesis. It will then describe the different subsets to which these methods were applied to.

Multilevel logistic regression

Multiple regression in general is capable of establishing a model to predict the outcome depending on the combination and distinctive prioritization of several independent variables, which is ultimately the goal of this study. This goes beyond the capabilities of

correlation analysis, which can only describe the variables' status and how they do or do not align (Field et al. 2012).

In single linear regression it does so by using the method of least squares to build a straight that best predicts the value of one dependent variable depending on one independent variable. Hence, the regression output basically follows a modified equation of a straight:

$$dv = B \times iv + I$$

In this formula, *dv* is the **dependent variable** that can to a certain degree be predicted by the **independent variable**, *iv*. Its influence on the development of the dependent variable is defined by its **regression coefficient** *B*, acting as the slope in the equation, and the **y intercept** *I*. This equation can be extended in multiple regression by adding further dependent variables with their respective regression coefficient (Field et al. 2012).

Yet, if the dependent variable is categorical, as the dichotomous irAE dummy variables used in this study, the linear regression method is not suitable because the assumption of a linear relationship between the dependent and independent variables is violated: There can be no linear relationship to a variable that only has two expressions (Berry 1993). Using the logarithmic transformation of the regression equation to express a non-linear relationship in a linear way, this assumption violation can be avoided (Berry et al. 1985). Hence, a kind of logistic regression had to be used for the analyses at hand. During the process of logarithmic transformation, the regression coefficient *B* of linear regression is replaced in its function by the **estimate** in logistic regression. For more information on this transformation, please refer to Field et al. (2012) or Berry et al. (1985). Conventional logistic regression, much like the linear regression, assumes the independence of errors. This assumption will be violated if, for example, the general tendency of a patient towards eosinophil levels above average biases the prediction model as it influences multiple measurements of the predictor variables. To avoid this violation, a multilevel approach of logistic regression is required. The principle of this method is to add another level of hierarchy to the regression model, in this case the CoT, which is defined as random intercept. This means that in principle, an individual logistic regression is conducted on the data of every single CoT. This way, the model could consider the multiple measurements of one CoT as an entity independent of the other CoT, thereby making the errors independent again. By adding this additional level, it could also be achieved that varying durations of therapy between CoT did not bias the model. For further information on the topic, please refer to Field et al. (2012).

The analyses were conducted with the statistical software R using the `glm()` function of the “stats” package (R Core Team 2017) for logistic regression and the `glmer()` function of the “lme4” package (Bates et al. 2015) for multilevel logistic regression.

Forced entry method

When building a multiple regression model, there are several methods of dealing with the independent variables to conclude the final model. They can be roughly divided into hierarchical, stepwise and forced entry methods (Field et al. 2012).

The hierarchical method depends on preexisting knowledge on the importance of the dependent variables to predict the outcome. Based on this knowledge, the most important factor is to be entered first into the model followed by the second important until the least important (Field et al. 2012). As shown in Section 1.4.3, there is insufficient information in literature on antecedents of irAE in each immunotherapy to be able to use this method.

The stepwise methods all rely on the principle of either adding or removing an independent variable from a pool of variables if the inclusion or exclusion will significantly improve the model. Methods would use either, combine both or try all possible combinations of independent variables to come up with a model built only from antecedents with a significant contribution to the model. It is therefore especially useful if there are many different independent variables, of which only the relevant ones shall be included into the model, and if there are no cues to further narrowing them down. However, some researchers state that stepwise methods provide results with low retest replicability and suggest the forced entry method as the only appropriate method for theory testing (Field et al. 2012; Studenmund et al. 1987). Additionally, as will be shown in Section 2.3.2, due to the assumptions of regressions, the amount of laboratory dummy variables was reduced to three, creating no special need for further reduction of variables.

In the forced entry method, much unlike in the stepwise method, all independent variables are forced into the model simultaneously. Similar to the hierarchical method, the selection of these predictors must be justified. Yet, the order, in which they are entered into the model, is of no importance (Field et al. 2012). The forced entry method is therefore the one conducted in this study in every case of multiple regression, as there are not many independent variables and no sufficient data is given for a definitive hierarchical order. The selection process of the independent variables used for these models is described in Section 2.3.2.

Subsets

Section 2.2.2 showed the probable necessity of a distinctive consideration of laboratory results raised at baseline and later on. Analogously to the subdivision conducted for medication, a three-fold subdivision was conducted for baseline consideration: One overall group making no distinction, one group considering only baseline parameters and one group excluding baseline. This way, if no differences between possible antecedents in the groups excluding baseline and baseline only would be found for an antecedent, the overall group would be the most suitable for interpretation due to its higher number of cases.

It is noteworthy that in the baseline only subset each CoT has only one measurement per variable. Therefore, a multilevel approach is not necessary and conventional logistic regression will be applied here.

The next subdivision bases on the two different kinds of dependent variables: Regressions predicting the occurrence of irAE of any grade formed one group, those that predicted irAEs necessitating steroid intervention the other.

As discussed in the sampling Section 2.1, the dataset this study relies on is designed to include patients receiving either PD-1 or CTLA-4 antibodies or a combination of both. Assuming that because of the similarities in irAEs between the two kinds of antibodies there were no difference in possible antecedents for irAEs, it would be possible to analyze the whole dataset as one with no differentiation in the medication received. This would additionally have the benefit of yielding a high number of cases and raise the chances for statistical significance in case an antecedent should exist. However, this assumption is not supported in literature and risky, given the differences of effect mechanisms as described in Section 1.3. It was therefore necessary to add a distinctive analysis of the three medications that would show differences in antecedents if present. If there are none, the overall analysis, which does not differentiate between the different medication groups, is favorable with regard to the number of cases and can be assumed valid. This results in a further four-fold distinction of the dataset.

Multiplying all necessary subdivisions of three baseline considerations, two outcome parameters and four medication considerations resulted in a total of 24 subsets the final regression analysis was to be applied to. These are illustrated in Figure 6.

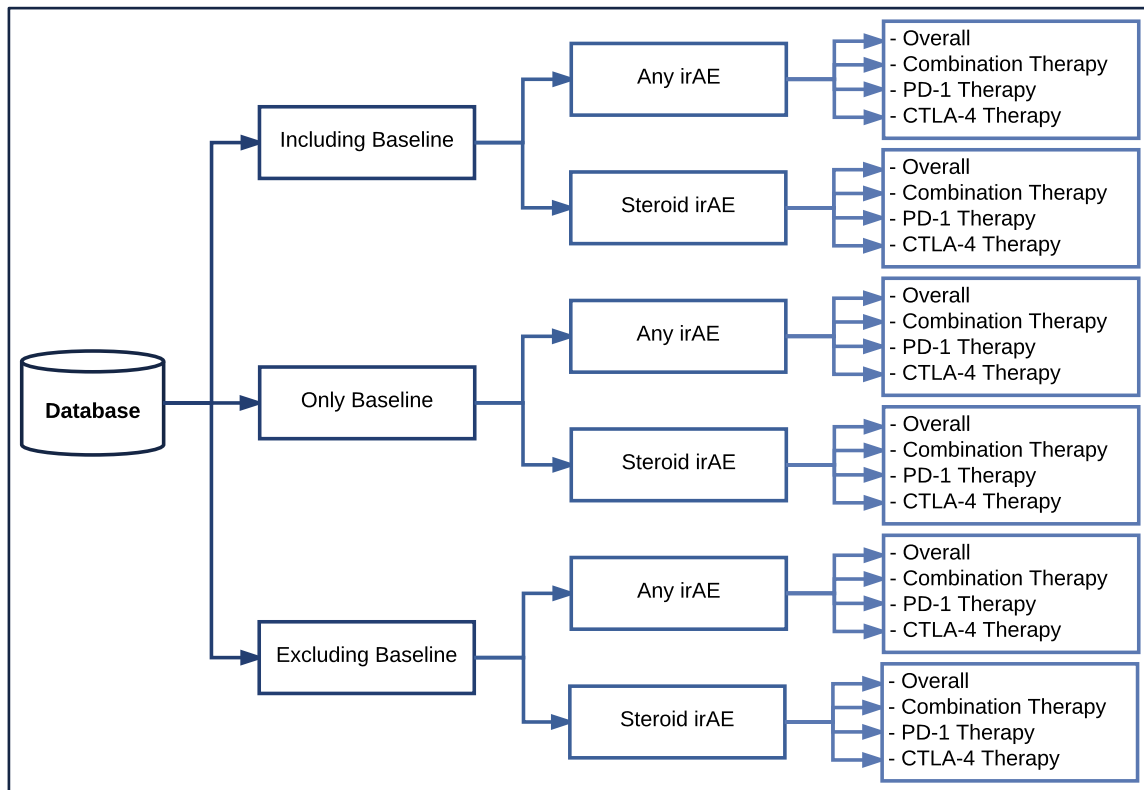


Figure 6: Subset tree

2.3.2. Selection of laboratory anomalies

Not every combination of laboratory analyses may be implemented in one regression model. It is another assumption that must be met for all independent variables in a model not to correlate too strongly with each other, which is the assumption of perfect multicollinearity. As a computer assesses a model of independent variables to predict the outcome, it calculates their individual influence on the model depending on how much variance of the actual outcome can be explained by that variable. If two or more antecedents correlate too strongly with each other, it cannot be determined which of the two variables actually explains the variance. According to Field et al. (2012), this assumption violation can lead to three-fold biasing of the model including the assessment of the importance of antecedents. Given that finding the most important antecedents of irAEs and irAEs with steroid intervention is the main goal of this study, it has been taken great care to avoid violating this assumption, not only by testing for the variance inflation factors (VIF) of the predictors later on. Following the logic of the problems arising from perfect multicollinearity it seems plausible that for example combining two different REC dummy variables would lead to a model, in which they, although depending on different thresholds, would partially explain the same variance of the outcome. This would lead to the independent variables consequentially weakening each other and the model. For instance, the first measurement of 16% REC would cause a “True” value in the dummy variables

REC W, REC E and REC DT. Additionally, in the case of the three leucocyte variables LC, REC and AEC, a high value of one variable might cause a high value of the other, again leading to two variables explaining the same variance of outcome in a model when implemented together.

For these reasons, the 24 final models had to have only three laboratory antecedents:

- LDH
- CRP
- One of the three leucocyte parameters REC, AEC and LC

To accomplish the reduction of the antecedents' count, it was necessary to identify those with the best chances of yielding the most meaningful results. Therefore, for each of the 27 laboratory dummy variables, one logistic regression in the baseline only, overall and excluding baseline were conducted, respectively. Only applying the different baseline considerations thereby assured comparability of the final results between the different treatment groups.

In the next step, for each of the abovementioned three groups of possible antecedents the resulting levels of significance were used to find the statistically most significant dummy variable of one group.

Because of the many factors involved in a multilevel regression, Kreft and de Leeuw (1998) state that creating a meaningful directive concerning a minimum sample size is impossible, but point out that it increases with each level added to a model. The method consulting of the University of Zurich (2016) suggests a minimum of 25 cases for logistic regression in every group created by a categorical variable. Hence, if the most significant dummy variable would not reach 25 cases even in the overall treatment group, it was replaced by the next best variable meeting the requirement.

2.3.3. Main analysis

The previously described intense subdivisions had to be considered in main analysis as well. Each of the six combinations of three baseline and two outcome considerations had a corresponding combination of predictors that were applied to all subordinated treatment groups, as determined in the last section. Ultimately, 24 regressions were conducted for the main analysis, with 6 combinations of laboratory predictors.

Additional to the laboratory predictors, the demographic variables discussed in Section 1.5.2 were also implemented, resulting in a total of five predictors per regression model. As described before, the six regressions conducted in the baseline only group do not

require a multilevel approach and where therefore executed using ordinary logistic regression. The remaining 12 regressions were conducted using the multilevel logistic regression with the additional level of CoT as random intercept.

The odds ratios (OR) of each predictor were calculated in sequence. They are the exponentials of the coefficients and a suitable effect size for logistic regression (Field et al. 2012). Every predictor's coefficient and their confidence intervals were calculated using R's `confint()` function on the coefficients of each predictor, followed by the `exp()` function to exponentiate each coefficient and its confidence intervals (Field et al. 2012). Both functions belong to the "stats" package (R Core Team 2017).

Expected issue: Subdivisions

Given the intensive subdivisions it had to be anticipated that some subsets would not meet the requirements to yield valid results because of the case count. Considering the fairly recent uprise of combination therapy, for example, until the end of the sampling process it was likely that only a small number of cycles could be included into the study, which would further be narrowed down subsequently, e.g. when only considering baseline data. When analyzing these data with a predictor that has proven to be the best predictor of its group and has > 25 cases in the overall group (see Section 2.3.2) but only few "True" entries, it could still be insufficient. This is due to the possibility that there may remain no "True" entry after excluding all cases from the predictor that are not baseline or combination therapy. It follows that with such a low number of cases, statistical significance consequentially is unlikely, but it must be considered during analysis and could cause the need for a corrective post-hoc regression depending on the regression output. Especially when there is no "True" value in a predictor of a regression model in a subset, establishing a model with this predictor is not possible. Consequently, in such cases the model has to be built without that respective predictor.

Expected issue: Convergence errors

Calculating a regression model with R is a repetitive approximation process, in which the computer tries in several iterations to approximate a model of differently weighted predictors that best fits the data it is based upon. Sometimes the default number of iterations is not enough to render such a model or building a model with a specific set of predictors is not possible. This is oftentimes due to one or more predictors disturbing it, which can either be solved by leaving them out of the model or rarely by increasing the number of iterations (Field et al. 2012). Because there were no specific reasons found in literature

demanding the testing of any of the predictors at question, it was decided to solve this issue by identifying and leaving out the respective responsible predictor.

2.4. Supplementary evaluation as diagnostic tests

As the abovementioned regression methods are the proper way to evaluate predictive values and ORs of the laboratory and demographic parameters analyzed in this study, it is interesting to gain even more insight on their informative value. This especially refers to laboratory anomalies that have shown statistical significance in regression. An additional descriptive approach has been chosen to provide a more holistic comprehension of the results that were shown to possess at least a statistical tendency towards a predictive value.

2.4.1. Concept

Unlike age or gender, laboratory anomalies ideally would serve as biomarkers indicating an imminent irAE and should therefore be interpreted as diagnostic tests. A value of “True” in a dummy variable means a positive test result, whereas an irAE is the event the test is to predict. This approach requires the calculation of true and false positive (TP, FP) as well as true and false negative (TN, FN) predictions, which can ultimately be used to calculate sensitivity (SEN), specificity (SPE), positive and negative predictive value (PPV, NPV) (Fletcher et al. 1996).

The results gained by this method are of descriptive nature: They basically are relative frequencies of four different scenarios. In the setup of this study, ...

- SEN described the relative frequency of a correct prediction of an irAE by the laboratory variable in all cases that an irAE occurred in.
- SPE described the relative frequency of when there correctly was no irAE predicted by the laboratory variable in all cases when no irAE occurred.
- PPV described the relative frequency of the correct positive predictions in all positive test results.
- NPV described the relative frequency of the correct negative predictions in all negative test results.

Considering this descriptive nature of the method and its lacking ability to consider the level of CoT for the independence of errors, it becomes clear that it can only be interpreted cautiously and in combination with the respective regression results.

Additionally, implemented functions of regression in R, such as identification of cases compromised by NA data, subset analyses, or the methods to calculate confidence intervals must be done manually here. The next section will explain these manual calculations and elaborate on how TN, FN, TP and FP for each subset and predictor of interest were calculated.

2.4.2. Algorithm of analysis

For each dummy variable on all laboratory anomalies, as well as the two types of irAEs with and without necessary steroid intervention as described in Section 2.2, a list was created of all cases in which the dummy variable was set “True”. In these lists, each case was made uniquely identifiable by adding the patient ID and the cycle of the case as well as its respective treatment group. It was ensured that two or more irAEs occurring during the same cycle would be merged into one entry to prevent them from being counted twice. Figure 7 illustrates the algorithm developed to calculate TP, FP, TN and FN. R was used to automatize this algorithm to provide minimal human error in this repetitive procedure and to maximize replicability of results.

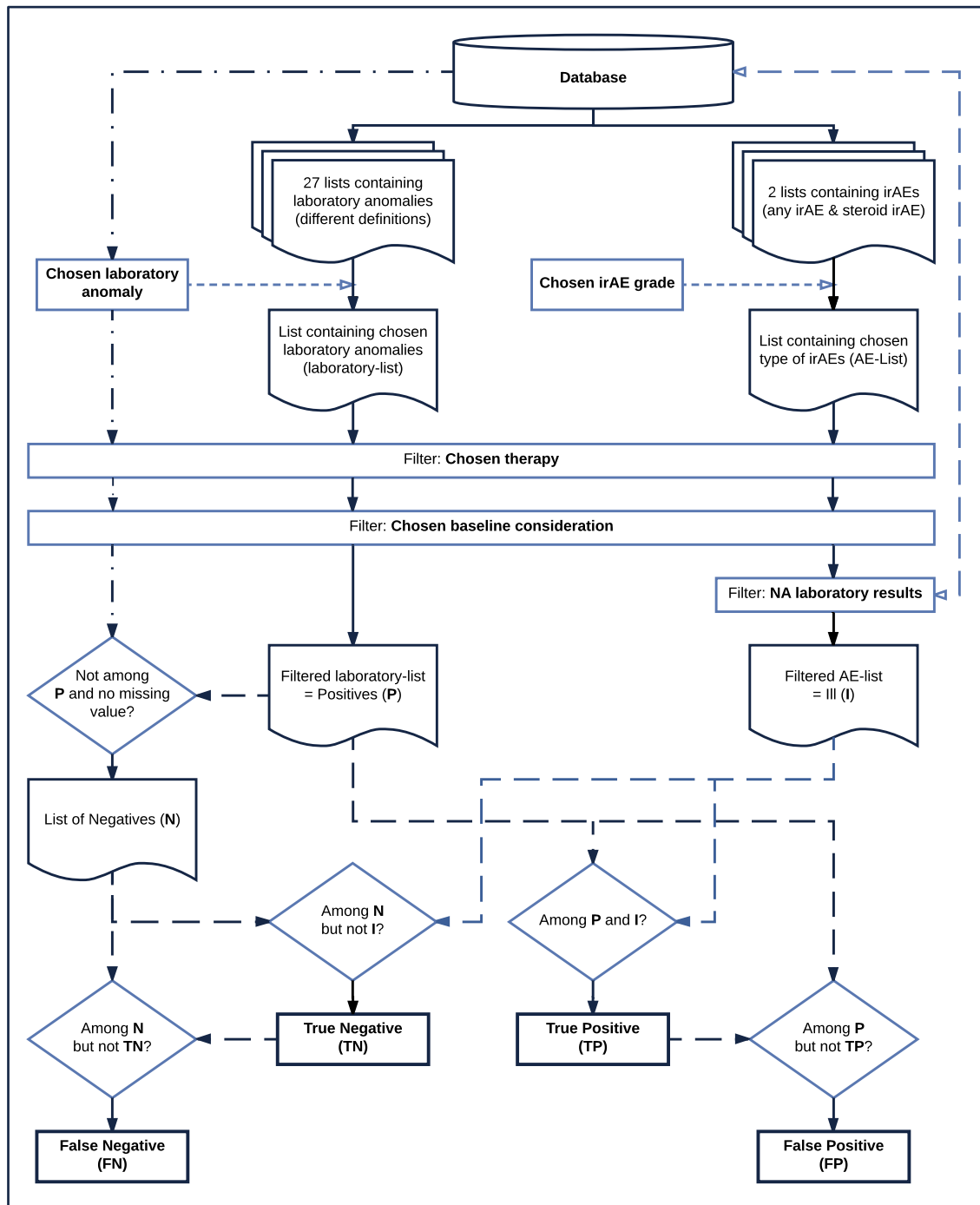


Figure 7: Algorithm for diagnostic test properties calculation

Depending on the required analysis, the correct lists out of the 27 laboratory lists and two irAE lists were chosen. As the regression analysis before, this analysis must as well be dividable into the subsets of the different therapies and baseline considerations described in Section 2.3.1. This was achieved by filtering all cases with the non-matching treatment or cycle from the lists. After that, the filtered laboratory-list contained all cases with the chosen laboratory anomaly that are considered as positive test results (P).

However, when the list of Positives and the AE-list are compared, there still is the issue of missing data in the laboratory parameters not being reflected in the AE-list. To solve this issue, every entry in the irAE-list was compared with the database to find and mark those irAE entries that had NA data in the corresponding cycle of the analyzed laboratory parameter. After that, the AE-list reflected the correct listing of cases of irAE illness (I), so that TPs and FPs could be calculated.

To calculate TNs and FNs, however, a third list reflecting the negative test results (N) was required. It was created only out of those cases that were set “False” in the respective laboratory dummy variable. After the same filtering processes as were conducted on the laboratory- and AE-list the list of negatives was completed.

To calculate each of the four parameters FN, TN, TP and FP, two of the three lists N, P and I were selected and compared to create a third list containing matching cases. The cases had to meet the following requirements to be passed on to the respective list:

TN: Listed among the negatives (N) but not among the ill (I).

TP: Listed among the positives (P) and among the ill (I).

FN: Listed among the negatives (N) but not among the true negatives (TN).

FP: Listed among the positives (P) but not among true positives (TP).

The number of cases contained in each list reflected the actual value of its parameter.

Adjustment of algorithm: Combinations of predictors

To calculate diagnostic test properties of a combination of laboratory anomalies, the lists containing the positives of each anomaly (see Figure 7) had to be merged into a new one. Only those entries would be accepted in the new list which were present in every of the single positives lists of each anomaly to be combined. This way, the new list only contained cycles in which all laboratory parameters had an entry that met the requirements of the respective laboratory anomaly.

Likewise, the lists containing the registered irAEs were merged. This was necessary to account for NA entries: irAEs would only then be taken into account if all laboratory parameters were available in the matching cycle and no value was missing. Proceeding with the negatives list calculations from here on could be conducted as usual.

Adjustment of algorithm: Negative coefficients

In the case of an antecedent significantly predicting lower probability of irAE occurrence, the list containing the entries of irAE occurrence would no longer stand for the event the test aimed to predict but for the opposite. Therefore, the definitions would switch: TN

became FN and vice versa, FP became TP and vice versa. In sequence, calculations could be proceeded.

2.4.3. Calculation of target parameters

To calculate SEN, SPE, PPV and NPV for each predictor-subset combination, the following equations were used (Fletcher et al. 1996):

$$\begin{aligned} SEN &= \frac{TP}{TP+FN} & PPV &= \frac{TP}{P} \\ SPE &= \frac{TN}{FP+TN} & NPV &= \frac{TN}{N} \end{aligned}$$

In this case, too, confidence intervals were necessary to reflect the statistical significance of each parameter. The standard approach would be to define an interval around the calculated parameter using a multiple of the standard error. This might however prove inaccurate in some cases with very small subsets. Altman et al. (2011) suggest another approach for calculations with small numbers and even zeros, which was used in this study to ensure valid results. The author's equations were adapted to calculate the 95% confidence interval:

$$\begin{aligned} A &= 2r + 1.96^2 & B &= 1.96 * \sqrt{1.96^2 + 4rq} & C &= 2(n + 1.96^2) \\ CI_l &= \frac{A-B}{C} & CI_u &= \frac{A+B}{C} \end{aligned}$$

In these equations, n is the sample size, r is the number of cases observed with the feature, p is the observed proportion of cases per sample size $p = r / n$ and $q = 1 - p$. This approach therefore utilizes the characteristic of SEN, SPE, PPV and NPV all being relative frequencies of different features. SEN for example describes the proportion of the feature of true positive predictions in the sample of all patients that got ill from irAEs. It follows that in this case $r = TP$, $n = I$ and $p = SEN$. All confidence intervals were calculated adapting this principle to the respective parameter.

3. Results

3.1. Patients / courses of therapy

This section will elaborate on the descriptive statistics of patients and their respective CoT analyzed in this study. It begins with the description of the characteristics of the sampling process. The treatment groups will then be described regarding gender, age, cycles of therapy received, duration of follow-up and experienced irAEs to give a distinctive overview on the population.

3.1.1. Sample

208 patients who received immunotherapy between 05/2011 and 05/2017 were assigned to the study. Following the method explained in section 2.1, 51 additional CoT could be harnessed where two different immunotherapies were conducted separately on the same patient. Furthermore, four patients received three therapies, thereby adding eight CoT, and two patients received the same therapy twice, but with ≥ 6 months of therapy-free period in-between. They were hence counted separately adding up to a total of 269 CoT, as can be reviewed in Figure 8.

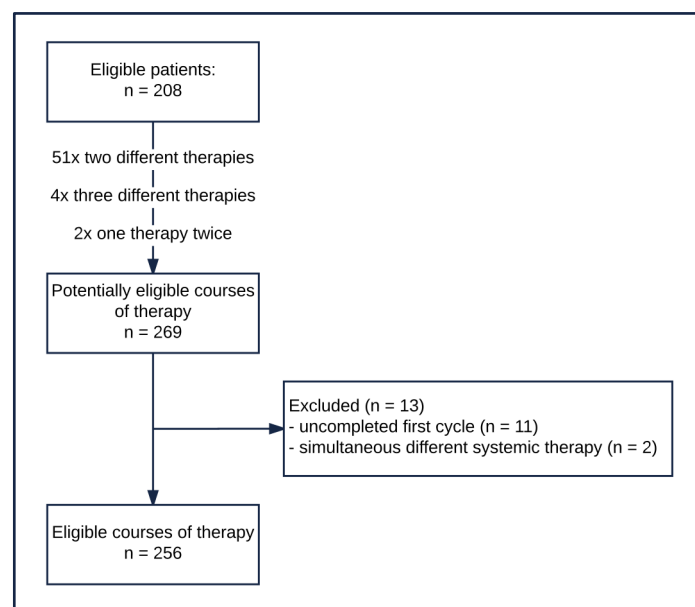


Figure 8: Process of sample inclusion

From this cohort, 11 CoT had to be excluded for an uncompleted first cycle of therapy not due to death or irAEs as well as two others because of simultaneous therapy with bevacizumab or vemurafenib, yielding a total of 195 patients with 256 CoT.

This total could be divided in 129 CoT (50%) with PD-1 antibodies, 108 CoT (42%) with the CTLA-4 antibody ipilimumab and 19 CoT (7%) with combination therapy. The PD-1 treatment group consisted of 95 treatments (37%) with pembrolizumab and 34 treatments (13%) with nivolumab.

3.1.2. Previous therapy

Of 256 CoT, 141 (55%) were preceded by any previous treatment, 115 (45%) were treatment naïve. Of the patients who were not treatment naïve 44 (17%) received more than one previous therapy, 39 (28%) had chemotherapy, 39 (28%) targeted therapy and 63 (45%) were administered another immunotherapy prior to their respective CoT. The mean timespan between previous therapy and the respective CoT was 18.6 weeks (median = 5.1) with a standard deviation (StD) of 43.4 weeks.

Concerning the PD-1 treatment group, other treatment was conducted prior to 65 CoT (50%), 64 (50%) began treatment naïve. There were multiple previous treatments conducted in 28 cases (22%), chemotherapy in 19 (15%), targeted therapy in 17 (13.2%) and another immunotherapy in 28 cases (22%). 23.9 weeks (median = 9.4) passed on average from the end of the last treatment to the beginning of the first cycle measured in this study. The StD was 38.1 weeks.

The CTLA-4 treatment group contained 63 CoT (58%) that were preceded by previous treatment and 45 (42%) that were not. These treatments were multiple in 11 cases (10%) and included chemotherapy 35 times (32%), targeted therapy 19 times (18%) and another immunotherapy eight times (7%). The mean period of time between the last treatment and the beginning of the respective CoT was 12.0 weeks (median = 4.7) with a StD of 43.5 weeks.

There were 19 patients who received combination therapy in this study, 13 of which (68%) received prior treatment and 6 (32%) were treatment naïve. Of these 13 patients, five (38%) had more than one preceding therapy, two (15%) had chemotherapy, seven (54%) received targeted and eight (62%) another immunotherapy. In this treatment group, the timespan between the previous and the treatment regarded in this study was 21.2 weeks (median = 2.9) with a StD of 63.7 weeks.

The distribution of CoT with no, one or more than one previous therapies can be reviewed in Figure 9. The timespan between the previous therapy and the respective CoT is illustrated in Figure 10.

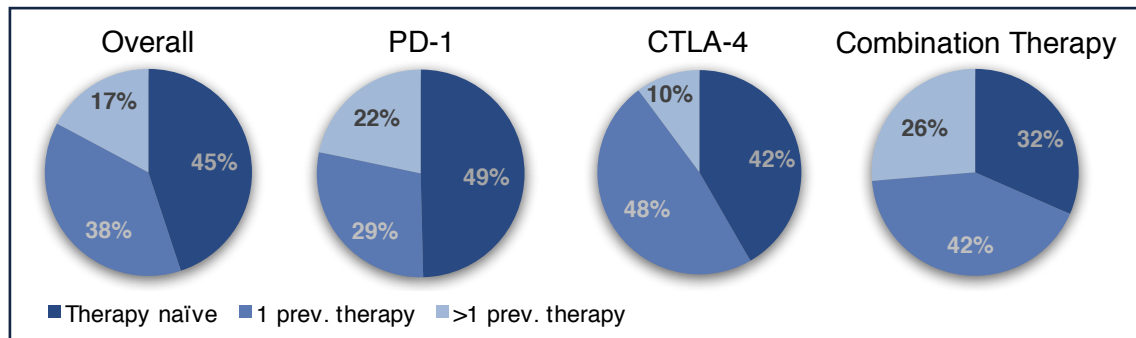


Figure 9: Therapy naïvety

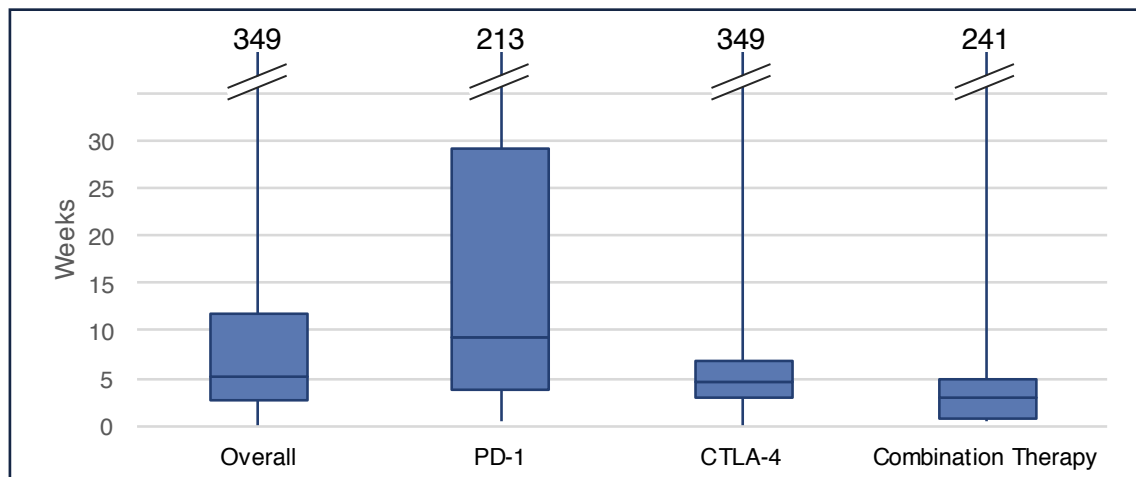


Figure 10: Time elapsed since last systemic treatment

3.1.3. Gender

Gender distribution was nearly equal in the overall population, with 133 (52%) CoT of male and 123 CoT (48%) of female patients.

This applies to the PD-1 treatment group as well, which consisted of 62 CoT (47%) of male and 67 CoT (52%) of female patients.

Slightly unequal was the distribution of gender in the CTLA-4 treatment group. It consisted of 62 CoT (57%) of male and 46 CoT (43%) of female patients.

The combination treatment group was also evenly distributed, with nine male (47%) and 10 female (53%) patients' CoT.

Generally, gender was evenly distributed over all treatment groups, with the moderate exception of the CTLA-4 treatment group, in which men were slightly overrepresented.

Gender distribution of the different subsets are illustrated in Figure 11.

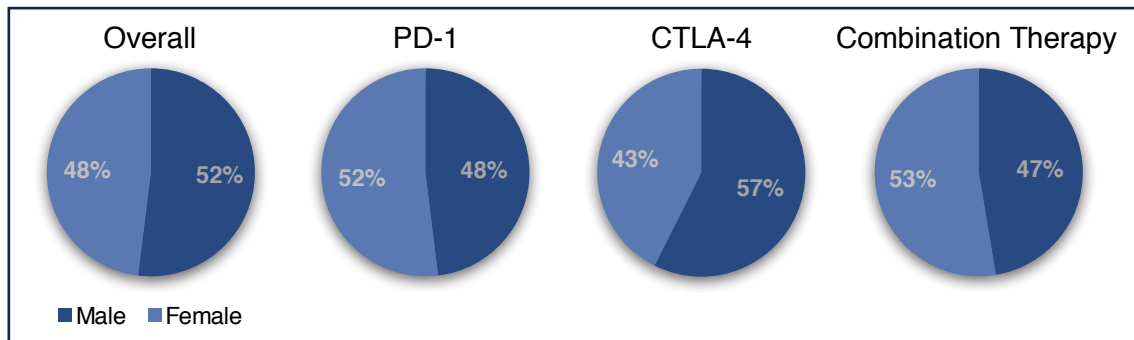


Figure 11: Gender distribution

3.1.4. Age

In the overall population, the mean age at the beginning of a CoT was 62.7 (median = 62). It ranged from 20 to 96 years with a StD of 14.3 years.

The mean age of the PD-1 treatment group was 64.0 (median = 62) with the youngest patient beginning the treatment at the age of 26 and the oldest at the age of 96. The StD was 13.8 years.

The CTLA-4 treatment group consisted of CoT starting at the mean age of 62.9 (median = 63.5) with a StD of 14.2 years. At the beginning of treatment, the youngest patient was 26 years old and the oldest 89.

The small group of CoT with ipilimumab and nivolumab combined started their treatment at the mean age of 52.7 years (median = 52). The age ranged from 20 to 67 with a StD from the mean of 14.2 years. See Figure 12 for a comparing illustration.

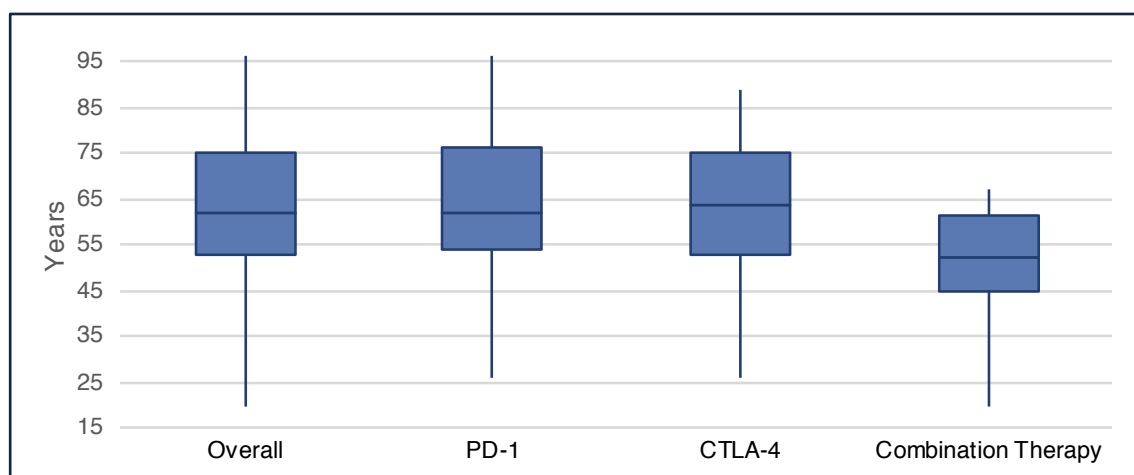


Figure 12: Age distribution

In general, age did not differ much across the overall, the PD-1 and the CTLA-4 treatment groups regarding their mean and quartile values. However, CoT in the combination therapy group started at younger age, which can be due to the small number of CoT meas-

ured. An alternative explanation might be that clinicians with the first few patients to receive combination therapy may tend to prefer younger, fitter patients for gaining therapy experience; they may also be assumed more resilient against the severe irAEs that must be expected in the CoT.

3.1.5. Cycles

For this study, 1,507 cycles of therapy were eligible, with parameters measured in each cycle as described in Section 2.2. In each treatment, a mean of 5.9 cycles (median = 4) were conducted in the overall population ranging from zero, meaning the patient died before the second cycle, to 45 cycles. StD was 6.6 cycles.

The PD-1 treatment group accounted for the majority of cycles with a count of 1,092 cycles (72%) and a mean of 8.5 cycles (median = 5) per treatment. It ranged from zero to 45 cycles with a StD of 8.4.

In the CTLA-4 treatment group, a total of 359 (24%) cycles of therapy were conducted, with a mean of 3.3 (median = 4) ranging from zero to four cycles per treatment. The StD was small with 0.9 cycles of therapy.

A total of 59 (4%) cycles of therapy were conducted in the combination therapy group. The mean value was 3.0 (median = 2), with a StD of 2.1 ranging from one to nine cycles. The distributions of cycles across the medication groups is illustrated in Figure 13, the distribution of cycles per treatment can be reviewed in Figure 14.

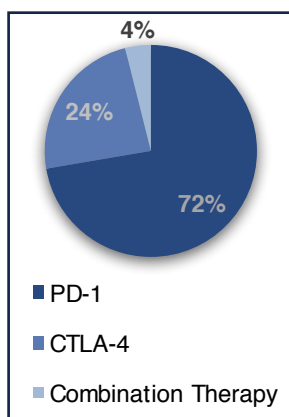


Figure 13: Distribution of cycles

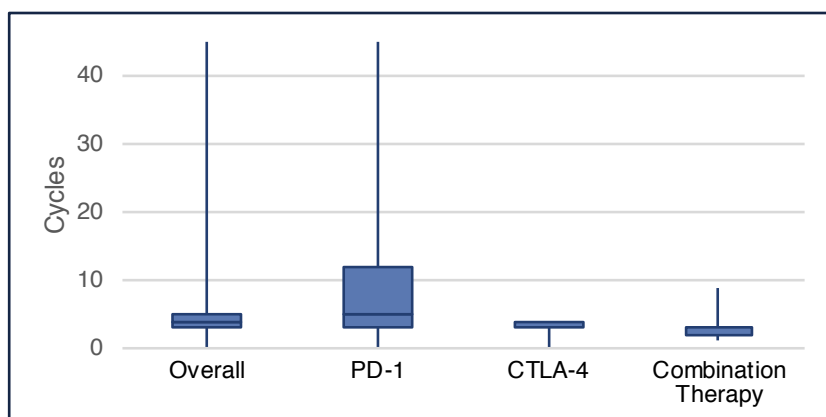


Figure 14: Cycles per treatment

3.1.6. Follow-up

The mean duration of one CoT was 18.1 weeks (median = 12.7). With a StD of 17.5 weeks, it varied strongly, ranging from zero, when patients died before an eligible second visit, to 110 weeks.

The mean duration of PD-1 treatment was 25 weeks (median = 15) with a StD of 22.0 weeks ranging from zero to 110. The CTLA-4 treatment group had a mean duration of 11.0 weeks (median = 12) per CoT and a StD of 3.6. It ranged from zero to 8 weeks again due to the therapeutic regime. Combination therapy lasted an average of 10 weeks (median = 7.1) with one week being the shortest and 36 weeks being the longest duration. The StD was 8.4 weeks.

The distribution of weeks of therapy over the different medication groups can be reviewed in Figure 15, the distribution of weeks per treatment is illustrated in Figure 16.

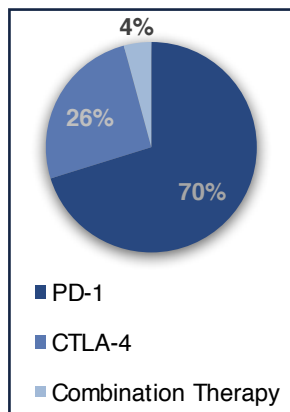


Figure 15: Distribution of weeks of therapy

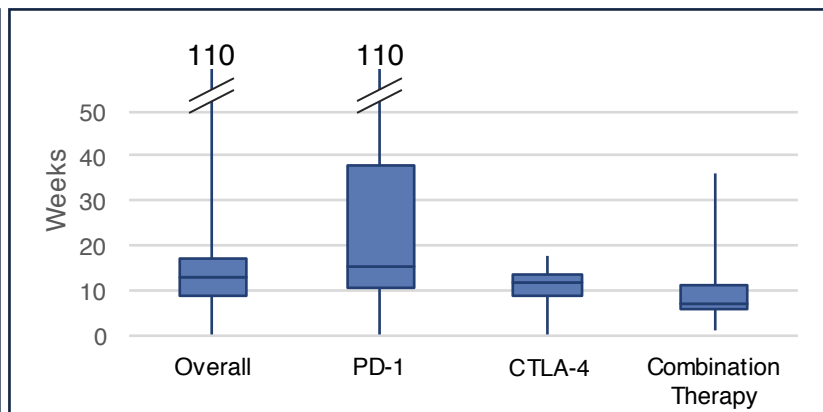


Figure 16: Weeks per treatment

As to be expected due to the shorter duration of a cycle of nivolumab therapy the overrepresentation of the PD-1 treatment group observed in the number of cycles slightly dropped to 70% of duration in total. However, looking at the 26% covered by the CTLA-4 treatment group it becomes clear that the body of measurement data is unevenly distributed despite the similar count of CoT. However, 359 measurements will still likely be sufficient for the analyses to be conducted.

This may not hold true for the much smaller combination therapy group, which is why the respective analyses' results should be interpreted with caution.

3.1.7. Laboratory parameters

Since the laboratory parameters regarded in this study are the main group of predictors to be quantitatively analyzed, they deserve special attention in form of preliminary description. Because of a total of 27 groups of categorical variables per treatment group resulting in a total of 108 laboratory parameters, it would extend the scope of this thesis to properly describe each individually. Additionally, a further filter will occur in the next step of analysis. At this point, the statistical description has to be limited to a superficial one.

Figure 17 on page 53 provides an overview on each laboratory dummy variable categorized as described in Section 2.2. It shows the distribution of the three possible parameter manifestations (True, False, NA).

Understandably, in many cases the higher the threshold value or interval the lower was the number of times it was met. An exception was the CRP. This is not much surprising as it often rose beyond the reference threshold value's triple, which was the highest general threshold condition posed in this study.

However, in some cases the condition was not met often or even once. Variables with few or no positives violate the distinctive purpose of the categorization and hence might compromise the regression analysis conducted in the next sections. The University of Zurich proposes a minimal size of 25 cases for each group created by a categorical variable (Universität Zürich 2016). This was not reached several times and must be considered when moving forward with the regressions by disregarding the respective variables.

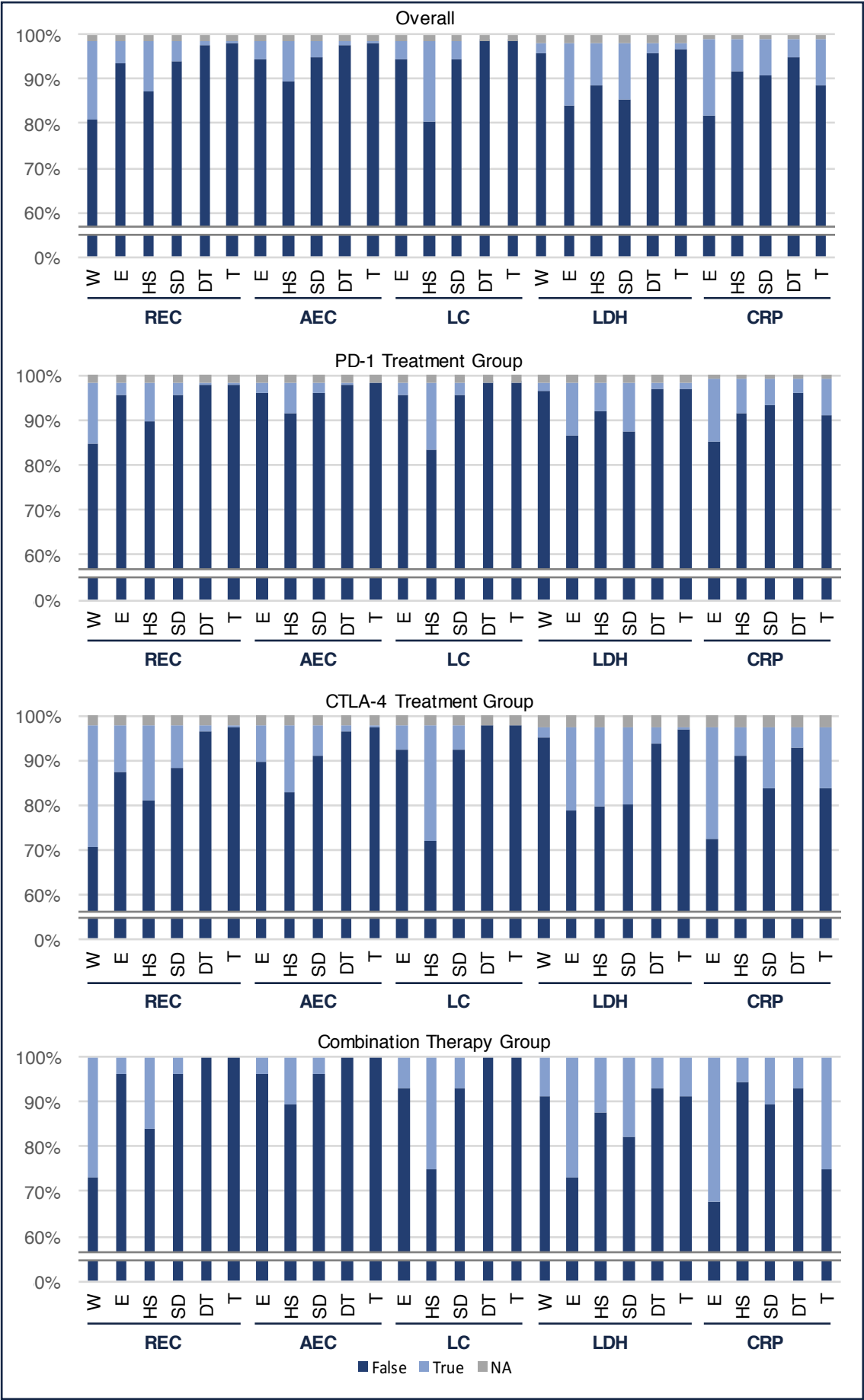


Figure 17: Laboratory parameters and their distribution of manifestations

3.1.8. Adverse events

A total of 282 irAEs were recorded in 160 CoT (63%). In 96 treatments (38%), no irAE occurred. With a mean of 1.1 irAEs per treatment (median = 1) and a StD of 1.2, the highest count in one treatment was eight irAEs. In 91 cases (32%) treatment with steroids was indicated, the highest grade reached was grade 1 in 125 (44%), grade 2 in 126 (45%) and grade 3 in 31 cases (11%). On average, the onset began at 3.8 cycles after the first dose (median = 2), with a StD of 5.3 reaching from cycle 1 to 41. Most frequent irAE was colitis (22%), followed by pruritus (21%) and fatigue (18%).

Concerning the PD-1 treatment group, 145 irAEs were counted in 72 CoT (56%), with patients experiencing none in 57 cases (44%). The average appearance was 1.1 per treatment (median = 1), with a StD of 1.4. There were up to eight irAEs counted in one CoT. Steroid intervention was required for 31 irAEs (21%), grade 1, as highest grade reached, occurred 76 times (52%), grade 2 occurred 58 times (40%) and grade 3 occurred 11 times (8%). The mean onset of irAEs was after 5.5 cycles of therapy (median = 3), with a StD of seven, reaching from cycle 1 to 41. Fatigue was the most common diagnosis for irAEs (23%), followed by pruritus (22%) and colitis (16%).

In the CTLA-4 treatment group, patients suffered from a total of 108 irAEs in 71 CoT (55%), 37 (29%) developed no irAEs. Mean and median was 1 irAE per treatment, with a maximum of 3 and a StD of 0.9. 46 times (43%) steroids were administered as a response to severe irAEs. The highest grade reached was grade 1 in 39 (26%), grade 2 in 58 (54%) and grade 3 in 11 cases (10%). On average, irAEs appeared after 2.1 cycles of therapy (median = 2), with a StD of 1 and reaching from cycle 1 to 4, the last cycle of a completed treatment with ipilimumab. Colitis occurred most frequently (31%), followed by dermatitis (25%) and pruritus (20%).

Patients of the combination therapy group experienced a total of 29 irAEs in 17 CoT (89%). Despite the short average duration of therapy in this treatment group, only 2 patients (11%) experienced no irAEs. The mean was 1.5 irAEs per treatment (median = 1), the StD was 0.9, with the highest count being 3 irAEs. Administration of steroids was necessary in 14 cases (48%), grade 1 was the highest grade reached in 10 cases (34%), another 10 times it was grade 2 (34%) and nine times grade 3 (31%). On average, the onset of irAEs occurred 1.7 cycles after therapy started (median = 2), with a StD of 0.8 and reaching up to 4 cycles after the first dose of therapy. Colitis was the most common irAE (21%), followed by fatigue (17%) and pruritus (14%).

In the following, Figure 18 illustrates the distribution of treatments with and without irAEs occurring, Figure 19 and Figure 20 give an overview on the distribution of irAE occurrence in the different medication subsets. Figure 21 visualizes the timing of irAE onsets.

The distribution of irAEs by means of their grades is demonstrated in Figure 22, whereas an illustration of the incidence of the most frequent irAEs can be reviewed in Figure 23.

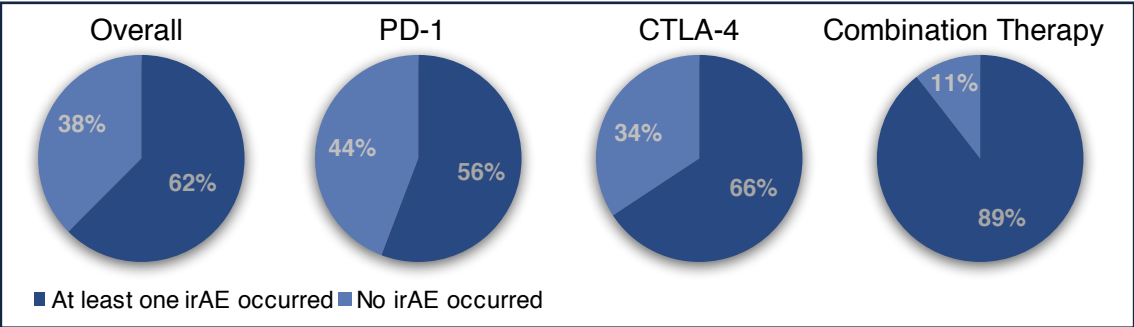


Figure 18: Distribution of treatments with and without irAEs

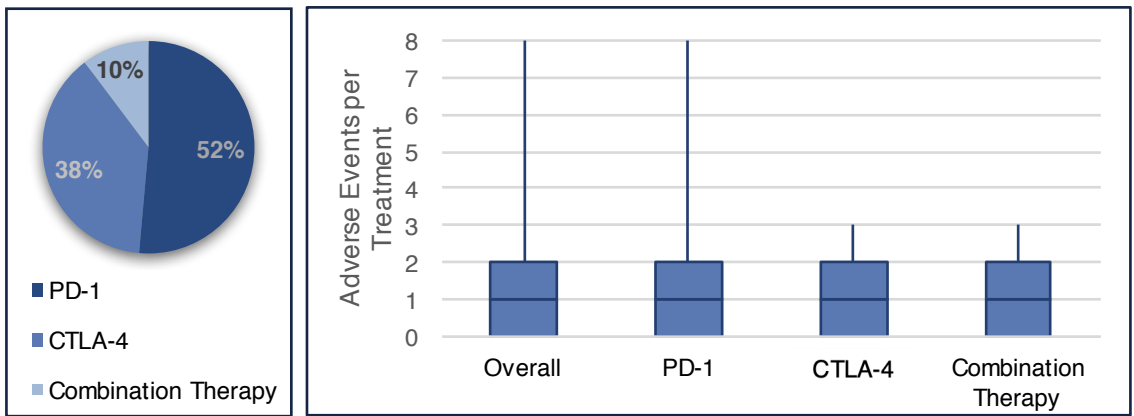


Figure 19: Distribution of irAEs

Figure 20: irAEs per treatment

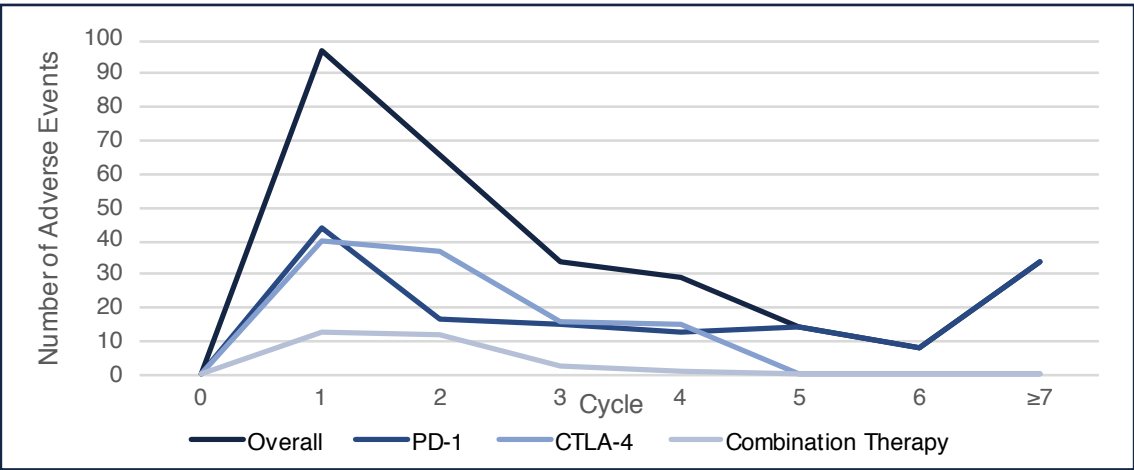


Figure 21: Onset of irAEs

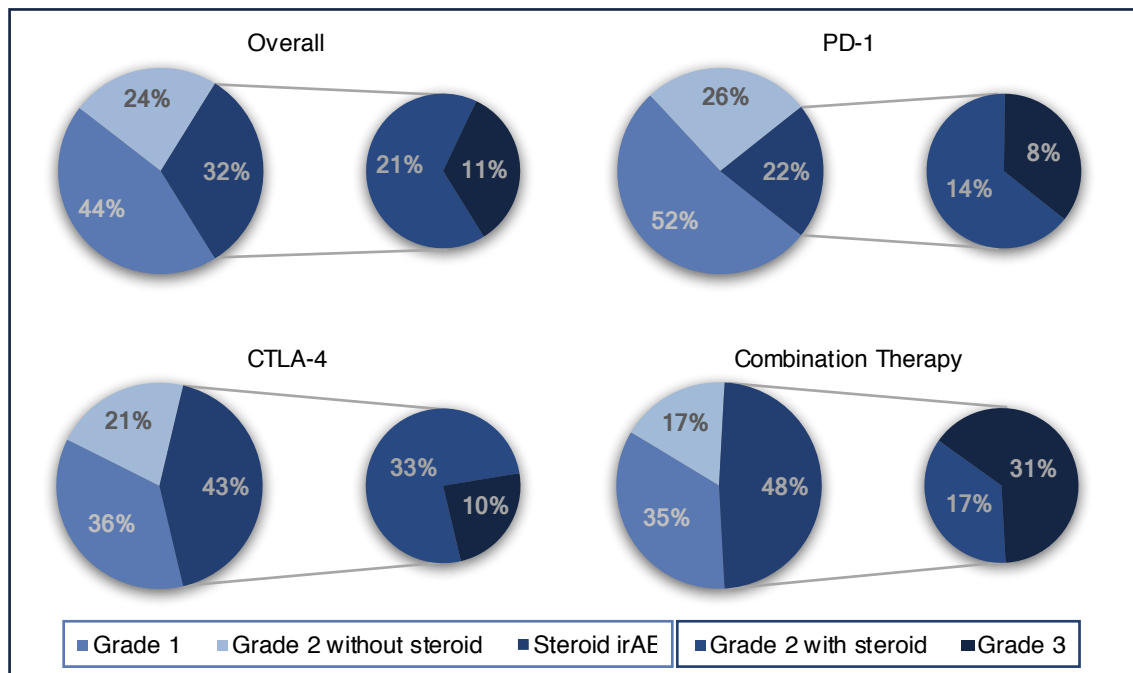


Figure 22: Distribution of irAE grades

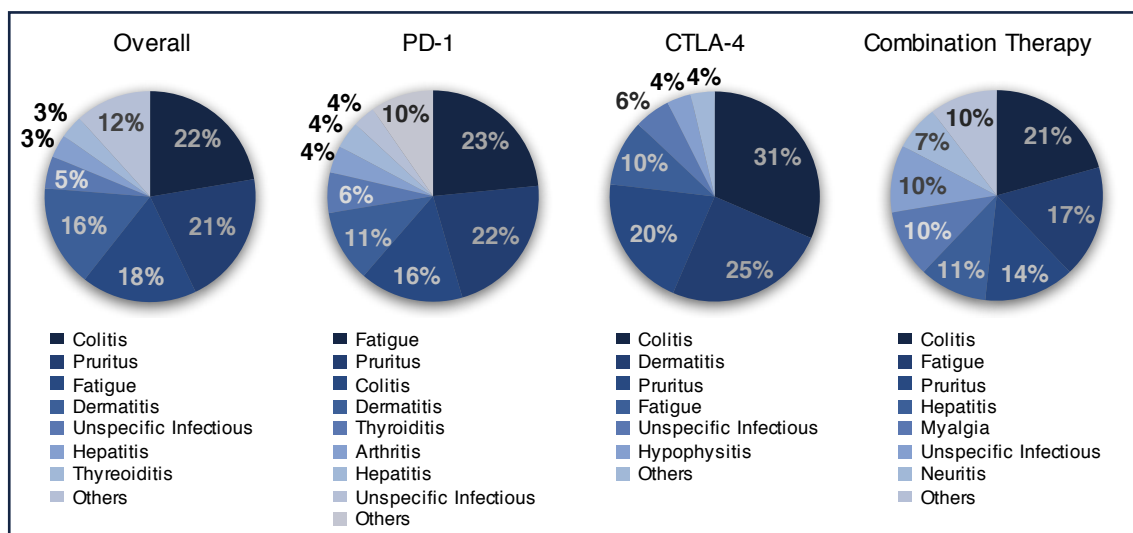


Figure 23: Types of adverse events

IrAE occurrence was similar over all treatment groups. They occurred more often than they did not and mostly early in therapy. Grades 1 and 2 were the most frequent. Concerning the type of irAE, colitis, fatigue and pruritus ranked among the top 3 in almost every subset.

The combination therapy, however, seems to be an exception in some respects: Although the average treatment duration of combination therapy was relatively short, the incidence of irAEs was even higher than monitored in the other groups and the distribution differed in favor of more severe grade 3 irAEs. This is not surprising, as it has been

shown that combination therapy induces better results but at the expense of higher rates of severe irAEs compared to monotherapy (Larkin et al. 2015).

3.2. Selection of laboratory parameters

As described in Section 2.3 a selection process was conducted to find the most suitable laboratory parameter of each of the three groups leucocyte (REC, AEC, LC), LDH and CRP. This was done six times to evaluate the best setup for every combination of treatment and baseline considerations, adding up to a total of 162 single regressions. This section will only document the relevant results. For the complete analysis including the R output, please refer to Appendix 1.

3.2.1. Subset: Including baseline

Using the whole dataset with no distinctive consideration of baseline data, several statistically significant results were obtained.

Looking for the best predictors of irAEs of any grade, the antecedents listed in Table 1 were selected³. All predictors were estimated to have a positive influence on the appearance of irAEs of any grade. The smallest group created by the categorical dummy variable of REC W consisted of 263 “True” entries. LDH HS had 142 “True” entries in the smallest group and CRP T 153. Following the protocol derived in Section 2.3.2, every primary choice was accepted.

Table 1: Chosen predictors (including baseline, any irAE)

Predictor	Estimate	p	OR
REC W	0.810	2.32 x10 ⁻⁶ ***	2.25
LDH HS	1.117	8.59 x10 ⁻⁸ ***	3.06
CRP T	0.626	0.004 **	1.87

Significance codes: *** p < 0.001 | ** p < 0.01 | * p < 0.05 | . p < 0.1

Analyzing the best predictors in the overall dataset for irAEs that required steroid intervention the predictors listed in Table 2 were selected. REC DT yielded the best results (Estimate = 1.58, p = 0.099) of the leucocyte group but had to be disregarded due to its smallest group consisting of only 10 entries. Instead, AEC HD was chosen, which had a smallest group size of 137. LDH E and CRP T had smallest group sizes of 212 and 153, respectively. Of the three groups of predictors, only CRP with its triple elevation threshold

³ Each row of all tables in this section contains the relevant regression results of a singular regression. The combined significance of the predictors chosen in this section is not reflected here and will be evaluated in Section 3.3.

showed a highly significant predictive value, tripling the odds of occurrence of irAEs with steroid intervention – different from the chosen predictors for irAEs of any grade, where all groups had at least one significant predictor.

Table 2: Chosen predictors (including baseline, steroid irAE)

Predictor	Estimate	p	OR
AEC HS	-0.643	0.202	2.25
LDH E	0.358	0.252	1.43
CRP T	1.169	1.00 x10 ⁻⁴ ***	3.22

Significance codes: *** p < 0.001 | ** p < 0.01 | * p < 0.05 | . p < 0.1

3.2.2. Subset: Baseline only

When exclusively considering laboratory anomalies measured at the beginning of the first cycle of therapy, much less significant results were noted.

Looking for predictors of irAEs of any grade, only REC HS showed statistical significance with the smallest categorical group size being 54, almost doubling the odds of irAE occurrence when “True”. LDH E had a sufficiently large smallest group size of 102 as the best representative laboratory anomaly of its group but did not reach statistical significance. CRP HS (smallest group size: 27) was not the best representative of its group and inferior to CRP DT, when considering statistical significance only. This anomaly, however, did not reach the required minimal group size of 25 and had to be disregarded. The final selection of predictors for this subset can be reviewed in Table 3.

Table 3: Chosen predictors (only baseline, any irAE)

Predictor	Estimate	p	OR
REC HS	0.690	0.030 *	1.99
LDH E	-0.410	0.149	0.66
CRP HS	-0.329	0.476	0.72

Significance codes: *** p < 0.001 | ** p < 0.01 | * p < 0.05 | . p < 0.1

The evaluation of predictors for irAEs with steroid intervention yielded no statistically significant antecedent. Only CRP T showed a statistical tendency toward doubling the odds of steroid irAE occurrence. Of the leucocyte group, three predictors prior to the final choice of REC W had to be disregarded due to smallest group sizes of only three “True” entries in AEC SD (Estimate = 2.95, p = 0.018), four in AEC E (Estimate = 2.25, p = 0.028) and seven in REC SD (Estimate = 1.32, p = 0.126). The smallest group size of REC W was 159, 142 of LDH HS and 59 of CRP T. The most suitable representative predictor of each group is listed in Table 4.

Table 4: Chosen predictors (only baseline, steroid irAE)

Predictor	Estimate	p	OR
REC W	-0.586	0.168	0.56
LDH HS	-0.511	0.220	0.66
CRP T	0.786	0.071 .	2.19

Significance codes: *** p < 0.001 | ** p < 0.01 | * p < 0.05 | . p < 0.1

3.2.3. Subset: Excluding baseline

This section is about the search of the best antecedents of irAEs after the start of therapy. Analyzing predictors of irAEs of any grade, cases in which the AEC E conditions were met (smallest group size: 56), showed a tendency of higher odds of irAE occurrence. Similar held true for the CRP group with its triple elevation threshold (smallest group size: 94). The representative variable of the LDH group, LDH SD (smallest group size: 107), did not yield such results. Concerning p, it was the third best predictor of the LDH group. Lower p values were attributed to LDH W (Estimate = -1.13, p = 0.28), with a smallest group size of 19, and to LDH T (Estimate = -0.94, p = 0.376), with a smallest group size of 16. See Table 5 for the final selection of predictors for main analysis of this subset.

Table 5: Chosen predictors (excluding baseline, any irAE)

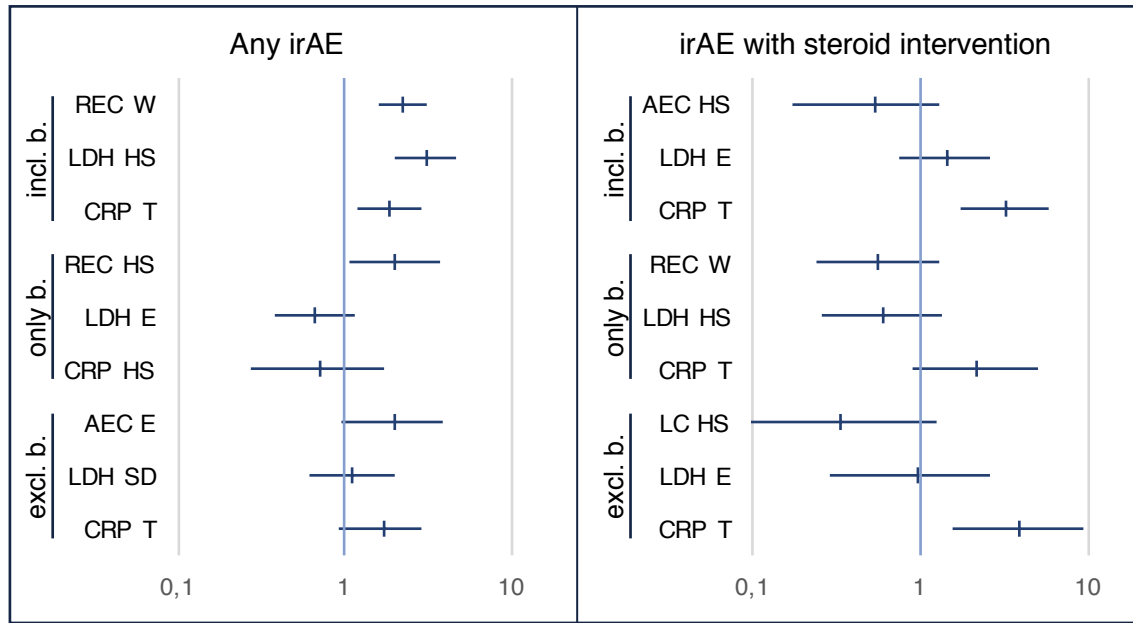
Predictor	Estimate	p	OR
AEC E	0.684	0.054 .	1.98
LDH SD	0.116	0.699	1.12
CRP T	0.525	0.070 .	1.69

Significance codes: *** p < 0.001 | ** p < 0.01 | * p < 0.05 | . p < 0.1

The predictors chosen for the model to predict steroid irAEs during therapy are listed in Table 6. Of these, only CRP T (smallest group size: 94) showed a high significance predicting this kind of irAEs with an OR of 3.8. REC DT also showed a statistical tendency (Estimate = 2.11, p = 0.061) but had to be disregarded due to its low smallest group size of nine “True” entries. Its successor LC HS had a smallest group size of 115. LDH E (smallest group size: 110) is a replacement as well, in this case for LDH DT, which had a smallest group with only 22 “True” entries. The ORs of every chosen predictor with its confidence interval are illustrated in Figure 24.

Table 6: Chosen predictors (excluding baseline, steroid irAE)

Predictor	Estimate	p	OR
LC HS	-1.123	0.167	0.33
LDH E	-0.037	0.946	0.96
CRP T	1.343	0.003 **	3.83

Significance codes: *** $p < 0.001$ | ** $p < 0.01$ | * $p < 0.05$ | . $p < 0.1$ Figure 24: ORs of all selected laboratory parameters
(incl. = including; excl. = excluding; b. = baseline)

3.3. Main results

In this section, the results of the final regressions building on the predictors age and gender as well as the ones selected in the previous section will be presented. For every laboratory anomaly reaching at least a significance level of $p < 0.1$, additional information on its diagnostic test properties will be provided. The reporting will be conducted by summarizing the results by their groups of the three baseline considerations. The results for the overall, PD-1 and CTLA-4 treatment group will be summarized separately. The combination therapy group will not be reported in detail; because of the low number of cases contained, it yielded results that reached no statistical significance in any subset. These could only be interpreted cautiously and in context of the results of the CTLA-4 and PD-1 groups since combination therapy is based on both therapies. This will be done in the Discussion in Section 4, where all five groups of predictors will be discussed across all subsets.

Each subsection will provide tables containing all relevant results of the regressions. At the end of this chapter, Figure 28 on page 70 will illustrate diagnostic test properties of all single antecedents with $p < 0.1$.

3.3.1. Assumption testing

The assumption of multicollinearity was checked for each of the six overall treatment groups by testing for VIF and the tolerance statistic ($= 1/\text{VIF}$). Myers (1990) suggests the VIF to be below 10, whereas according to Menard (1995) its reciprocal should be above 0.2. Both VIF and its reciprocal resulted in values around 1 in each subset, suggesting that the assumption has been met.

The whole R output of the regressions including the tests for multicollinearity and every calculated OR can be reviewed in Appendix 2.

As anticipated, some problems emerged with predictors preventing the model from converging, which consequently had to be eliminated. These problems will be discussed in the last section of this chapter.

3.3.2. Subset: Including baseline

The analysis of all data including baseline measurements yielded ten statistically significant results - the majority among the three baseline consideration subsets, which is possibly due to the larger number of cases. Table 7 and Table 8 contain the results of all regressions concerning this baseline-subset, whereas Figure 25 on page 64 illustrates the results' effect sizes.

Table 7: Results (including baseline, any irAE)

	Estimate	p	95% CI for odds ratio		
			Lower	OR	Upper
Overall					
Intercept	-2.04	< 0.001 ***			
LDH HS	0.87	< 0.001 ***	1.50	2.39	3.79
REC W	0.50	0.012 *	1.11	1.64	2.40
CRP T	0.68	0.002 **	1.27	1.97	3.01
Sex: Female	0.16	0.363	0.83	1.18	1.68
Age	-	-	-	-	-
Combination Therapy					
Intercept	-0.14	0.903			
LDH HS	1.19	0.212	0.52	3.27	24.99
REC W	-0.01	0.987	0.22	0.99	3.92
CRP T	0.96	0.150	0.69	2.62	10.16
Sex: Female	0.68	0.315	0.43	1.97	7.90
Age	-0.02	0.441	0.93	0.98	1.03
PD-1 Antibody Therapy					
Intercept	-2.87	< 0.001 ***			
LDH HS	1.01	0.003 **	1.40	2.75	5.36
REC W	0.64	0.021 *	1.09	1.89	3.22
CRP T	0.45	0.166	0.81	1.56	2.87
Sex: Female	0.00	0.988	0.62	1.00	1.60
Age	0.01	0.371	0.99	1.01	1.03
CTLA-4 Antibody Therapy					
Intercept	-1.90	0.002 **			
LDH HS	0.53	0.102	0.89	1.71	3.22
REC W	0.18	0.543	0.67	1.20	2.11
CRP T	0.51	0.130	0.85	1.67	3.20
Sex: Female	0.50	0.046 *	1.01	1.65	2.69
Age	0.01	0.472	0.99	1.01	1.02

Significance codes: *** p < 0.001 | ** p < 0.01 | * p < 0.05 | . p < 0.1

Table 8: Results (including baseline, steroid irAE)

	Estimate	p	95% CI for odds ratio		
			Lower	OR	Upper
Overall					
Intercept	-3.47	< 0.001 ***			
CRP T	1.24	< 0.001 ***	1.83	3.47	6.41
AEC HS	-0.62	0.224	0.18	0.54	1.33
LDH E	-0.02	0.945	0.48	0.98	1.86
Sex: Female	0.29	0.335	0.74	1.34	2.47
Age	-	-	-	-	-
Combination Therapy					
Intercept	-2.18	0.157			
CRP T	0.59	0.488	0.31	1.81	10.57
AEC HS	-0.29	0.816	0.03	0.75	6.87
LDH E	0.06	0.951	0.15	1.06	5.43
Sex: Female	-0.65	0.470	0.05	0.52	2.83
Age	0.02	0.510	0.96	1.02	1.10
PD-1 Antibody Therapy					
Intercept	-5.07	< 0.001 ***			
CRP T	1.88	< 0.001 ***	2.71	6.52	15.67
AEC HS	-0.91	0.384	0.05	0.40	3.10
LDH E	0.12	0.82	0.39	1.13	3.24
Sex: Female	0.14	0.734	0.52	1.15	2.55
Age	0.02	0.335	0.98	1.02	1.05
CTLA-4 Antibody Therapy					
Intercept	-3.42	< 0.001 ***			
CRP T	0.62	0.181	0.71	1.86	4.45
AEC HS	-0.76	0.227	0.11	0.47	1.39
LDH E	-0.40	0.419	0.23	0.67	1.67
Sex: Female	0.83	0.020 *	1.15	2.30	4.71
Age	0.02	0.243	0.99	1.02	1.04

Overall:

LDH HS, REC W and CRP T predicted higher incidence of any irAE occurrences. CRP T also predicted higher incidence of steroid irAE occurrence when considering no baseline-differentiation.

Including all treatment groups all three selected laboratory anomalies showed significant predictive value for irAEs of any grade. LDH HS highly significantly ($p < 0.001$) increased the odds of irAEs occurrence by 2.39. It detected 20.2% of all irAEs (SEN), with 34.5% of its predictions being correct (PPV). SPE was at 93.6%, the absence of irAEs in the next cycle was predicted correctly in 87.6% of cases (NPV).

CRP T almost doubled the odds highly significantly ($p = 0.002$), with a SEN of 16.4% and a PPV of 22.0%. Its SPE shows a coverage of 90.4% of all cycles without irAE onset, correctly predicting them in 86.7% of cases.

REC W significantly ($p = 0.012$) increased the odds by the 1.64-fold, covering 29.8% of all irAEs (SEN). 26.4% of its predictions correctly indicated an upcoming irAE (PPV), while it correctly predicted none in 87.8% of cases (NPV). SPE was at 85.8%.

If both anomalies REC W and CRP T occurred simultaneously, their OR would be at 3.23. They covered 4.5% of irAEs combined (SEN) and predicted an irAE occurrence correctly in 29.7% of cases (PPV). SPE was at 98.2%, while 86.3% of negative predictions were correct (NPV).

REC W and LDH HS combined reached an OR of 3.92 and a SEN of 15.5%. Positive predictions were true in 38.1% of cases, SPE was at 95.9% and NPV reached 87.5%.

Combining CRP T and LDH HS led to an OR of 4.71. When both anomalies occurred simultaneously, they covered 3.3% of irAEs (SEN) and predicted them correctly in 53.3% of cases (PPV). 99.5% of the cycles without irAE onset were correctly recognized (SPE); 86.3% of the negative predictions were true (NPV).

When all three antecedents were present, they reached a combined OR of 7.72 and correctly predicted irAEs in 66.7% of cases (PPV), thereby covering 2.5% of irAEs (SEN). SPE was at 99.8%, whereas negative predictions were true in 86.1% of cases (NPV). Gender had no significant influence on irAE occurrence and age had to be excluded from the model due to causing a convergence error (see Section 3.3.5).

To predict irAEs with steroid intervention, only one predictor showed significant influence on steroid irAE occurrence. CRP T significantly increased the odds of occurrence by the 3.5-fold, which is an increase of its predictive value in OR and significance ($p < 0.001$) compared to its predictive value for any irAEs. Its SEN increased as well, covering 26.9% of steroid irAE and correctly predicting them in 11.5% (PPV). SPE remained similar at 90.2%, while NPV increased by 10 percent points to 96.3%. All other predictors did not lead to significant results; again, age had to be left out due to convergence issues (see Section 3.3.5).

PD-1 treatment group

LDH HS and REC W predicted higher incidence of any irAE occurrences. CRP T predicted higher incidence of steroid irAE occurrence when considering no baseline-differentiation.

Two antecedents showed significant predictive values concerning the occurrence of any irAEs in the PD-1 treatment group. The OR of LDH HS ($p = 0.003$) was calculated to be 2.75, covering 17.3% of occurred irAEs. 30.6% of the positive predictions were correct (PPV), reaching a SPE of 95.3%. Negative predictions were made correctly in 90.6% of cases.

REC W ($p = 0.021$) showed an OR of 1.89 in this subset. SEN was at 27.3% and PPV at 21.9%. In 91.0%, cycles with no irAE onset were correctly predicted (NPV), covering 88.2% of cycles without an onset (SPE).

If both laboratory anomalies occurred simultaneously, the OR would be 5.20. They would cover 13.6% of irAEs combined, correctly predicting them in 32.7% of cases. Negative predictions were true in 90.5% of cases (NPV), SPE was at 96.7%.

All other predictors, including CRP T, had no significant influence on the occurrence of irAE of any grade.

When predicting steroid irAEs, however, CRP T was the only antecedent to reach statistical significance ($p < 0.001$). It was calculated to increase the odds of an upcoming irAE that ultimately needed steroid intervention by the 6.5-fold in this subset, correctly predicting them in 8.9% of cases (PPV) and covering 33.3% of steroid irAEs (SEN). Of the cycles that contained no steroid irAE onset, 92.2% were covered (SPE) and correctly predicted in 98.4% of cases (NPV).

All other antecedents of this model showed no significant predictive value for steroid irAE occurrence.

CTLA-4 treatment group

Female gender predicted higher incidence of any and steroid irAE occurrences when considering no baseline-differentiation.

The only significant predictor in both analyses of predictors of irAEs of any grade as well as those with required steroid intervention was gender. Female patients had significantly higher odds to develop irAEs of any grade ($p = 0.046$, OR = 1.65) and even more so concerning irAEs with necessary steroid intervention ($p = 0.020$, OR = 2.3). Other than that, no significant antecedents were found. LDH HS ($p = 0.102$) was on the margin of a statistical tendency ($p < 0.1$) to increase the probability of any irAEs to occur.

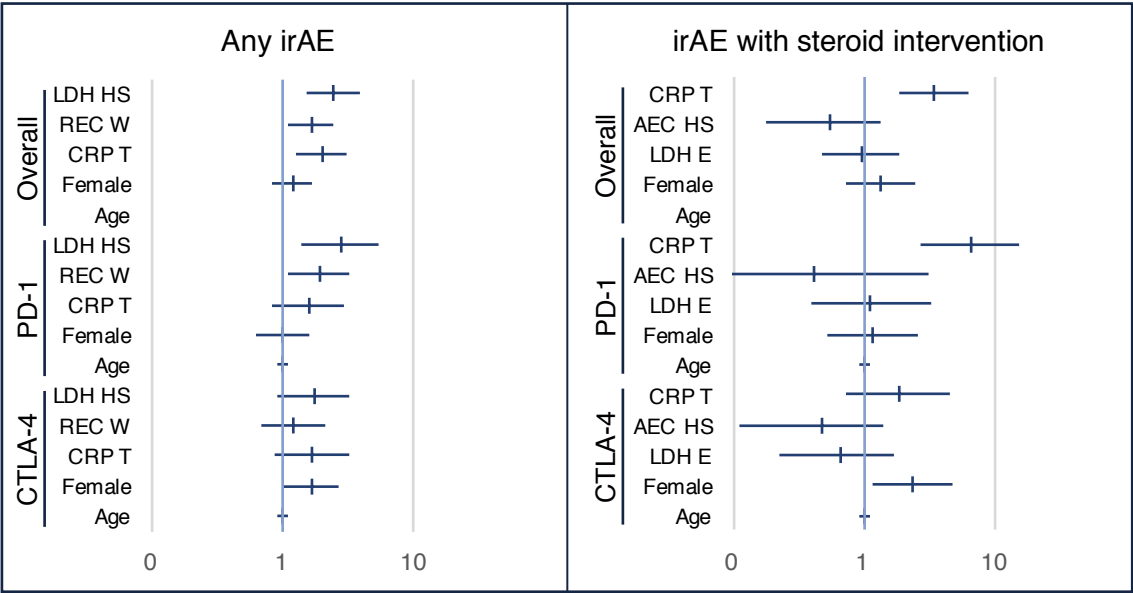


Figure 25: Odds ratios of predictors (Subset: Including baseline)

3.3.3. Subset: Baseline only

Analyzing the predictive value of laboratory measurements exclusively at baseline yielded only few results worth mentioning, with only one reaching statistical significance. Table 9 and Table 10 show the results of the main regressions of this subset. Figure 26 on page 66 illustrates their ORs as a measure of effect size.

Table 9: Results (only baseline, any irAE)

	Estimate	p	95% CI for odds ratio		
			Lower	OR	Upper
Overall					
Intercept	-0.34	0.614			
REC HS	0.62	0.064 .	0.96	1.86	3.59
LDH E	-0.38	0.208	0.38	0.68	1.23
CRP HS	-0.64	0.201	0.38	0.68	1.23
Sex: Female	0.40	0.166	0.85	1.48	2.61
Age	-0.01	0.385	0.97	0.99	1.01
Combination Therapy					
Intercept	1.55	0.434			
REC HS	-0.27	0.863	0.04	7.66	15.90
LDH E	0.37	0.742	0.16	1.44	12.88
CRP HS	17.47	0.994	0.00	> 100	> 100
Sex: Female	0.73	0.515	0.23	2.07	18.55
Age	-0.04	0.351	0.89	0.96	1.04
PD-1 Antibody Therapy					
Intercept	-2.24	0.048 *			
REC HS	0.70	0.137	0.79	2.02	5.07
LDH E	-1.05	0.034 *	0.13	0.35	0.90
CRP HS	-0.29	0.651	0.19	0.75	2.49
Sex: Female	-0.06	0.885	0.39	0.94	2.24
Age	0.02	0.178	0.99	1.02	1.06
CTLA-4 Antibody Therapy					
Intercept	0.22	0.848			
REC HS	0.71	0.198	0.69	2.02	5.98
LDH HS	-0.27	0.575	0.29	0.76	1.94
CRP HS	-1.55	0.167	0.01	0.21	1.36
Sex: Female	0.75	0.096 .	0.88	2.13	5.26
Age	-0.02	0.244	0.95	0.98	1.01

Table 10: Results (only baseline, steroid irAE)

	Estimate	p	95% CI for odds ratio		
			Lower	OR	Upper
Overall					
Intercept	-1.86	0.109			
CRP T	0.82	0.101	0.84	2.27	6.02
REC W	-0.50	0.267	0.25	0.61	1.48
LDH HS	-0.06	0.905	0.37	0.94	2.49
Sex: Female	0.15	0.729	0.49	1.17	2.81
Age	-0.01	0.721	0.96	0.99	1.03
Combination Therapy					
Intercept	-231.60	0.999			
CRP T	143.38	0.999	0.00	> 100	> 100
REC W	-66.30	0.999	0.00	0.00	> 100
LDH HS	-72.87	1.000	0.00	> 100	> 100
Sex: Female	-126.32	0.999	0.00	0.00	> 100
Age	3.40	0.999	0.00	29.90	> 100
PD-1 Antibody Therapy					
Intercept	-2.67	0.202			
CRP T	0.39	0.639	0.25	1.48	7.40
REC W	0.00	0.997	0.23	1.00	5.30
LDH HS	-0.40	0.608	0.14	0.67	3.12
Sex: Female	-0.22	0.755	0.18	0.80	3.29
Age	0.01	0.845	0.95	1.01	1.06
CTLA-4 Antibody Therapy					
Intercept	-2.47	0.162			
CRP T	1.21	0.120	0.69	3.36	15.66
REC W	-0.46	0.503	0.16	0.63	2.48
LDH HS	0.41	0.581	0.37	1.51	7.31
Sex: Female	1.28	0.087	0.90	3.59	18.29
Age	-0.01	0.667	0.94	0.99	1.04

Significance codes: *** p < 0.001 | ** p < 0.01 | * p < 0.05 | . p < 0.1

Overall

At baseline, REC HS showed a trend to predict a higher incidence of any irAE occurrence.

The highest level of significance in the group including all therapies was reached by REC HS (p = 0.064) in terms of a tendency to indicate a probability increase of an irAE onset of any grade with an of OR 1.86. SEN reached was at 30.4%, PPV was 44.4%. Negative predictions were true in 71.5% of cases, covering 82.1% of cycles without irAE onset. In the model to predict steroid irAEs, only CRP T (p = 0.101) came close to a statistical tendency. All other predictors of both any and steroid irAEs showed no noteworthy predictive power.

PD-1 treatment group

At baseline, LDH E predicted lower incidence of any irAE occurrence.

In the PD-1 treatment group, only the LDH elevation above 250 U/l showed a significant predictive value for irAEs of any grade not to occur (p = 0.034). It is the only significant

predictor in the subset only baseline, and one of only two antecedents predicting a lower probability of irAE occurrence in the whole analysis. Its OR was calculated to be at 0.35, correctly predicting the absence of irAE in 83.0% of cases (PPV), thereby covering 46.8% of all cycles without irAE onset (SEN). In 32.4% of cases when the anomaly was not present, the irAE occurred (NPV), covering 72.7% of irAE (SPE). Other than that, no tendentious or significant predictive values were found in this treatment group.

CTLA-4 treatment group

At baseline, female gender tendentially showed a trend to predict a higher incidence of any and steroid irAE occurrence.

The results yielded in this baseline subset were similar to the ones of the overall subset: The highest predictive value was expressed as a tendency of the female gender to increase the occurrence of irAEs of any grade ($p = 0.096$, $OR = 2.13$). Even more so concerning steroid irAEs ($p = 0.087$, $OR = 3.59$). Besides this, no antecedent showed significant predictive value.

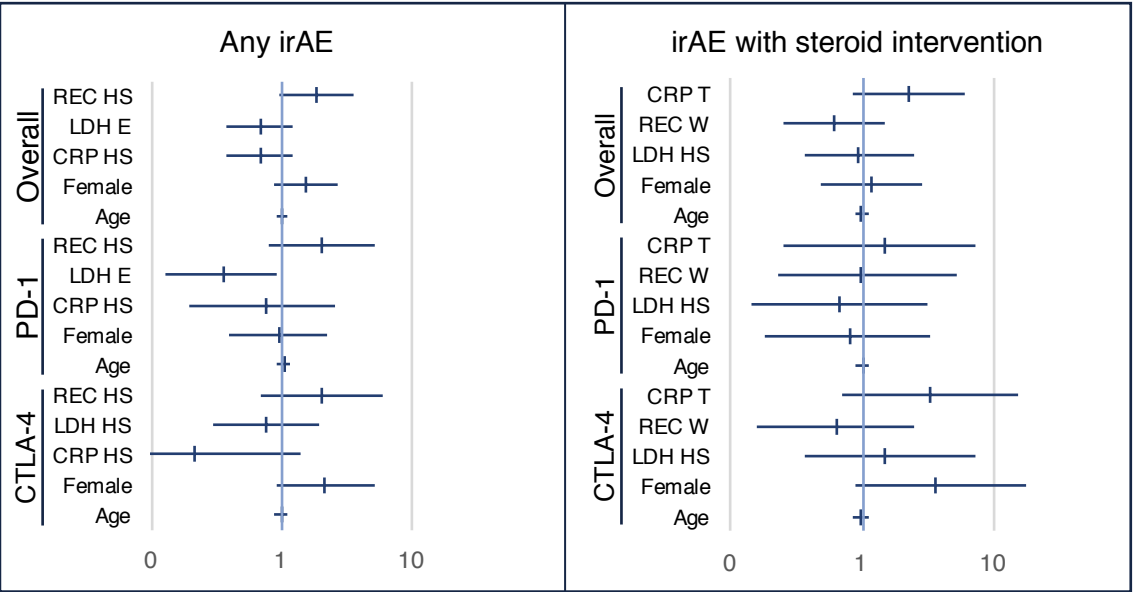


Figure 26: Odds ratios of predictors (Subset: Only baseline)

3.3.4. Subset: Excluding baseline

Compared to the subset that exclusively analyzed baseline parameters, the excluding baseline subset yielded more significant results but also convergence issues in three regression models.

Table 11 and Table 12 summarize the results of the regressions conducted. Figure 27 illustrates the respective ORs.

Table 11: Results (excluding baseline, any irAE)

95% CI for odds ratio					
	Estimate	p	Lower	OR	Upper
Overall					
Intercept	-2.03	< 0.001 ***			
CRP T	0.55	0.058 .	0.96	1.73	3.01
AEC E	0.76	0.032 *	1.03	2.13	4.18
LDH SD	0.09	0.759	0.59	1.10	1.93
Sex: Female	0.08	0.709	0.72	1.08	1.63
Age	-	-	-	-	-
Combination Therapy					
Intercept	1.04	0.655			
CRP T	-0.34	0.786	0.03	0.71	7.92
AEC E	-	-	-	-	-
LDH SD	-0.31	0.843	0.02	0.74	13.68
Sex: Female	0.90	0.447	0.13	2.45	83.02
Age	-0.04	0.412	0.82	0.96	1.06
PD-1 Antibody Therapy					
Intercept	-2.72	< 0.001 ***			
CRP T	0.38	0.355	0.66	1.46	3.24
AEC E	1.25	0.015 *	1.28	3.50	9.61
LDH SD	0.25	0.515	0.61	1.28	2.71
Sex: Female	0.02	0.926	0.63	1.02	1.66
Age	0.01	0.550	0.99	1.01	1.02
CTLA-4 Antibody Therapy					
Intercept	-2.45	0.001 **			
CRP T	0.47	0.293	0.64	1.60	3.80
AEC E	0.12	0.803	0.41	1.12	2.71
LDH SD	-0.30	0.551	0.25	0.74	1.88
Sex: Female	0.38	0.215	0.80	1.46	2.69
Age	0.02	0.133	1.00	1.02	1.04

Table 12: Results (excluding baseline, steroid irAE)

	Estimate	p	95% CI for odds ratio		
			Lower	OR	Upper
Overall					
Intercept	-4.34	< 0.001 ***			
CRP T	1.52	0.002 **	1.78	4.58	11.77
LC HS	-1.55	0.088 .	0.04	0.21	1.26
LDH E	-0.22	0.698	0.26	0.80	2.48
Sex: Female	0.44	0.328	0.64	1.56	3.79
Age	0.00	0.962	0.97	1.00	1.03
Combination Therapy					
Intercept	-0.96	0.753			
CRP T	-0.02	0.994	0.02	0.98	48.44
LC HS	-1.79	0.453	0.00	0.17	17.79
LDH E	0.96	0.621	0.06	2.62	118.81
Sex: Female	0.19	0.913	0.04	1.21	37.55
Age	0.00	0.947	0.88	1.00	1.13
PD-1 Antibody Therapy					
Intercept	-5.71	< 0.001 ***			
CRP T	2.20	< 0.001 ***	2.99	9.04	23.36
LC HS	-	-	-	-	-
LDH E	0.20	0.794	0.18	1.23	4.67
Sex: Female	0.40	0.788	0.56	1.49	5.33
Age	0.02	0.396	0.98	1.02	1.06
CTLA-4 Antibody Therapy					
Intercept	-3.90	< 0.001 ***			
CRP T	0.40	0.504	0.40	1.50	4.53
LC HS	-0.97	0.363	0.02	0.38	2.06
LDH E	-0.84	0.286	0.06	0.43	1.65
Sex: Female	0.73	0.082 .	0.92	2.08	4.82
Age	0.02	0.131	0.99	1.02	1.06

Significance codes: *** p < 0.001 | ** p < 0.01 | * p < 0.05 | . p < 0.1

Overall

During therapy, AEC E predicted higher incidence of any irAE occurrence. CRP T especially predicted higher incidence of steroid irAE occurrence during therapy. LC HS showed a trend to predict lower steroid irAE occurrence.

Similar to the subset including baseline, CRP T proved predictive value. For irAE of any grade, significance was of a statistical tendency ($p = 0.058$, OR = 1.73) to increase the odds of occurrence. SEN was at 11.5%, SPE was at 92.2%. Positive predictions were true in 15.7% of cases (PPV) and negative ones were true in 89.2% (NPV).

Effect size and level of significance for the same anomaly were higher for irAE with steroid intervention ($p = 0.002$, OR 4.58). It covered 21.2% of steroid irAEs (SEN), correctly predicting them in 9.1% of cases (PPV). 97.0% of negative predictions were true (NPV), covering 92.2% of cycles without steroid irAEs (SPE).

Additionally, for both irAE types the leucocyte group proved valuable, in this case rather to predict any grade irAE than those with required steroid intervention. AEC E ($p = 0.032$) more than doubled the odds of any irAE occurrence, predicting 7.8% of irAEs (SEN) in predictions that were correct in 20.6% of cases (PPV). NPV was at 88.9% and covered 96.1% of cycles without steroid irAEs (SPE).

LC HS, on the other hand, showed more of a tendency ($p = 0.088$) to lower the odds of new steroid irAE occurrence to a fifth. When this laboratory anomaly was present, it was followed by steroid irAEs in 9.9% of cases (PPV), covering 9.3% of them (SEN). NPV was at 37.8%, SPE was at 96.2%.

When occurring simultaneously, the laboratory anomalies CRP T and AEC E reached an OR of 3.68 to predict the onset of any irAE, theoretically. In this subset, however, the simultaneous presence of both anomalies occurred rarely and did not lead to no true positive prediction, making the diagnostic test statistics uninterpretable.

When CRP T and the absence of LC HS occurred simultaneously, their OR reached 21.8⁴. They covered 19.2% of steroid irAEs, predicting them correctly in 9.9% of cases. SPE was at 93.6% and negative predictions were true in 97.0%.

Besides that, no significant predictive value could be determined. The predictor age caused a convergence error in the model for any irAEs (see Section 3.3.5).

PD-1 treatment group

During therapy, AEC E predicted higher incidence of any irAE occurrence. CRP T predicted higher incidence of steroid irAE occurrence.

In this treatment group, there is again some difference between the model predicting any irAE and the one predicting steroid irAE. Although CRP T is the only and highly significant predictor, which increases steroid irAE occurrence by a nine-fold ($p < 0.001$, SEN = 35.3%, SPE = 93.9%, PPV = 8.5%, NPV = 98.9%), it seems to play no relevant role when predicting irAEs of any grade. Here, only AEC E proved statistical significance by raising the odds of occurrence by a 3.5-fold ($p = 0.015$), thereby covering 6.3% of irAEs (SEN), being predicted correctly in 22.2% of cases (PPV). Its predictions covered 97.8% of cycles without irAE onset (SPE), correctly predicting them in 91.4% of cases (NPV). LC HS caused a convergence error in the model for steroid irAEs (see Section 3.3.5).

⁴ The OR of the absence of LC HS was calculated as $\frac{1}{OR}$ because of the negative estimate.

CTLA-4 treatment group

During therapy, female gender showed a trend to predict higher incidence of steroid irAE occurrence.

Regression analysis yielded no significant results in this treatment group. Only a tendency of female gender to positively influence the odds of occurrence of steroid irAEs could be shown (p = 0.082).

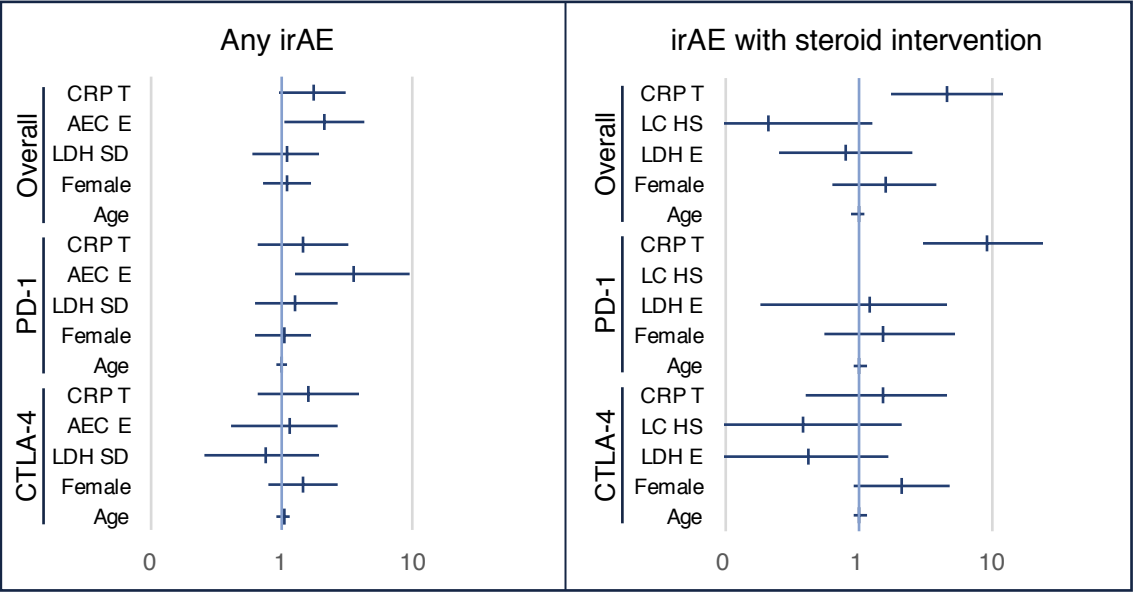


Figure 27: Odds ratios of predictors (Subset: Excluding baseline)

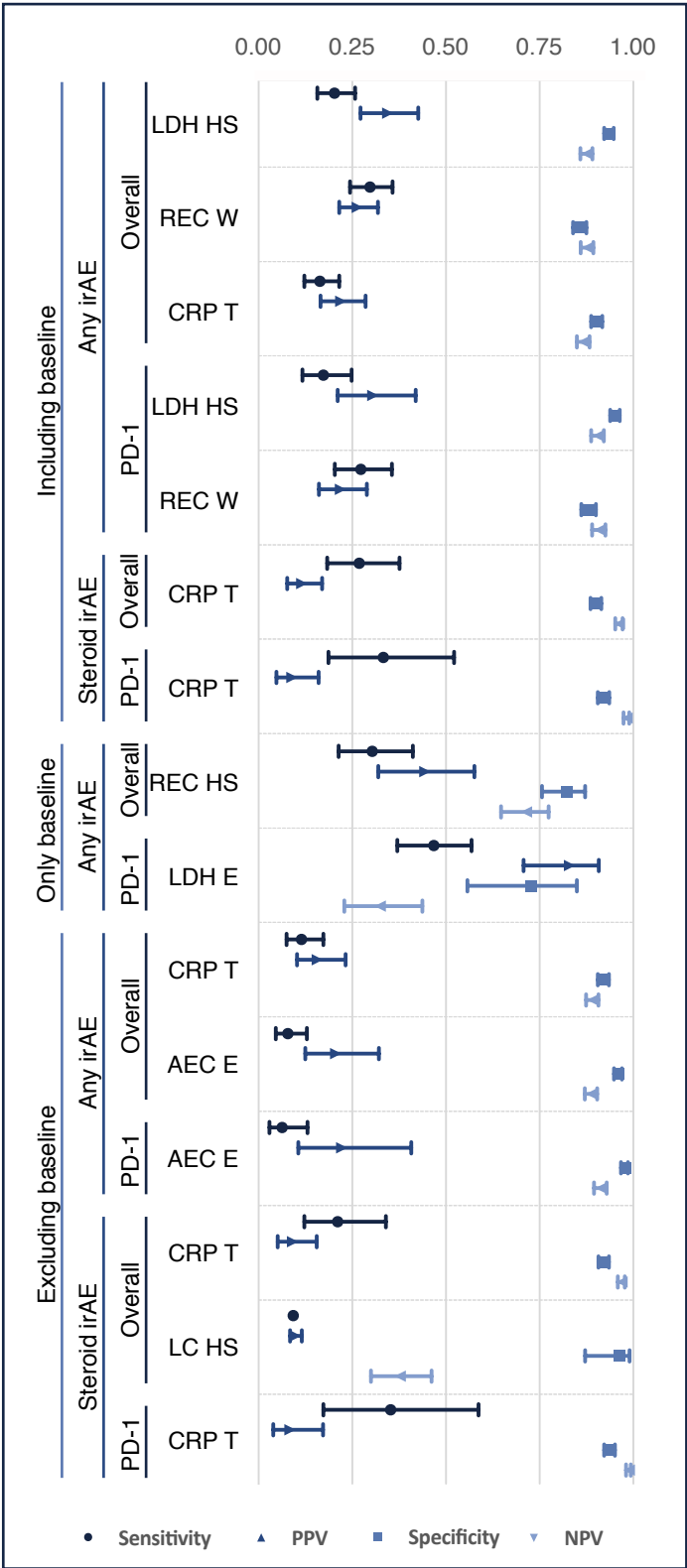


Figure 28: Diagnostic test properties⁵

⁵ All listed predictors had at least a statistical tendency towards predicting irAE in the respective regression models. All but two predicted higher probability of occurrence. LDH E (only baseline subset to predict any irAE occurrence in the PD-1 treatment group) and LC HS (excluding baseline subset to predict steroid irAE occurrence in the overall treatment group) predicted a lower probability of irAE occurrence.

3.3.5. Convergence issues

As discussed in Section 2.3.3, convergence errors can become an issue when working with a set of predictors with previously unknown association to the dependent variable. In such cases, it was decided to identify and exclude the predictor responsible for the error. This was done five times in total.

The demographic variable age was responsible for convergence errors in the regressions of the following three subsets:

- Including baseline and all treatment groups to predict any irAEs,
- Including baseline and all treatment groups to predict steroid irAEs,
- Excluding baseline but including all treatment groups to predict any irAEs.

It is noteworthy that in every other regression age achieved ORs close to 1, reflecting a low or non-existent predictive value. This low predictive value has probably disturbed the model building too much and had therefore to be removed.

Two other variables caused convergence errors and had to be removed from their models:

- AEC E in the subset that excluded baseline and analyzed only the combination therapy group to predict any irAEs,
- LC HS in the subset that excluded baseline and analyzed only the PD-1 treatment group to predict steroid irAEs.

The removal of AEC E was probably necessary due to the relatively low number of cases in the combination therapy group, which made the model more vulnerable to convergence errors. LC HS, however, prevented convergence despite a large subset. The most likely explanation for the convergence error might therefore be the bad predictive performance of this predictor in this particular subset, similar to the issues experienced with the variable age.

3.4. Post-hoc analyses

Because of the many laboratory anomalies to be tested as antecedents for irAEs, only the best of each group was included in the final regression models. It follows that not all anomalies that were significant in one subset would be included in a model in another subset. However, for interpretability it might be interesting to know how certain anomalies would have performed under different circumstances. Therefore, two additional post-hoc tests were conducted in this study.

LDH HS was not analyzed with baseline excluded despite significantly ($p = 0.003$) predicting any irAEs in the PD-1 treatment group when including baseline. This additional combination was analyzed post-hoc. The same was done with LDH E, which in the only baseline subset was a significant ($p = 0.034$) marker for a lower irAE onset probability. In both cases, regression yielded no significant results. Even when excluding age and gender, which previously led to convergence issues, the inclusion of both LDH HS and E led to convergence errors in the new model. Their significant predictive values may not be applied to the excluding baseline subset subsequently. For the full R output, please refer to Appendix 3.

4. Discussion

In this section, the focus is on recognition of possible limitations for the interpretability of these results. They will in sequence be applied to all subsets in order to create a summary of the conclusions that may be drawn from this study. Finally, future perspectives for further research will be suggested.

4.1. Limitations

There are some limitations that must be considered when interpreting the results of this study. These limitations will be reported in this section.

4.1.1. *Sample*

This study compares four of the most common groups of immunotherapies. Their differences, however, were not only in the antibodies applied but also in different application modalities as described earlier. This led to every patient with ipilimumab treatment being represented by a maximum of four measurements, so late onset irAEs could not be covered. This has to be considered when comparing therapy regimens where there was no general limitation concerning the number of measurements.

A different issue is to be considered concerning the different anti-PD-1 agents nivolumab and pembrolizumab, the cycles of which differ in their duration as stated earlier. Although this might inflict comparability within a unified treatment group, in this dataset patients developed irAEs usually a few days after an infusion of immunotherapy. Therefore, this difference was regarded as tolerable.

Combination therapy as the newest therapy regime of the four immunotherapies investigated was represented in this study by 19 patients with a total of 59 cycles of therapy. They reflected 4% of the investigated cycles in this study. Although this included all cycles of combination therapy that were ever administered at the University Hospital in Cologne until the end of data collection, this number of measurements was too small to yield definitive results, especially for a multilevel regression. Since recent information on this new and uprising therapy with its high potential for irAE is highly appreciated, data were included disregarding the low number of cases. Caution should be applied when using the associated statistical analyses.

4.1.2. Adverse events

AEs were recorded retrospectively by reviewing documented doctor-patient conversations. IrAEs would be recognized when noted by the attending physician. This probably worked more accurately with higher grade irAEs. Low grade irAEs have a tendency to become less frequently noted, in particular if patients show a higher than normal degree of indolence, which may vary widely. Consequently, analyses of low grade irAE may be inaccurate because of their actual incidence probably being higher.

Additionally, not all kinds of irAEs are easy to detect even if asked for and sometimes may have other causes but immunotherapy. This holds true for AEs such as fatigue, a very common mostly grade 1 irAE, which can be due not only to immunotherapy but for example to cancer in general (Hofman et al. 2007).

All this holds especially true for low grade irAEs. Because of their treatment relevance, severe irAEs were screened more thoroughly. Therefore, especially high grade irAEs, which were focused on in particular in this study, were not affected as much.

4.1.3. Threshold values

Definition of laboratory anomalies are based upon threshold values that refer to the reference values of the laboratory, which furnishes the results. In this study, data were used that were provided by the Institute of Clinical Chemistry of the University Hospital of Cologne (Institut für Klinische Chemie der Uniklinik Köln). Generally, every laboratory defines its own reference values according to the method of assessment they use (Renz-Polster et al. 2013). This is a common limitation to all research relying on laboratory parameters.

Another potential issue to affect the results is the choice of intervals. For each parameter's laboratory anomalies, the same steps of intervals were used relative to the upper reference values: half, single, double- and three-fold. This was done regardless of the parameter's typical behavior during an episode of elevation. While three-fold elevations were quite common with CRP, for example, REC elevations of the threefold were far less common. This limits comparability between intervals and thresholds of different parameters, they should therefore be interpreted independently.

4.1.4. Method

Employing various tests comes at a risk. Statistical significance is based upon a significance level α , which is to be defined prior to the test at question and is often set to 5%.

It describes the probability of the type I error, the incorrect rejection of a true null hypothesis (Field et al. 2012), which is basically the probability of a statistical test to show an association when in truth its appearance in the population occurred by chance. It follows that conducting a large number of statistical tests, as it was done in this study, increases the risk of a result to be declared significant although it is not. This has to be kept in mind when considering the different results of the conducted regressions. It emphasizes the importance of interpreting the given results in the context of independent subsets and of the additional descriptive analysis (CRP T, for example, was a significant predictor in multiple independent subsets and has therefore low probability of being falsely declared significant). In doing so, this inflation of type I errors becomes acceptable.

4.2. Biomarkers for immune related adverse events

Various laboratory anomalies reached statistical significance in some subset combinations. This section will evaluate the found biomarkers and discuss their potential use in clinical practice. The difference found in the subsets of baseline consideration will be interpreted as well – therein, it should be remembered that including baseline can be considered the subset with the most general and least specific analyses, and results found in the only baseline subset contain information of irAEs of the first cycle only. The subset excluding baseline, however, contains the analyses with the greatest impact on daily clinical practice as it is the very subset that analyzes only measurements and irAEs that were monitored during therapy and after the first cycle.

4.2.1. Timing

Although it has not been tested as a biomarker, the aspect of timing deserves some consideration in the context of this topic. In the population analyzed in this study, all medication groups showed similar behavior of irAE onset, as Figure 21 on page 55 illustrates. Most irAEs developed during the first cycle of therapy, followed by the second cycle. After that, irAE onsets became far less frequent and late onsets were uncommon, which concurs with the findings of Callahan et al. (2017).

This was not analyzed any further in this study because of the different focus chosen and also because of the results of other authors regarding irAEs in a more distinctive way, for example by differentiation according to organs and types of irAE entities. This seems to represent an important differentiation concerning the timing of irAE onsets (Champiat et al. 2016; Iglesias 2017).

4.2.2. Leucocyte group

In the leucocyte group, there was a lot of variance concerning what anomaly would reach the highest level of significance in the preselection step described in Section 2.3.2. This makes it difficult to determine an anomaly that definitively has the best test properties. However, the anomalies that reached statistical significance to predict higher irAE onset probability in the next cycle of therapy were REC W and AEC E. They both were statistically significant in the overall treatment group of the respective baseline consideration and besides were only significant in the PD-1 treatment group. This suggests that these biomarkers might only be valid for anti-PD-1 therapy and should not be utilized for anti-CTLA-4 treatment.

Additionally, significance was not reached by any leucocyte parameter when predicting steroid irAEs. This suggests that REC W and AEC E should only be considered for general irAE surveillance with no focus on severe irAEs.

Considering the threshold values of both antecedents, it seems there is no definite interval that is typical for an irAE in development. Furthermore, the association of relative eosinophils $\geq 1.5\%$ at baseline with a superior outcome proposed by Weide et al. (2016) seems to be translatable to irAE onset in a longitudinal setup. This result may back up the assumption of irAE occurrence being linked to therapy outcome. However, because of its threshold value far below the upper reference value of 7.6%, REC W might be deemed unsuitable as a red flag because it includes a large amount of values considered normal in daily clinical practice. For the same reason, it scored higher in SEN compared to AEC E simply because a true positive prediction is more likely when more positive predictions are made.

In the excluding baseline subset, the subset best reflecting immunotherapy surveillance in clinical practice, AEC E reached a higher level of significance than REC W in the including baseline subset. A new elevation of absolute eosinophils $> 59 \times 10^7/l$ may therefore be the preferable biomarker as it is easier to recognize and raises the probability of any irAE to occur by the 3.5-fold. Although this laboratory anomaly in the data at hand only correctly predicted an irAE in 22.2%, only 2.2% of irAEs occurred in its absence. Therefore, it has a good predictive value for no irAEs to occur in its absence.

Not only was none of the leucocyte group a significant predictor of an upcoming steroid irAE, but LC HS even showed a tendency of lowering the occurrence probability in the overall treatment group of the subset excluding baseline. This is both interesting and surprising because low values of leucocyte parameters, as in REC W, seemed to do the opposite when predicting irAEs of any grade. A possible interpretation would be that low

values of LC are associated with low risk of irAEs. This could not be confirmed in the PD-1 treatment group when excluding baseline in a post-hoc test because LC HS caused convergence issues – possibly due to bad model fit – and had to be excluded.

4.2.3. LDH

The universal marker for increased cell damage, LDH, which has also been associated with melanoma activity (Martens et al. 2016a; Weide et al. 2016), showed an interesting association with irAEs of any grade. LDH HS was a highly significant predictor of **increased** any irAE risk in the including baseline subset of the overall and PD-1 treatment groups, correctly predicting 34.5% and 30.6% of any irAEs. LDH E, however, significantly predicted a **decrease** to a third of the universal risk of any irAE to occur in the only baseline subset of the PD-1 treatment group. These results suggest a tipping point near 250 U/l: Values below this threshold signal low tumor activity, but seemingly for high immunologic activity in the manifestation of irAEs as well. Values above this value may rather be an indicator of high tumor activity and low immunologic activity.

When considering the results of Martens et al. (2016a), Weide et al. (2016) and others who established LDH as a prognostic marker for melanoma, it seems possible that primarily the weakened immune system leads to the loss of tumor control. Tumor growth then leads to high levels of LDH which indicate bad prognosis even within immunotherapy. One possible explanation for these findings may be that the weakened immune system, not anymore capable of a proper antitumor response, is also unable to induce an irAE. In this concern, further research is required, and this interpretation is limited by the fact that neither LDH E nor LDH HS yielded interpretable results in the excluding baseline subset in post-hoc tests.

Concluding, LDH also seems to be an antecedent validly applicable only to anti-PD-1 treatment and irAEs of any grade, although insignificant results in some of the other subsets point towards a similar direction.

4.2.4. CRP

Of the CRP anomalies, CRP T was predominantly calculated to have the best biomarker characteristics. This unspecific, IL-6 induced acute phase protein (Renz-Polster et al. 2013) reached statistical significance predominantly when predicting steroid irAEs, the only exception was the overall treatment group in the subset including baseline. CRP T did not significantly predict irAEs in the only baseline subset and performed best in the PD-1 treatment group of the excluding baseline subset best reflecting the situation of

irAE surveillance during treatment. In this subset, CRP T highly significantly predicted a nine-fold probability increase for steroid irAEs to occur. Correlation analysis showed that this biomarker's predictions with the available data, although covering 35.3% of irAEs, were only correct in 8.5% of cases. This suggests that CRP increased above 15 mg/l far too often to be a helpful antecedent for a steroid irAE on its own. The CRP elevations above 15 mg/l that were not associated with irAE onsets were probably associated with different inflammations. Therefore, when other possible causes like an infection can be ruled out in case of such a CRP elevation, or when an irAE manifests itself shortly after the measurement, the attending dermatooncologist can now assume that this irAE might very well require eventual steroid intervention. Figure 29 illustrates a recommended decision tree for dermatooncologists facing a new CRP elevation above 15 mg/l.

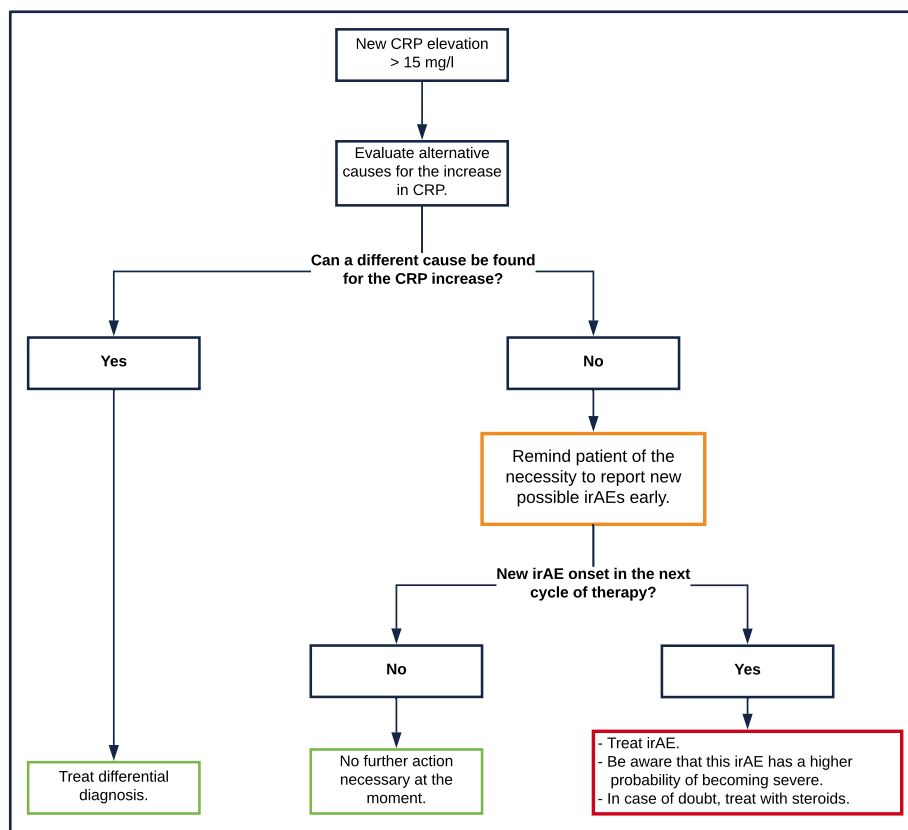


Figure 29: Decision tree for new CRP elevation > 15 mg/l in anti-PD-1 treatment

In addition to that, the found antecedents could be useful the other way around: CRP is elevated beyond the three-fold upper reference value frequently, presumably for many different reasons – and so it also increases almost always shortly before an upcoming steroid irAE and there is rarely any steroid irAE with no preceding threefold elevation of CRP. Therefore, if clinical symptoms arise that could be due to a severe irAE but CRP was below 15 mg/l right before it occurred, the diagnosis of a severe irAE and the subsequent need of steroid administration should be considered less likely.

It is therefore surprising that this antecedent almost did not become significant for irAEs of any grade as well. It can be assumed that for mild irAEs with therefore mild underlying inflammations CRP did not always rise beyond the triple threshold and consequently did not build an association strong enough to be significant against the many other events of CRP to rise. It then makes sense that only in the largest subset for irAEs of any grade CRP T reached statistical significance, suggesting an underlying trend that needs a large number of cases to reach statistical significance.

4.2.5. Predictive value of antecedent combinations

Because multiple combinations of biomarkers were rare, the comparison of such antecedent combinations is questionable, and SEN is generally very low in all observed combinations (0 - 15.5%). Yet, combined biomarkers in regression sometimes had very high ORs with values of up to 21.8, thereby promising strong improvements of each individual predictor's PPV. When looking at the diagnostic test characteristics, this was not always reflected in the data. When comparing the PPV, the frequency of irAEs to actually follow a biomarker, of all combinations of found antecedents in their respective subset, a general increase compared to the single predictors could be noted.

Mainly combinations predicting any grade irAE in the including baseline subset of the overall treatment group yielded interpretable results. However, not always was the increase of PPV proportionate to the consequential decrease of SEN. For example, CRP T had a PPV of 22.0% and a SEN of 16.4%, while REC W had a PPV of 26.4% and a SEN of 29.8%. Its combination led to a marginal increase of the highest PPV from 26.4% (REC W) to 29.7% combined at the expense of a major decrease from the lowest SEN of 16.4% (CRP T) to 4.6% combined. Given that SEN even before combination was a relatively low rated test characteristic among the found predictors for irAEs, this makes clear that a model of antecedents jointly predicting irAEs is not to be recommended, their use very limited. Clinicians may keep their predictive power in mind for the rare events of occurrence. Because then with the combinations LDH HS + REC W + CRP T and CRP T + LDH HS, in the next cycle of therapy there occurred any irAEs in 66.7% and 53.3% of cases, concurring with their increased ORs of 7.72 and 4.71.

When combining the two antecedents of the PD-1 treatment group LDH HS and REC W in the including baseline subset, ORs raised from 2.8 and 1.9, respectively, to 5.2 combined. However, PPV only increased marginally compared to the highest individual PPV

of 30.6% (LDH HS) to 32.7%, whereas SEN only decreased mildly as well from the lowest individual SEN of 17.3% (LDH HS) to 13.6% combined. The result of the regression analysis for the combination to have an OR of 5.2 should therefore be seen critical for it found no concurring reflection in the data.

The next combination of the antecedents CRP T and AEC E in order to predict any irAE in the excluding baseline subset of the overall treatment group yielded completely different results in the correlation analysis: Whenever both anomalies occurred simultaneously, not a single irAE followed, leading to zero true positive predictions. While this means that the combined OR was not at all reflected in the data, it also means that the potential of these two antecedents may not lie in their simultaneous occurrence. However, when either the one or the other antecedent occurs, their SEN adds up to 19.3% and their PPV to 36.3%. This may be a promising approach because CRP T has shown to be especially applicable for steroid irAEs. It underlines that when AEC E is true, a low grade irAE is more likely to occur, whereas if CRP T is true, a high grade irAE is more likely to occur.

The last possible combination of antecedents found in one subset is CRP T and LC HS to predict steroid irAEs in the excluding baseline subset of the overall treatment group. Because LC HS in occurrence tendentially predicted the absence of steroid irAEs, a combination of both antecedents to predict the onset of a steroid irAE would be the one of CRP T plus the absence of LC HS. However, this combination is not only difficult to utilize in daily clinical work, its predictions also were correct in only 9.9% of cases (PPV). For these reasons the combination CRP T + (- LC HS) does not seem to yield practical improvements of predictive value compared to the predictors being separated.

4.2.6. Predictive value of the demographic variables

Complementary to the laboratory parameters, which were assessed longitudinally, two additional variables were implemented in the regression models that had the characteristics of baseline biomarkers: Age and gender performed differently as antecedents for irAEs.

Age

Age showed no association with the occurrence of irAEs within each subset. This lack of association was not only shown by age never reaching statistical significance but by the fact that it never reached statistical significance despite its very small confidence interval

as illustrated in Figure 25, Figure 26 and Figure 27. The graphs show that the ORs of age only varied little around 1 in every subset. Age therefore is very likely to have no association at all with the occurrence of irAEs.

Gender

Female gender reached statistical significance or tendency to be associated with higher irAE probability only in the CTLA-4 treatment group. It did so in almost every subset of this group, regardless of different considerations of baseline measurements. The association does not seem to be very strong with estimated ORs reaching from 1.46 to 3.59, only reaching $p < 0.5$ in the including baseline subset, where more data led to smaller confidence intervals. Additionally, the association seems strongest with steroid irAEs and with those occurring after the first dose of ipilimumab. This association with the first dose may again be due to the high density of irAEs in the first cycle (see Figure 21 on page 55), leading to smaller data in all other cycles, thereby likely affecting confidence intervals. Alternatively, it could reflect a slightly stronger association of female gender with early irAEs. It seems, however, as if women generally have a higher potential to develop irAEs especially of higher grades when receiving ipilimumab.

4.2.7. Consideration of baseline measurements

As the conducted analyses suggest, considering baseline measurements separately made a difference. It indeed seems like predictive values of baseline measurements and those during treatment vary - especially if they are inflammation parameters. It is somewhat surprising that regression analysis yielded only few significant results in the baseline only subset, although most of the irAEs occurred right after the first dose of immunotherapy (see Figure 21 on page 55) and so a lack of data should not have been an issue. It seems like inflammation parameters should only be interpreted in their dynamics when interacting with immunotherapy. This might be one reason why Khoja et al. (2016a) did not find any biomarker for irAEs in the blood count in ipilimumab treated patients. It implicates that the immunologic potential of a patient to develop irAEs cannot be found in the investigated inflammation parameters and that research should focus on longitudinal studies to find applicable biomarkers.

It is, however, remarkable that LDH E did indeed reach statistical significance in the PD-1 treatment group of the only baseline subset to predict any irAE *not* to occur. This concurs with the hypothesis proposed in Section 4.2.3, in which high measurements of LDH might be an indirect indicator of low immunologic potential concerning both antitumor response and irAEs.

4.2.8. Consideration of treatment

The data underline that treating the different immunotherapies as one is not legitimated in terms of irAE antecedents despite the many similarities also concerning irAEs that anti-CTLA-4 and anti-PD-1 therapies share, as reviewed in Section 11. Therefore, leaving the overall treatment group aside, no predictor reached statistical significance in more than one treatment group. It seems like in anti-PD-1 treatment, there is a variety of antecedents to choose from associated with real time irAE onset risk, both of any grade and of those with necessary steroid intervention. In contrast, in anti-CTLA-4 treatment, there is none but the baseline predictor of female gender that can predict a higher risk especially for steroid irAEs independently of baseline considerations.

This diversity in the differently targeted immunotherapies makes it very hard to draw implications for antecedents from the analyses conducted on the combination therapy group. Not a single antecedent reached statistical significance. It seems like this is not only due to the low number of cases but also to the divergent antecedents found in the monotherapies: It might be assumed that a potential mutually significant predictor in both the PD-1 and the CTLA-4 treatment groups would reach low p-values in the combination therapy group as well because of the synergistic statistical effect and despite the low number of cases. However, because there were no mutually significant predictors, this synergistic effect did not occur.

Because of both monotherapies being used in combination therapy, it is a logical assumption that each of the different antecedents does indeed possess a certain predictive value for those irAEs induced by their respective agent. As such, female gender was among the antecedents with the lowest p-values in the combination therapy group. Additionally, LDH H and CRP T were comparably low when predicting any irAE in the including baseline subset – the same subset in which these antecedents reached very high statistical significance ($p < 0.001$ & $p = 0.002$) in the overall treatment group. Although these indications are circumstantial and conclusions must be drawn very cautiously, it seems plausible that predictors for irAEs in monotherapies translate to combination therapies as well. This is despite them probably possessing even less predictive value, as the predictors will only count for a certain subset of irAEs occurring during combination therapy.

4.3. Conclusion

Many steps of analysis have been conducted in this study, with many results shedding light on the different onset dynamics of irAEs in the various subsets. This section will

conclude the most relevant findings, evaluate the overall contributions of this study to theory and practice and make suggestions on the deriving perspectives for future research.

4.3.1. Summary

A main result of this study is that there have been statistically significant antecedents found for irAEs in immunotherapy. Of these, the most important are:

- An elevation of absolute eosinophils above $59 \times 10^7/l$ significantly ($p = 0.015$) predicts the onset of any irAEs in anti-PD-1 treatment when excluding baseline. (SEN = 6.3%, SPE = 97.8%, PPV = 22.2%, NPV = 91.4%)
- An elevation of CRP above 15 mg/l significantly ($p < 0.001$) predicts the onset of severe irAEs in anti-PD-1 treatment when excluding baseline (SEN = 35.3%, SPE = 93.9%, PPV = 8.5%, NPV = 98.9%)
- An elevation of LDH above 250 U/l at baseline indicates a significantly ($p = 0.034$) lower probability of any irAE to occur in anti-PD-1 treatment. (SEN = 46.8%, SPE = 72.7%, PPV = 83.0%, NPV = 32.4%)
- Female gender is significantly associated with higher probability of any ($p = 0.046$) and severe irAE ($p = 0.020$) to occur in anti-CTLA-4 treatment regardless of the baseline consideration.
- Age seems to be irrelevant for irAE onset prediction.

Another important finding is that these antecedents cannot be used interchangeably despite all similarities between irAEs of anti-CTLA-4 and anti-PD-1 treatments: It seems like there was a fundamental difference in the dynamics of irAE onset between those two treatment groups or at least how they are reflected in laboratory inflammation parameters. This also makes the translation of the found antecedents to irAEs of combination therapy difficult, for there is no common antecedent to be used but only antecedents that would at least theoretically account for an undefinable subset of irAEs in combination therapy.

It has also been found that, at least for the researched laboratory parameters, the consideration of baseline parameters is relevant. Neither AEC nor CRP were a statistically significant predictor for the first cycle of therapy, and the antecedents found statistically significant in the subset including baseline were not found to be significant in any of the other subsets. This limits the interpretability of these antecedents, although the combination of the three parameters LDH HS, REC W and CRP T for any irAE in the overall subset showed a combined PPV of 66.7% (SEN = 2.5%, SPE = 97.8%, NPV = 91.4%).

It is, however, at least suggested that there is an association between these high-normal LDH, REC $\geq 1.5\%$, CRP > 15 mg/l and irAEs of any grade – although it was not replicable in more specific subsets.

4.3.2. Contributions to clinical practice

What is needed most by clinicians is an antecedent that specifically warns of an upcoming irAE requiring eventual treatment. Although an AEC elevation generally is a marker for more specific inflammation than CRP (Renz-Polster et al. 2013) and predicted irAEs correctly more frequently (in 22.2% of cases) in anti-PD-1 treatment, its predictive capabilities seem limited to irAEs of any grade. AEC E might help to identify an upcoming symptom as an irAE but does not indicate its severity.

The threefold elevation of CRP was shown to do just that in anti-PD-1 treatment. However, CRP itself is a parameter whose elevation occurs in many different sorts of inflammation and is therefore not very specific towards irAEs. Hence, it is not surprising that an elevation of CRP > 15 mg/l, although significantly associated with severe irAE onset, was only followed by an irAE that eventually needed steroid intervention in 8.5%. By ruling out differential diagnoses in case of a new threefold CRP elevation, this lack of specificity towards irAEs can be coped with. The according decision tree can be reviewed in Figure 29 on page 78.

In addition to that, the found antecedents could be useful the other way around: The high specificity found means that only few irAEs occur without the elevation of the predictor. Therefore, if clinical symptoms arise that could be due to a severe irAE, yet CRP was below 15 mg/l right before it occurred, the diagnosis of a severe irAE and the subsequent need of steroid administration should be considered less likely.

Clinicians should also be encouraged to routinely keep on measuring laboratory parameters every cycle, which is due to the fact that all inflammatory blood parameters were without predictive power when measured at baseline. Dynamic changes in inflammatory blood parameters have the highest predictive power over an imminent irAE. This, too, can support early recognition and help to ensure the patients' awareness to come forward when irAEs occur⁶.

⁶ In the population of this study, some severe irAEs started with patients not reporting symptoms of irAEs when they occurred. They waited until the next scheduled appointment or until the symptoms became too severe, thereby preventing early treatment and enforcing therapy disruptions.

Considering the preceding choice of therapy, two implications can be derived from this study. First, females are more likely to develop irAEs than males in anti-CTLA-4, but not in anti-PD-1 treatment, which makes the latter favorable for female patients.

Second, when discussing treatment options, patients with high LDH are considered to have a high tumor burden and therefore to profit from the combination therapy. Its higher effectivity and faster response comes at the expense of a far higher risk of irAEs compared to monotherapies. This study implies that at least with PD-1 blockade this risk is reduced when LDH is high at baseline. As nivolumab is an anti-PD-1 antibody used in combination therapy, it may be assumed that this effect in anti-PD-1 treatment at least partially translates into combination therapy. Therefore, this study supports the practice of offering combination therapy to patients with high LDH at baseline, although this implication will have to be confirmed by further research with a higher number of cases with combination therapy.

4.3.3. Contributions to research

This study allows new insights contributing to a better understanding of the genesis of irAE. In particular, it underpins the extent to which antecedents differ depending on the treatment. It is now very clear that irAEs of anti-PD-1 and anti-CTLA-4 therapy, although very similar in many aspects, must be analyzed separately: Not only are there no laboratory antecedents significant for anti-CTLA-4 therapy while for anti-PD-1 therapy there are, but also gender influences anti-CTLA-4 therapy irAEs, although it has no influence on irAEs of anti-PD-1 therapy.

Another relevant finding for research is the importance of baseline considerations concerning laboratory biomarkers for irAEs. It could be shown in this study that highly statistically significant antecedents measured after the first dose of immunotherapy may not be even close to being significant when measured at baseline. This concurs with the findings of Schindler et al. (2014), who found significant correlation of REC and AEC with irAE occurrence in week 4 and 7 of therapy, but not at baseline. It seems that laboratory antecedents may be dependent on the body's reaction to immunotherapy and that they should be interpreted as a reaction to immunotherapy, not as a general potential to develop irAEs.

One exception was detected: In anti-PD-1 treatment, an LDH elevation above 250 U/l at baseline significantly ($p = 0.034$) predicted a lower probability of irAEs to occur in the first cycle. It may therefore be assumed that high LDH indeed signals a potential to reduce

irAE risk. Potential explanations would include an association of tumor burden and the patient's immunologic capabilities.

4.3.4. *Directions for future research*

Although some questions concerning irAE dynamics could be answered in this study, some new ones have arisen as well. The fact that none of the investigated antecedents is applicable to both anti-CTLA-4 and anti-PD-1 treatments was surprising, and the question to why they performed so differently could serve as a starting point for further research. To answer this question might help understanding how irAEs develop, how they can be predicted and ultimately how they can be controlled more effectively.

Additionally, further researching the different irAE onset dynamics might lead to the recognition of different patient groups with different respective risks of irAE occurrence at baseline, thereby offering guidance which therapy to prefer for each individual patient.

Much of the research conducted concerning irAEs did not focus on irAEs in general but mostly on one or a distinctive group of irAEs only. In this thesis, biomarkers were analyzed that can be applied to irAEs in general. It would be interesting for further research to investigate in a similar way how the antecedents found in this thesis or others perform when focusing on particular irAEs. This could enhance previously published approaches to further understanding the different mechanisms leading to the respective entities of irAEs.

An LDH elevation above 250 U/l to predict lower any irAE probability at baseline and an LDH elevation to a value between 125 and 250 U/l to predict a higher irAE probability at any time of therapy is a remarkable finding to be researched further. It would be interesting to investigate whether this general marker of cell damage and immunotherapy response (Diem et al. 2016) generally points to an immunologic potential to develop irAEs. If this was the case, it raises the question which one comes first: The immunologic incapability for antitumor response and irAEs leading to tumor progression with high LDH, or the LDH indicated high tumor burden that suppresses the immune antitumor and irAE response? Could this immunologic incapability be reactivated by immunotherapy? And if so: Would especially patients with high LDH at baseline profit from the more aggressive combination therapy compared to the monotherapies? Answering these questions would help in the decision making which treatment to recommend to affected patients.

A prospective longitudinal study design otherwise similar to the one used in this study with more potential biomarkers included could help finding and validating more suitable biomarkers than found in this study. Especially the detection of low grade irAEs could be improved and more specific laboratory parameters could be analyzed to further improve therapy and patients' quality of life.

To cope with the even higher number of parameters, a possible approach could be to use a more sophisticated method: As this study was conducted, many decisions were made with regard to the disabilities of regression, such as the limited number of variables taken into account, the grouping of the leucocyte group or the extensive previous selection process. Although this study yielded significant and interpretable results, a more sophisticated method such as random forest machine learning could increase informative value and may give the clinician a more practical assist. This method can be used to build a comprehensive decision tree, which can be followed by dermatooncologists to support the diagnostics of irAEs (Breiman 2001; Cox-Martin et al. 2018).

This approach is currently being applied to the same dataset involving further parameters such as body mass index or previous therapy and is subject to a planned publication by Nätlitz et al. of the University of Cologne, which shows promising preliminary results.

5. Summary

Immunotherapies have proven to be a promising innovation in the treatment of the metastasized malignant melanoma concerning response and survival. Yet, this new treatment's benefits come at the cost of a new set of manifold immune related adverse events (irAEs). In this dissertation, selective threshold crossings of five laboratory parameters (LDH, CRP, relative and absolute eosinophil count and leucocyte count) as well as age and gender are analyzed for their potential to serve as irAE biomarkers in anti-PD-1, anti-CTLA-4 and combination therapy (nivolumab + ipilimumab).

For this purpose, a retrospective, longitudinal study design is used. Laboratory parameters are raised at baseline and continuously every cycle after the first dose of therapy and considered in three variations: Only baseline measurements, all measurements, and excluding baseline measurements. The analyses are conducted separately on each of the three therapy groups and all groups combined. Outcome parameters are the laboratory parameters' predictive values concerning either irAEs of any grade or severe irAEs ultimately necessitating steroid intervention (steroid irAEs). By conducting the analyses in the resulting 24 subdivisions, it is possible to analyze the respective predictive values in a particularly differentiated way. Statistically, algorithms of logistic and multilevel logistic regression models are used in a two-phase approach as well as an additional descriptive method to help relating the results to their practical application.

In total, 256 courses of therapy are analyzed, dividable in 129 courses of anti-PD-1, 108 courses of anti-CTLA-4 and 19 courses of combination therapy. The results concerning the demographic parameters show an association of female gender with irAEs in anti-CTLA-4 treatment throughout all three respective considerations of baseline. This includes a minimum of a statistical tendency up to statistical significance (p from 0.087 to 0.020). Age has no influence on any or steroid irAE occurrence. Of the laboratory parameters, none reaches statistical significance in the anti-CTLA-4 subsets. In anti-PD-1 treatment considering only baseline parameters, only an LDH elevation > 250 U/l is associated with irAE onsets of any grade ($p = 0.034$). When considering only parameters measured after the first cycle of therapy, absolute eosinophil count $> 59 \times 10^7/l$ is associated with irAE onsets of any grade ($p = 0.015$), while a CRP elevation > 15 mg/l is strongly associated with the onset of steroid irAEs ($p < 0.001$).

In addition to the found antecedents, which may be of assistance in clinical practice, this dissertation's results strongly highlight a differentiated consideration of baseline parameters. In most of the few publications concerning this topic, baseline parameters are used to search for irAE antecedents. Yet for this purpose, this thesis emphasizes the importance of measurements after the first dose of immunotherapy to yield significant results. This might be crucial in order to be able to understand and someday even prevent irAEs in modern oncology in a reliable way, not only in the treatment of the malignant melanoma.

6. Zusammenfassung

Immuntherapien haben sich als vielversprechende Innovation in der Behandlung des metastasierten malignen Melanoms hinsichtlich Ansprechen und Überleben erwiesen. Die Vorteile dieser neuen Behandlungsmethode gehen jedoch zu Lasten eines neuen Spektrums von vielfältigen immunvermittelten Nebenwirkungen (ivNW). In dieser Dissertation werden selektive Schwellenüberschreitungen von fünf Laborparametern (LDH, CRP, relative und absolute Eosinophilenzahl und Leukozytenzahl) sowie Alter und Geschlecht auf ihr Potenzial als Biomarker für ivNW in Anti-PD-1, Anti-CTLA-4 und Kombinationstherapie (Nivolumab + Ipilimumab) untersucht.

Hierfür wird ein retrospektives, längsschnittliches Studiendesign verwendet. Die Laborparameter werden zu Beginn und nach der ersten Dosis der Therapie kontinuierlich in jedem Zyklus erhoben und in drei unterschiedlichen Varianten betrachtet: Nur Baseline-Messungen, alle Messungen ohne Baseline sowie alle Messungen ohne Ausnahme. Die Analysen werden separat für jede der drei Therapiegruppen sowie für alle Gruppen zusammen durchgeführt. Ergebnisparameter sind die prädiktiven Werte der Laborparameter, die entweder ivNW jedweden Grades oder schwere ivNW betrafen, die im Verlauf eine Steroidintervention erforderten (Steroid-ivNW). Durch die Durchführung der Analysen in den daraus resultierenden 24 Unterteilungen können die jeweiligen Vorhersagewerte besonders differenziert analysiert werden. Statistisch werden Algorithmen von logistischen und multilevel logistischen Regressionsmodellen in einem zweistufigen Verfahren sowie eine zusätzliche deskriptive Methode verwendet, um die Ergebnisse mit ihrer praktischen Anwendung in Beziehung zu setzen.

Insgesamt werden 256 Therapieverläufe analysiert, teilbar in 129 Verläufe von Anti-PD-1, 108 Verläufe von Anti-CTLA-4 und 19 Verläufe von Kombinationstherapie. Die Ergebnisse zu den demographischen Parametern zeigen eine Assoziation von weiblichem Geschlecht mit irAEs in der Anti-CTLA-4-Behandlung in allen drei Einbeziehungen des Ausgangswerts. Dies reicht von einer statistischen Tendenz bis hin zur statistischen Signifikanz (p von 0,087 bis 0,020). Das Alter hat keinen Einfluss auf das Auftreten einer der beiden Gruppen von ivNW. Von den Laborparametern erreicht keiner die statistische Signifikanz in den Anti-CTLA-4-Untergruppen. In der Anti-PD-1-Therapie, bei der nur die Baseline-Messungen berücksichtigt werden, wird lediglich eine LDH-Erhöhung > 250 U/l mit dem Auftreten von ivNW beliebigen Grades assoziiert ($p = 0,034$). Werden nur die Parameter betrachtet, die nach dem ersten Therapiezyklus gemessen

werden, so ist eine absolute Eosinophilenzahl $> 59 \times 10^7/l$ mit dem Auftreten von ivNW beliebigen Grades assoziiert ($p = 0,015$), während eine CRP-Erhöhung $> 15 \text{ mg/l}$ stark mit dem Auftreten von Steroid-ivNW assoziiert ist ($p < 0,001$).

Zusätzlich zu den ermittelten Markern, die in der klinischen Anwendung als Hilfsmittel dienen können, verdeutlichen die Ergebnisse dieser Dissertation die Rolle einer differenzierten Betrachtung von Baseline-Parametern. In den meisten der wenigen Publikationen zu diesem Thema werden lediglich bei Baseline erhobene Parameter genutzt, um nach Biomarkern für ivNW zu suchen. Diese Doktorarbeit unterstreicht jedoch die Bedeutung von Messungen nach der ersten Dosis der Immuntherapie, um signifikante Ergebnisse zu erzielen. Dies könnte entscheidend sein, um ivNW in der modernen Onkologie nicht nur bei der Behandlung des malignen Melanoms zuverlässig verstehen und eines Tages sogar vorbeugen zu können.

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8. Preliminary Publications

- Knüver, J., Gerecht, L., Mauch, C. & Schlaak, M. 2017a, 'P120 | Eosinophilia during immunotherapy of metastatic melanoma: A warning signal for possible side effects?', in *JDDG: Journal der Deutschen Dermatologischen Gesellschaft*, vol. 15, Mainz, pp. 70–71, viewed 28 February 2018, <<http://doi.wiley.com/10.1111/ddg.13299>>.
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9. Appendix

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1. Parameter selection

Including baseline

any AE

- [REC]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.weide + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1295.5	1311.4	-644.8	1289.5	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.9264	-0.4299	-0.3537	-0.3021	3.4940

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4933	0.7023

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.8061	0.1041	-17.347	< 2e-16 ***
rec.weideTRUE	0.8099	0.1715	4.724	2.32e-06 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
rec.wedTRUE -0.460

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1329071	0.1643011	0.2005341
2 rec.weideTRUE	1.6005657	2.2477910	3.1379982

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.high + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1316.4	1332.3	-655.2	1310.4	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.7510	-0.4453	-0.3829	-0.3225	3.4487

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.57	0.755

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.6193	0.0959	-16.886	<2e-16 ***
rec.highTRUE	0.1329	0.3331	0.399	0.69

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
rec.hghTRUE -0.184

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1629017	0.1980295	0.2380169
2 rec.highTRUE	0.5745035	1.1420937	2.1385175

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']

Family: binomial (logit)
Formula: ae.any ~ rec.half + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1306.5	1322.4	-650.2	1300.5	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.9523	-0.4472	-0.3718	-0.3149	3.5152

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5234	0.7234

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.7066	0.0987	-17.290	< 2e-16 ***
rec.halfTRUE	0.6747	0.2056	3.282	0.00103 **

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
rec.hlfTRUE -0.336

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1484815	0.1814829	0.2193312
2 rec.halfTRUE	1.3023493	1.9634015	2.9211371

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']

Family: binomial (logit)
Formula: ae.any ~ rec.single + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1316.5	1332.4	-655.2	1310.5	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.7517	-0.4459	-0.3833	-0.3225	3.4441

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5711	0.7557

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.61798	0.09582	-16.886	<2e-16 ***
rec.singleTRUE	0.11337	0.34428	0.329	0.742

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

```

      (Intr)
rc.snglTRUE -0.177

- Odds Ratios
  row.labels      or.l      or      or.u
1  (Intercept) 0.1631452 0.1982984 0.2383008
2 rec.singleTRUE 0.5495378 1.1200423 2.1389853

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.double + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1316.5	1332.4	-655.3	1310.5	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.7541	-0.4460	-0.3848	-0.3225	3.4180

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5748	0.7581

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.61351	0.09462	-17.052	<2e-16 ***
rec.doubleTRUE	0.13824	0.086768	0.159	0.873

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
rec.dblTRUE -0.065

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1642083	0.1991872	0.2387671
2 rec.doubleTRUE	0.1553388	1.1482532	5.4416556

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.triple + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1316.6	1332.5	-655.3	1310.6	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.7547	-0.4468	-0.3849	-0.3225	3.4182

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5759	0.7589

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.61233	0.09459	-17.046	<2e-16 ***
rec.tripleTRUE	-0.05448	1.14352	-0.048	0.962

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
rc.trplTRUE -0.052

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.16439345	0.1994225	0.2390086
2 rec.tripleTRUE	0.04696868	0.9469759	6.5330374

- [AEC]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.high + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1313.2	1329.1	-653.6	1307.2	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.8116	-0.4473	-0.3820	-0.3219	3.5556

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5538	0.7442

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.64290	0.09562	-17.182	<2e-16 ***
aec.highTRUE	0.62631	0.32986	1.899	0.0576 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
aec.hghTRUE -0.194

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1591748	0.1934181	0.2323155
2 aec.highTRUE	0.9561182	1.8706932	3.5116601

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.half + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1316.3	1332.2	-655.1	1310.3	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.7531	-0.4454	-0.3825	-0.3218	3.4295

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.564	0.751

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.62540	0.09725	-16.713	<2e-16 ***
aec.halfTRUE	0.13222	0.24540	0.539	0.59

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
aec.hlfTRUE -0.254

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1615619	0.1968326	0.2373076
2 aec.halfTRUE	0.6936178	1.1413644	1.8207628

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.single + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1313.5	1329.4	-653.7	1307.5	1480

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.8199	-0.4476	-0.3819	-0.3215	3.5641

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5604	0.7486

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.6397	0.0956	-17.151	<2e-16 ***
aec.singleTRUE	0.6404	0.3517	1.821	0.0686 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ac.snglTRUE -0.181

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1596756	0.194044	0.2330382
2 aec.singleTRUE	0.9257743	1.897206	3.7102444

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.double + (1 | pid)

```

Data: final.data
      AIC      BIC    logLik deviance df.resid
1315.6   1331.5   -654.8   1309.6     1480

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.8416 -0.4461 -0.3840 -0.3220  3.4207

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.5739   0.7576
Number of obs: 1483, groups: pid, 252

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.61936    0.09475  -17.092  <2e-16 ***
aec.doubleTRUE  0.78505    0.75999   1.033   0.302
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
aec.dblTRUE -0.083

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1631966 0.1980246 0.2374119
2 aec.doubleTRUE 0.4229498 2.1925116 9.1238686

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ aec.triple + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1315.6   1331.5   -654.8   1309.6     1480

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.7549 -0.4471 -0.3853 -0.3228  3.4163

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.5752   0.7584
Number of obs: 1483, groups: pid, 252

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.610e+00  9.234e-02  -17.44  <2e-16 ***
aec.tripleTRUE -2.374e+01  2.010e+05   0.00   1
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
ac.trplTRUE 0.000
convergence code: 0
unable to evaluate scaled gradient
Hessian is numerically singular: parameters are not
uniquely determined

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1667535 1.998380e-01 0.2394866
2 aec.tripleTRUE 0.0000000 4.917641e-11 Inf

- [LC]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ lc.high + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1316.4   1332.3   -655.2   1310.4     1480

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.7599 -0.4477 -0.3842 -0.3221  3.4225

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.5856   0.7653
Number of obs: 1483, groups: pid, 252

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.60526    0.09619  -16.689  <2e-16 ***
lc.highTRUE  -0.16392    0.38589   -0.425   0.671
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.highTRUE -0.171

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1651366 0.2008378 0.2415722
2 lc.highTRUE 0.3781192 0.8488065 1.7388038

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ lc.half + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1308.9   1324.8   -651.5   1302.9     1480

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.8476 -0.4468 -0.3660 -0.3076  3.5417

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.5373   0.733
Number of obs: 1483, groups: pid, 252

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.7231    0.1031  -16.715  <2e-16 ***
lc.halfTRUE   0.4959    0.1755   2.825   0.00473 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.halfTRUE -0.422

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1447663 0.1785088 0.2175194
2 lc.halfTRUE 1.1580574 1.6419520 2.3071903

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ lc.single + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1316.4   1332.3   -655.2   1310.4     1480

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.7594 -0.4476 -0.3840 -0.3221  3.4223

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.5847   0.7646
Number of obs: 1483, groups: pid, 252

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -1.60621    0.09614  -16.707  <2e-16 ***
lc.singleTRUE -0.14476    0.38698   -0.374   0.708
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.snglTRUE -0.170

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1649954 0.2006475 0.241322
2 lc.singleTRUE 0.3847058 0.8652316 1.776600

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ lc.double + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1315.6   1331.5   -654.8   1309.6     1480

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.7618 -0.4468 -0.3835 -0.3205  3.4339

```

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 0.5942 0.7709
 Number of obs: 1483, groups: pid, 252

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -1.612e+00 9.289e-02 -17.35 <2e-16 ***
 lc.doubleTRUE -2.917e+01 2.781e+06 0.00 1

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 lc.doblTRUE 0.000
 convergence code: 0
 unable to evaluate scaled gradient
 Hessian is numerically singular: parameters are not uniquely determined

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.1662998 1.995065e-01 0.2393439
 2 lc.doubleTRUE 0.0000000 2.135325e-13 Inf

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.any ~ lc.triple + (1 | pid)
 Data: final.data

AIC	BIC	logLik	deviance	df.resid
1316.2	1332.1	-655.1	1310.2	1480

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.7545 -0.4469 -0.3851 -0.3227 3.4166

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 0.5747 0.7581
 Number of obs: 1483, groups: pid, 252

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -1.611e+00 9.233e-02 -17.45 <2e-16 ***
 lc.tripleTRUE -2.372e+01 3.562e+05 0.00 1

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 lc.trplTRUE 0.000
 convergence code: 0
 unable to evaluate scaled gradient
 Hessian is numerically singular: parameters are not uniquely determined

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.1665598 1.996022e-01 0.2391996
 2 lc.tripleTRUE 0.0000000 4.993875e-11 Inf

- [LDH]

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.any ~ ldh.weide + (1 | pid)
 Data: final.data

AIC	BIC	logLik	deviance	df.resid
1305.6	1321.5	-649.8	1299.6	1477

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.7544 -0.4359 -0.3841 -0.3116 3.3945

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 0.5773 0.7598
 Number of obs: 1480, groups: pid, 254

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -1.61661 0.09556 -16.917 <2e-16 ***
 ldh.weideTRUE -0.45632 0.56913 -0.802 0.423

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 ldh.wedTRUE -0.133

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.1633654 0.1985705 0.2384265
 2 ldh.weideTRUE 0.1781436 0.6336098 1.7523095

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.any ~ ldh.high + (1 | pid)
 Data: final.data

AIC	BIC	logLik	deviance	df.resid
1305.3	1321.2	-649.7	1299.3	1477

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.7295 -0.4478 -0.3769 -0.3179 3.4071

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 0.5526 0.7434
 Number of obs: 1480, groups: pid, 254

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -1.6634 0.1008 -16.51 <2e-16 ***
 ldh.highTRUE 0.2046 0.2025 1.01 0.312

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 ldh.hghTRUE -0.360

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.1544285 0.1894922 0.2299903
 2 ldh.highTRUE 0.8168363 1.2269829 1.8099173
 Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.any ~ ldh.half + (1 | pid)
 Data: final.data

AIC	BIC	logLik	deviance	df.resid
1279.8	1295.7	-636.9	1273.8	1477

Scaled residuals:
 Min 1Q Median 3Q Max
 -1.0790 -0.4276 -0.3593 -0.3052 3.4824

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 0.5044 0.7102
 Number of obs: 1480, groups: pid, 254

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -1.7889 0.1004 -17.811 < 2e-16 ***
 ldh.halfTRUE 1.1169 0.2086 5.354 8.59e-08 ***

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 ldh.hlfTRUE -0.370

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.1360454 0.1671376 0.2023733
 2 ldh.halfTRUE 2.0206752 3.0552285 4.5871630

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.any ~ ldh.single + (1 | pid)
 Data: final.data

AIC	BIC	logLik	deviance	df.resid
1304.7	1320.6	-649.4	1298.7	1477

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.7307 -0.4486 -0.3755 -0.3182 3.4107

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 0.55 0.7416
 Number of obs: 1480, groups: pid, 254

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -1.66970 0.09997 -16.701 <2e-16 ***
 ldh.singleTRUE 0.26883 0.20926 1.285 0.199

```

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
ldh.sngTRUE -0.343

- Odds Ratios
  row.labels      or.l      or      or.u
1  (Intercept) 0.1536717 0.1883029 0.2281519
2  ldh.singleTRUE 0.8591371 1.3084299 1.9551275

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ ldh.double + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1306.3   1322.2   -650.1   1300.3     1477

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.7535 -0.4449 -0.3827 -0.3208  3.4015

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 0.5796   0.7613
Number of obs: 1480, groups: pid, 254

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.62495    0.09576  -16.97  <2e-16 ***
ldh.doubleTRUE -0.12225    0.48903   -0.25   0.803
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
ldh.dblTRUE -0.141

- Odds Ratios
  row.labels      or.l      or      or.u
1  (Intercept) 0.1619592 0.1969218 0.2365518
2  ldh.doubleTRUE 0.3098979 0.8849244 2.1700328

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ ldh.triple + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1304.9   1320.8   -649.4   1298.9     1477

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.7555 -0.4464 -0.3842 -0.3115  3.3952

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 0.5793   0.7611
Number of obs: 1480, groups: pid, 254

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.61490    0.09521  -16.961 <2e-16 ***
ldh.tripleTRUE -0.85853    0.77862   -1.103   0.27
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
ldh.trpTRUE -0.094

- Odds Ratios
  row.labels      or.l      or      or.u
1  (Intercept) 0.16376307 0.1989113 0.2386843
2  ldh.tripleTRUE 0.06447075 0.4237829 1.5912272

- [CRP]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.high + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1313.7   1329.7   -653.9   1307.7     1487

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.7865 -0.4447 -0.3719 -0.3143  3.4767

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 0.5496   0.7414
Number of obs: 1490, groups: pid, 254

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.6920    0.1028  -16.459 <2e-16 ***
crp.highTRUE   0.2934    0.1853   1.583   0.113
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
crp.hghTRUE -0.406

- Odds Ratios
  row.labels      or.l      or      or.u
1  (Intercept) 0.1494048 0.1841421 0.2242808
2  crp.highTRUE 0.9259386 1.3409185 1.9170899

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.half + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1315.8   1331.7   -654.9   1309.8     1487

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.8079 -0.4417 -0.3796 -0.3176  3.4480

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 0.5832   0.7636
Number of obs: 1490, groups: pid, 254

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.64340    0.09747  -16.861 <2e-16 ***
crp.halfTRUE   0.17197    0.27517   0.625   0.532
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
crp.hlfTRUE -0.228

- Odds Ratios
  row.labels      or.l      or      or.u
1  (Intercept) 0.1583843 0.1933221 0.2328484
2  crp.halfTRUE 0.6772483 1.1876392 2.0025995

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.single + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
1316.1   1332.0   -655.1   1310.1     1487

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.7480 -0.4431 -0.3804 -0.3192  3.4375

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 0.5769   0.7595
Number of obs: 1490, groups: pid, 254

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.63664    0.09777  -16.739 <2e-16 ***
crp.singleTRUE 0.07172    0.26482   0.271   0.787
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
crp.sngTRUE -0.249

- Odds Ratios
  row.labels      or.l      or      or.u
1  (Intercept) 0.1594465 0.1946337 0.2346743
2  crp.singleTRUE 0.6258155 1.0743548 1.7751179

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ crp.double + (1 | pid)
Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	1315.7	1331.6	-654.8	1309.7	1487

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-0.7482	-0.4419	-0.3805	-0.3182	3.4424

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.575	0.7583

Number of obs: 1490, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.64180	0.09627	-17.053	<2e-16 ***
crp.doubleTRUE	0.25362	0.35814	0.708	0.479

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)
crp.dblTRUE	-0.183

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.1590417	0.1936317	0.2327541
2	crp.doubleTRUE	0.6143950	1.2886843	2.5291001

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ crp.triple + (1 | pid)
Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	1308.4	1324.3	-651.2	1302.4	1487

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-0.7820	-0.4494	-0.3657	-0.3168	3.5421

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5316	0.7291

Number of obs: 1490, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.71739	0.09983	-17.203	< 2e-16 ***
crp.tripleTRUE	0.62612	0.21751	2.879	0.00399 **

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)
crp.trpTRUE	-0.348

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.146405	0.1795347	0.2172773
2	crp.tripleTRUE	1.210364	1.8703479	2.8463149

AE with steroid intervention

- [REC]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ rec.weide + (1 | pid)
Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	604.8	620.7	-299.4	598.8	1480

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-0.4700	-0.2065	-0.1779	-0.1548	5.9127

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.404	1.185

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.2253	0.2070	-15.578	<2e-16 ***
rec.weideTRUE	0.3357	0.2879	1.166	0.244

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)
rec.wedTRUE	-0.241

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02504943	0.03974581	0.05738199
2	rec.weideTRUE	0.77715386	1.39893539	2.41713047

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ rec.high + (1 | pid)
Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	606.1	622.0	-300.0	600.1	1480

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-0.5127	-0.1888	-0.1745	-0.1534	5.8315

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.573	1.254

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.1716	0.2053	-15.451	<2e-16 ***
rec.highTRUE	-0.1330	0.5712	-0.233	0.816

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)
rec.hghTRUE	-0.081

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02636395	0.0419372	0.06014954
2	rec.highTRUE	0.24360734	0.8754813	2.41299167

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ rec.half + (1 | pid)
Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	606.1	622.0	-300.0	600.1	1480

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-0.5087	-0.1882	-0.1767	-0.1548	5.8960

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.554	1.246

Number of obs: 1483, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.18144	0.20820	-15.281	<2e-16 ***
rec.halfTRUE	0.05366	0.37489	0.143	0.886

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)
rec.hlfTRUE	-0.196

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02599018	0.04152564	0.0599414
2	rec.halfTRUE	0.47809906	1.05512510	2.1121506

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ rec.single + (1 | pid)
Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	606.1	622.0	-300.0	600.1	1480

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.5119 -0.1887 -0.1773 -0.1534 5.8504

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.568 1.252
 Number of obs: 1483, groups: pid, 252

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.17344 0.20507 -15.475 <2e-16 ***
 rec.singleTRUE -0.08282 0.57452 -0.144 0.885

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 rc.snglTRUE -0.075

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.02632581 0.04185929 0.06001396
 2 rec.singleTRUE 0.25473867 0.92051306 2.55595186

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ rec.double + (1 | pid)
 Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	603.8	619.7	-298.9	597.8	1480

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.6435 -0.1874 -0.1763 -0.1529 5.8949

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.543 1.242
 Number of obs: 1483, groups: pid, 252

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.1921 0.2050 -15.57 <2e-16 ***
 rec.doubleTRUE 1.5826 0.9589 1.65 0.0989 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 rec.dblTRUE -0.107

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.02583381 0.04108396 0.05884588
 2 rec.doubleTRUE 0.57642656 4.86746361 29.07242648

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ rec.triple + (1 | pid)
 Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	605.4	621.3	-299.7	599.4	1480

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.5109 -0.1890 -0.1775 -0.1536 5.8773

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.559 1.249
 Number of obs: 1483, groups: pid, 252

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.1711 0.2044 -15.515 <2e-16 ***
 rec.tripleTRUE -20.4044 295.6033 -0.069 0.945

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 rc.trplTRUE 0.000

convergence code: 0
 Model is nearly unidentifiable: large eigenvalue ratio
 - Rescale variables?

- Odds Ratios
 row.labels or.l or or.u

1 (Intercept) 2.810726e-02 4.195693e-02 6.263092e-02
 2 rec.tripleTRUE 3.279856e-261 1.375613e-09 5.769490e+242

- [AEC]

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ aec.high + (1 | pid)
 Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	605.8	621.7	-299.9	599.8	1480

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.5030 -0.1882 -0.1771 -0.1555 5.9958

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.518 1.232
 Number of obs: 1483, groups: pid, 252

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.1845 0.2040 -15.607 <2e-16 ***
 aec.highTRUE 0.3290 0.5326 0.618 0.537

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 aec.hghTRUE -0.089

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.02611392 0.04139784 0.05923659
 2 aec.highTRUE 0.43452505 1.38958474 3.64419290

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ aec.half + (1 | pid)
 Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	604.2	620.1	-299.1	598.2	1480

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.5500 -0.1876 -0.1727 -0.1477 5.7916

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.672 1.293
 Number of obs: 1483, groups: pid, 252

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.1454 0.2081 -15.112 <2e-16 ***
 aec.halfTRUE -0.6430 0.5035 -1.277 0.202

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 aec.hlfTRUE -0.069

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.02683529 0.04304808 0.0620837
 2 aec.halfTRUE 0.17183473 0.52569076 1.2866140

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ aec.single + (1 | pid)
 Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	605.4	621.3	-299.7	599.4	1480

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.4998 -0.1882 -0.1772 -0.1557 6.0583

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.499 1.224
 Number of obs: 1483, groups: pid, 252

Fixed effects:

```

      Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.1866    0.2034  -15.664  <2e-16 ***
aec.singleTRUE  0.4841    0.5415   0.894   0.371
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
ac.snglTRUE -0.087

- Odds Ratios
      row.labels      or.l      or      or.u
1      (Intercept) 0.02609951 0.04131163 0.05904232
2 aec.singleTRUE 0.49998826 1.62271367 4.34377755

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ aec.double + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
605.7      621.6   -299.8    599.7    1480

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.5109 -0.1876 -0.1764 -0.1527  5.8956

Random effects:
      Groups Name      Variance Std.Dev.
pid      (Intercept) 1.573      1.254
Number of obs: 1483, groups: pid, 252

Fixed effects:
      Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.1860    0.2058  -15.48  <2e-16 ***
aec.doubleTRUE  0.8006    1.1605   0.69   0.49
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
aec.dblTRUE -0.100

- Odds Ratios
      row.labels      or.l      or      or.u
1      (Intercept) 0.02592701 0.04133807 0.05929319
2 aec.doubleTRUE 0.10762195 2.22693299 16.12705644

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ aec.triple + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
605.7      621.6   -299.8    599.7    1480

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.5120 -0.1885 -0.1771 -0.1532  5.8848

Random effects:
      Groups Name      Variance Std.Dev.
pid      (Intercept) 1.571      1.253
Number of obs: 1483, groups: pid, 252

Fixed effects:
      Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.1757    0.1628  -19.503  <2e-16 ***
aec.tripleTRUE -15.4561  5197.4327  -0.003   0.998
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
ac.trplTRUE 0.000
convergence code: 0
unable to evaluate scaled gradient
Hessian is numerically singular: parameters are not
uniquely determined

- Odds Ratios
      row.labels      or.l      or      or.u
1      (Intercept) 0.03035145 4.176278e-02 0.05746446
2 aec.tripleTRUE 0.00000000 1.938565e-07 Inf

- [LC]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.high + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
605.9      621.8   -299.9    599.9    1480

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.4949 -0.1882 -0.1771 -0.1537  5.8812

Random effects:
      Groups Name      Variance Std.Dev.
pid      (Intercept) 1.522      1.234
Number of obs: 1483, groups: pid, 252

Fixed effects:
      Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.1838    0.2045  -15.566  <2e-16 ***
lc.highTRUE    0.2666    0.5370   0.496   0.62
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.highTRUE -0.095

- Odds Ratios
      row.labels      or.l      or      or.u
1      (Intercept) 0.02610363 0.04142977 0.05933191
2 lc.highTRUE 0.40452368 1.30552078 3.45077467

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.half + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
605.6      621.5   -299.8    599.6    1480

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.4929 -0.1918 -0.1784 -0.1538  5.9596

Random effects:
      Groups Name      Variance Std.Dev.
pid      (Intercept) 1.473      1.214
Number of obs: 1483, groups: pid, 252

Fixed effects:
      Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.2095    0.2080  -15.430  <2e-16 ***
lc.halfTRUE    0.2241    0.2956   0.758   0.448
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.halfTRUE -0.242

- Odds Ratios
      row.labels      or.l      or      or.u
1      (Intercept) 0.02540235 0.04037792 0.05842643
2 lc.halfTRUE 0.68153535 1.25118952 2.18759816

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.single + (1 | pid)
Data: final.data

      AIC      BIC    logLik deviance df.resid
605.8      621.8   -299.9    599.8    1480

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.4938 -0.1882 -0.1772 -0.1537  5.8807

Random effects:
      Groups Name      Variance Std.Dev.
pid      (Intercept) 1.519      1.232
Number of obs: 1483, groups: pid, 252

Fixed effects:
      Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.1840    0.2044  -15.575  <2e-16 ***
lc.singleTRUE  0.2843    0.5382   0.528   0.597
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.snglTRUE -0.094

```



```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.02610279 0.04141928 0.05930552
2 lc.singleTRUE 0.41086608 1.32882489 3.52159859

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.double + (1 | pid)
Data: final.data

```

	AIC	BIC	logLik	deviance	df.resid
	605.5	621.4	-299.8	599.5	1480

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.5663 -0.1875 -0.1760 -0.1521  5.9022

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 1.61      1.269
Number of obs: 1483, groups: pid, 252

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.1839      0.1636  -19.458  <2e-16 ***
lc.doubleTRUE -15.4679    4033.8537  -0.004    0.997
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

Correlation of Fixed Effects:
      (Intr)
lc.doblTRUE 0.000
convergence code: 0
unable to evaluate scaled gradient
Model failed to converge: degenerate Hessian with 1 negative eigenvalues

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.03005869 4.142422e-02 0.05708719
2 lc.doubleTRUE 0.00000000 1.915999e-07      Inf

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.triple + (1 | pid)
Data: final.data

```

	AIC	BIC	logLik	deviance	df.resid
	606.0	621.9	-300.0	600.0	1480

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.5102 -0.1887 -0.1773 -0.1535  5.8803

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 1.558      1.248
Number of obs: 1483, groups: pid, 252

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.1745      0.2042  -15.548  <2e-16 ***
lc.tripleTRUE -14.1148    512.0000  -0.028    0.978
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

Correlation of Fixed Effects:
      (Intr)
lc.trplTRUE 0.000
convergence code: 0
Model is nearly unidentifiable: large eigenvalue ratio
- Rescale variables?

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.02802516 4.181642e-02 0.06239439
2 lc.tripleTRUE 0.00000000 7.413598e-07      Inf

```

- [LDH]

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ ldh.weide + (1 | pid)
Data: final.data

```

	AIC	BIC	logLik	deviance	df.resid
	605.4	621.3	-299.7	599.4	1477

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.5209 -0.1866 -0.1751 -0.1511  5.8717

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 1.646      1.283
Number of obs: 1480, groups: pid, 254

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.1912      0.2092  -15.255  <2e-16 ***
ldh.weideTRUE  -0.1150      0.8048  -0.143    0.886
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

Correlation of Fixed Effects:
      (Intr)
ldh.wedTRUE -0.075

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.02553557 0.04112241 0.05932744
2 ldh.weideTRUE 0.12949698 0.89139330 3.54435764

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ ldh.high + (1 | pid)
Data: final.data

```

	AIC	BIC	logLik	deviance	df.resid
	604.2	620.1	-299.1	598.2	1477

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.4852 -0.1885 -0.1763 -0.1511  5.9159

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 1.525      1.235
Number of obs: 1480, groups: pid, 254

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.2411      0.2122  -15.277  <2e-16 ***
ldh.highTRUE   0.3578      0.3122   1.146    0.252
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

Correlation of Fixed Effects:
      (Intr)
ldh.hghTRUE -0.236

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.02428082 0.03912254 0.05690827
2 ldh.highTRUE 0.75197473 1.43021221 2.57892625

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ ldh.half + (1 | pid)
Data: final.data

```

	AIC	BIC	logLik	deviance	df.resid
	604.7	620.6	-299.4	598.7	1477

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.5019 -0.1888 -0.1749 -0.1531  5.8861

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 1.536      1.239
Number of obs: 1480, groups: pid, 254

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.2138      0.2082  -15.434  <2e-16 ***
ldh.halfTRUE   0.3011      0.3609   0.834    0.404
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

Correlation of Fixed Effects:
      (Intr)
ldh.hlfTRUE -0.143

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.02511398 0.04020425 0.05800778
2 ldh.halfTRUE 0.63496647 1.35138185 2.64427456

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ ldh.single + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
604.4	620.3	-299.2	598.4	1477

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.4896	-0.1887	-0.1765	-0.1511	5.9130

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.548	1.244

Number of obs: 1480, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.2345	0.2117	-15.28	<2e-16 ***
ldh.singleTRUE	0.3439	0.3274	1.05	0.293

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ldh.sngTRUE -0.223

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.0244478	0.03938016	0.05722331
2	ldh.singleTRUE	0.7163373	1.41041243	2.61069166

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ ldh.double + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
605.2	621.1	-299.6	599.2	1477

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5162	-0.1860	-0.1747	-0.1510	5.8771

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.622	1.274

Number of obs: 1480, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.2016	0.2095	-15.284	<2e-16 ***
ldh.doubleTRUE	0.3164	0.6797	0.466	0.642

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ldh.dblTRUE -0.100

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02525972	0.04069572	0.05873675
2	ldh.doubleTRUE	0.29364548	1.37224416	4.59974023

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ ldh.triple + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
605.2	621.1	-299.6	599.2	1477

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5219	-0.1869	-0.1753	-0.1512	5.8686

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.65	1.285

Number of obs: 1480, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.1873	0.2089	-15.255	<2e-16 ***
ldh.tripleTRUE	-0.4347	1.0940	-0.397	0.691

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ldh.trpTRUE -0.058

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02564388	0.041284	0.05952307
2	ldh.tripleTRUE	0.03320664	0.647436	3.75796104

- [CRP]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.high + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
602.9	618.9	-298.5	596.9	1487

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.4681	-0.2088	-0.1750	-0.1499	5.5286

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.377	1.173

Number of obs: 1490, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.2820	0.2101	-15.623	<2e-16 ***
crp.highTRUE	0.5427	0.2833	1.915	0.0554 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
crp.hghTRUE -0.276

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02352019	0.03755491	0.0545046
2	crp.highTRUE	0.96687108	1.72056605	2.9527540

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.half + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
605.9	621.8	-299.9	599.9	1487

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5184	-0.1886	-0.1716	-0.1510	5.8749

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.61	1.269

Number of obs: 1490, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.1704	0.2094	-15.142	<2e-16 ***
crp.halfTRUE	-0.3749	0.5494	-0.682	0.495

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
crp.hlfTRUE -0.150

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02611965	0.04198478	0.06063295
2	crp.halfTRUE	0.19820995	0.68735784	1.81354127

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.single + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
606.3	622.3	-300.2	600.3	1487

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5145	-0.1860	-0.1748	-0.1525	5.9291

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.611 1.269
 Number of obs: 1490, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.20234	0.20923	-15.305	<2e-16 ***
crp.singleTRUE	0.08637	0.42000	0.206	0.837

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 crp.sngTRUE -0.143

— Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02532653	0.04066687	0.05876484
2	crp.singleTRUE	0.44474395	1.09021250	2.35550856

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ crp.double + (1 | pid)
 Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	606.3	622.2	-300.1	600.3	1487

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-0.5195	-0.1867	-0.1720	-0.1516	5.9074

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.636 1.279
 Number of obs: 1490, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.1909	0.2083	-15.317	<2e-16 ***
crp.doubleTRUE	-0.1886	0.6488	-0.291	0.771

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 crp.dblTRUE -0.083

— Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02562998	0.04113527	0.05929291
2	crp.doubleTRUE	0.18554849	0.82815539	2.56959330

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ crp.triple + (1 | pid)
 Data: final.data

	AIC	BIC	logLik	deviance	df.resid
	593.3	609.2	-293.7	587.3	1487

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-0.5253	-0.1834	-0.1694	-0.1492	5.4522

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 1.254 1.12
 Number of obs: 1490, groups: pid, 254

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.3401	0.2114	-15.802	< 2e-16 ***
crp.tripleTRUE	1.1693	0.3025	3.865	0.000111 ***

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
 (Intr)
 crp.trpTRUE -0.310

— Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.02208131	0.03543308	0.05136279
2	crp.tripleTRUE	1.74515840	3.21967067	5.75112579

Baseline only

any AE

— [REC]

```
glm(formula = ae.any ~ rec.weide, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

Deviance Residuals:

	Min	1Q	Median	3Q	Max
	-0.9214	-0.9214	-0.8035	1.4571	1.6049

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.9651	0.2399	-4.023	5.74e-05 ***
rec.weideTRUE	0.3280	0.2921	1.123	0.261

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
 Residual deviance: 307.56 on 244 degrees of freedom
 (8 observations deleted due to missingness)
 AIC: 311.56

Number of Fisher Scoring iterations: 4

— Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.2335978	0.3809524	0.6009538
2	rec.weideTRUE	0.7890947	1.3882212	2.4889173

```
glm(formula = ae.any ~ rec.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

Deviance Residuals:

	Min	1Q	Median	3Q	Max
	-1.1774	-0.8701	-0.8701	1.5197	1.5197

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.7763	0.1395	-5.563	2.64e-08 ***
rec.highTRUE	0.7763	0.7207	1.077	0.281

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
 Residual deviance: 307.71 on 244 degrees of freedom
 (8 observations deleted due to missingness)
 AIC: 311.71

Number of Fisher Scoring iterations: 4

— Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.3482604	0.4601227	0.6023194
2	rec.highTRUE	0.5017991	2.1733333	9.4154914

```
glm(formula = ae.any ~ rec.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

Deviance Residuals:

	Min	1Q	Median	3Q	Max
	-1.0842	-0.8216	-0.8216	1.2735	1.5812

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.9126	0.1596	-5.717	1.08e-08 ***
rec.halfTRUE	0.6895	0.3170	2.175	0.0296 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
 Residual deviance: 304.19 on 244 degrees of freedom
 (8 observations deleted due to missingness)

AIC: 308.19

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.291363 0.4014599 0.5454756
2 rec.halfTRUE 1.065709 1.9927273 3.7090709

```

```

glm(formula = ae.any ~ rec.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.3018  -0.8679  -0.8679   1.5225   1.5225

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7824    0.1394  -5.613 1.99e-08 ***
rec.singleTRUE  1.0701    0.7764   1.378   0.168
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 306.93 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 310.93

```

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.3462199 0.4573171 0.5984744
2 rec.singleTRUE 0.6279874 2.9155556 15.1080228

```

```

glm(formula = ae.any ~ rec.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.8823  -0.8823  -0.8823   1.5045   1.5045

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7425    0.1367  -5.433 5.56e-08 ***
rec.doubleTRUE -13.8235   882.7434  -0.016   0.988
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 308.06 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 312.06

```

Number of Fisher Scoring iterations: 13

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.364059 4.759036e-01 0.6221086
2 rec.doubleTRUE 0.000000 9.920148e-07      Inf

```

```

glm(formula = ae.any ~ rec.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.8802  -0.8802  -0.8802   1.5072   1.5072

```

```

Coefficients: (1 not defined because of singularities)
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7485    0.1366  -5.482 4.21e-08 ***
rec.tripleTRUE    NA         NA      NA      NA
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 308.84 on 245 degrees of freedom

```

(8 observations deleted due to missingness)
AIC: 310.84

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) NA NA NA

```

- [AEC]

```

glm(formula = ae.any ~ aec.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.6651  -0.8683  -0.8683   1.5220   1.5220

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7813    0.1385  -5.641 1.69e-08 ***
aec.highTRUE  1.8799    1.1630   1.616   0.106
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 305.69 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 309.69

```

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.3472440 0.4578313 0.5981306
2 aec.highTRUE 0.8240066 6.5526316 133.6482625

```

```

glm(formula = ae.any ~ aec.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.0108  -0.8618  -0.8618   1.5301   1.5301

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7993    0.1471  -5.434 5.52e-08 ***
aec.halfTRUE   0.3938    0.4007   0.983   0.326
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 307.90 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 311.9

```

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.3350900 0.4496644 0.5970789
2 aec.halfTRUE 0.6614098 1.4825871 3.2249764

```

```

glm(formula = ae.any ~ aec.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.8661  -0.8661  -0.8661   1.5247   1.5247

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7873    0.1384  -5.690 1.27e-08 ***
aec.singleTRUE 16.3533   840.2742   0.019   0.984
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 301.95 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 305.95

Number of Fisher Scoring iterations: 14

```

- Odds Ratios
  row.labels    or.l      or      or.u
1 (Intercept)  0.3469886 4.550898e-01 0.596869
2 aec.singleTRUE 0.0000000 1.265204e+07      Inf

```

```

glm(formula = ae.any ~ aec.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.8823	-0.8823	-0.8823	1.5045	1.5045

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.7425	0.1367	-5.433	5.56e-08 ***
aec.doubleTRUE	-13.8235	882.7434	-0.016	0.988

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 308.06 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 312.06

Number of Fisher Scoring iterations: 13

```

- Odds Ratios
  row.labels    or.l      or      or.u
1 (Intercept)  0.364059 4.759036e-01 0.6221086
2 aec.doubleTRUE 0.0000000 9.920148e-07      Inf

```

```

glm(formula = ae.any ~ aec.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.8802	-0.8802	-0.8802	1.5072	1.5072

Coefficients: (1 not defined because of singularities)

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.7485	0.1366	-5.482	4.21e-08 ***
aec.tripleTRUE	NA	NA	NA	NA

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 308.84 on 245 degrees of freedom
(8 observations deleted due to missingness)
AIC: 310.84

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) NA NA NA

```

- [LC]

```

glm(formula = ae.any ~ lc.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.8908	-0.8908	-0.8908	1.4941	1.7011

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.7195	0.1408	-5.11	3.23e-07 ***
lc.highTRUE	-0.4592	0.5889	-0.78	0.436

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 308.19 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 312.19

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels    or.l      or      or.u
1 (Intercept)  0.3677714 0.4870130 0.6392734
2 lc.highTRUE  0.1733816 0.6317949 1.8549865

```

```

glm(formula = ae.any ~ lc.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.8880	-0.8757	-0.8757	1.4976	1.5128

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.72705	0.22616	-3.215	0.00131 **
lc.halfTRUE	-0.03376	0.28372	-0.119	0.90529

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 308.83 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 312.83

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels    or.l      or      or.u
1 (Intercept)  0.3061475 0.4833333 0.7457544
2 lc.halfTRUE  0.5563112 0.9668063 1.6965108

```

```

glm(formula = ae.any ~ lc.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.8884	-0.8884	-0.8884	1.4971	1.6651

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.7259	0.1407	-5.161	2.46e-07 ***
lc.singleTRUE	-0.3727	0.5942	-0.627	0.531

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 308.84 on 245 degrees of freedom
Residual deviance: 308.43 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 312.43

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels    or.l      or      or.u
1 (Intercept)  0.3654959 0.4838710 0.634946
2 lc.singleTRUE 0.1876695 0.6888889 2.052981

```

```

glm(formula = ae.any ~ lc.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.8802	-0.8802	-0.8802	1.5072	1.5072

Coefficients: (1 not defined because of singularities)

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.7485	0.1366	-5.482	4.21e-08 ***
lc.doubleTRUE	NA	NA	NA	NA

```

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 308.84  on 245  degrees of freedom
Residual deviance: 308.84  on 245  degrees of freedom
(8 observations deleted due to missingness)
AIC: 310.84

Number of Fisher Scoring iterations: 4

- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) NA NA NA

glm(formula = ae.any ~ lc.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.8823 -0.8823 -0.8823  1.5045  1.5045

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7425     0.1367  -5.433 5.56e-08 ***
lc.tripleTRUE -13.8235    882.7434  -0.016  0.988
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 308.84  on 245  degrees of freedom
Residual deviance: 308.06  on 244  degrees of freedom
(8 observations deleted due to missingness)
AIC: 312.06

Number of Fisher Scoring iterations: 13

- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.364059 4.759036e-01 0.6221086
2 lc.tripleTRUE 0.000000 9.920148e-07 Inf

- [LDH]

glm(formula = ae.any ~ ldh.weide, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.8814 -0.8814 -0.8814  1.5057  1.7552

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7451     0.1402  -5.314 1.07e-07 ***
ldh.weideTRUE -0.5542     0.6663  -0.832  0.406
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 308.09  on 246  degrees of freedom
Residual deviance: 307.33  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 311.33

Number of Fisher Scoring iterations: 4

- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.3588357 0.4746835 0.6223068
2 ldh.weideTRUE 0.1272056 0.5745455 1.9042479

glm(formula = ae.any ~ ldh.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.9311 -0.9311 -0.7842  1.4456  1.6304

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.6115     0.1739  -3.516 0.000438 ***
ldh.highTRUE  -0.4102     0.2839  -1.445 0.148554
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 308.09  on 246  degrees of freedom
Residual deviance: 305.96  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 309.96

Number of Fisher Scoring iterations: 4

- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.3832931 0.5425532 0.7591786
2 ldh.highTRUE 0.3769652 0.6635294 1.1507545

glm(formula = ae.any ~ ldh.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.920 -0.920 -0.804  1.459  1.604

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.9634     0.2183  -4.414 1.01e-05 ***
ldh.halfTRUE   0.3227     0.2807   1.149  0.25
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 308.09  on 246  degrees of freedom
Residual deviance: 306.75  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 310.75

Number of Fisher Scoring iterations: 4

- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.2449493 0.3815789 0.5783222
2 ldh.halfTRUE 0.8000724 1.3807935 2.4111859

glm(formula = ae.any ~ ldh.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.8937 -0.8937 -0.8262  1.4906  1.5753

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7115     0.1662  -4.282 1.85e-05 ***
ldh.singleTRUE -0.1880     0.2936  -0.640  0.522
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 308.09  on 246  degrees of freedom
Residual deviance: 307.67  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 311.67

Number of Fisher Scoring iterations: 4

- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.3520519 0.4909091 0.6762876
2 ldh.singleTRUE 0.4610307 0.8286252 1.4629127

glm(formula = ae.any ~ ldh.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.8791 -0.8791 -0.8791  1.5085  1.7125

Coefficients:

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7514    0.1401  -5.364 8.13e-08 ***
ldh.doubleTRUE -0.4526    0.6730  -0.672  0.501
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 308.09  on 246  degrees of freedom
Residual deviance: 307.60  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 311.6

Number of Fisher Scoring iterations: 4

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.3566694 0.4716981 0.6182043
2 ldh.doubleTRUE 0.1396089 0.6360000 2.1497283

```

```

glm(formula = ae.any ~ ldh.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
      Min       1Q   Median       3Q      Max
-0.8797 -0.8797 -0.8797  1.5079  1.9728

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7499    0.1383  -5.423 5.85e-08 ***
ldh.tripleTRUE -1.0418    1.0889  -0.957  0.339
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

    Null deviance: 308.09  on 246  degrees of freedom
Residual deviance: 306.94  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 310.94

```

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.35850641 0.4723926 0.6170015
2 ldh.tripleTRUE 0.01851142 0.3528139 2.1142924

```

- [CRP]

```

glm(formula = ae.any ~ crp.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
      Min       1Q   Median       3Q      Max
-0.8876 -0.8876 -0.8675  1.4981  1.5230

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -0.72824    0.18789  -3.876 0.000106 ***
crp.highTRUE -0.05529    0.27327  -0.202 0.839653
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

    Null deviance: 309.61  on 246  degrees of freedom
Residual deviance: 309.57  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 313.57

```

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.3310418 0.4827586 0.6929414
2 crp.highTRUE 0.5525209 0.9462081 1.6163878

```

```

glm(formula = ae.any ~ crp.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
      Min       1Q   Median       3Q      Max
-0.8904 -0.8904 -0.8904  1.4946  1.6431

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7205    0.1437  -5.015 5.31e-07 ***
crp.halfTRUE  -0.3293    0.4621  -0.713  0.476
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

    Null deviance: 309.61  on 246  degrees of freedom
Residual deviance: 309.08  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 313.08

```

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.3652281 0.4864865 0.6420923
2 crp.halfTRUE 0.2717868 0.7194444 1.7074737

```

```

glm(formula = ae.any ~ crp.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
      Min       1Q   Median       3Q      Max
-0.9282 -0.8682 -0.8682  1.5221  1.5221

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.7814    0.1498  -5.218 1.81e-07 ***
crp.singleTRUE  0.1624    0.3638   0.446  0.655
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

    Null deviance: 309.61  on 246  degrees of freedom
Residual deviance: 309.42  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 313.42

```

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.3393003 0.4577465 0.610956
2 crp.singleTRUE 0.5642268 1.1763314 2.370775

```

```

glm(formula = ae.any ~ crp.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
      Min       1Q   Median       3Q      Max
-0.903  -0.903  -0.903   1.479   1.948

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -0.6865    0.1406  -4.881 1.05e-06 ***
crp.doubleTRUE -1.0481    0.6418  -1.633  0.102
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

    Null deviance: 309.61  on 246  degrees of freedom
Residual deviance: 306.35  on 245  degrees of freedom
(7 observations deleted due to missingness)
AIC: 310.35

```

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.38027752 0.5033113 0.6605808
2 crp.doubleTRUE 0.08010068 0.3506192 1.0838093

```

```

glm(formula = ae.any ~ crp.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.938 -0.859 -0.859  1.437  1.534

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.8071    0.1579  -5.111 3.2e-07 ***
crp.tripleTRUE  0.2140    0.3144   0.681  0.496
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 309.61 on 246 degrees of freedom
Residual deviance: 309.15 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 313.15

Number of Fisher Scoring iterations: 4

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.3251839 0.4461538 0.6046583
2 crp.tripleTRUE 0.6613345 1.2386570 2.2794593

```

AE with steroid intervention

- [REC]

```

glm(formula = ae.steroid ~ rec.weide, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.5448 -0.5448 -0.4130 -0.4130  2.2378

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.8326    0.3109  -5.894 3.76e-09 ***
rec.weideTRUE  -0.5861    0.4248  -1.380  0.168
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 159.82 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 163.82

Number of Fisher Scoring iterations: 5

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.08267885 0.1600000 0.2828314
2 rec.weideTRUE 0.24076918 0.5565068 1.2947811

glm(formula = ae.steroid ~ rec.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.7585 -0.4508 -0.4508 -0.4508  2.1618

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.2351    0.2194 -10.188 <2e-16 ***
rec.highTRUE   1.1365    0.8455   1.344  0.179
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 160.19 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 164.19

Number of Fisher Scoring iterations: 5

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.06773614 0.1069767 0.1607157

```

```
2 rec.highTRUE 0.43936924 3.1159420 14.4534944
```

```

glm(formula = ae.steroid ~ rec.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.4813 -0.4813 -0.4813 -0.3923  2.2815

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.0971    0.2312  -9.070 <2e-16 ***
rec.halfTRUE  -0.4286    0.5687  -0.754  0.451
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.08 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 165.08

Number of Fisher Scoring iterations: 5

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.07580597 0.1228070 0.1885317
2 rec.halfTRUE 0.18368399 0.6514286 1.8082531

glm(formula = ae.steroid ~ rec.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.8203 -0.4499 -0.4499 -0.4499  2.1638

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.2398    0.2193 -10.21 <2e-16 ***
rec.singleTRUE  1.3235    0.8649   1.53  0.126
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 159.77 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 163.77

Number of Fisher Scoring iterations: 5

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.06742815 0.1064815 0.1599539
2 rec.singleTRUE 0.51793001 3.7565217 18.5451266

glm(formula = ae.steroid ~ rec.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.464 -0.464 -0.464 -0.464  2.137

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.1748    0.2111 -10.304 <2e-16 ***
rec.doubleTRUE -13.3913  1455.3975 -0.009  0.993
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.48 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 165.48

Number of Fisher Scoring iterations: 14

- Odds Ratios
  row.labels      or.l      or      or.u

```



```
1 (Intercept) 0.07513827 1.136364e-01 0.1718595
2 rec.doubleTRUE 0.00000000 1.528358e-06 Inf
```

```
glm(formula = ae.steroid ~ rec.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.463 -0.463 -0.463 -0.463  2.138
```

```
Coefficients: (1 not defined because of singularities)
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    -2.179      0.211  -10.33  <2e-16 ***
rec.tripleTRUE      NA           NA      NA      NA
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(Dispersion parameter for binomial family taken to be 1)
```

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.69 on 245 degrees of freedom
(8 observations deleted due to missingness)
AIC: 163.69
```

```
Number of Fisher Scoring iterations: 4
```

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept)  NA NA  NA
```

- [AEC]

```
glm(formula = ae.steroid ~ aec.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.1774 -0.4469 -0.4469 -0.4469  2.1695
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    -2.2536      0.2192  -10.281  <2e-16 ***
aec.highTRUE    2.2536      1.0237   2.201   0.0277 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(Dispersion parameter for binomial family taken to be 1)
```

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 157.54 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 161.54
```

```
Number of Fisher Scoring iterations: 5
```

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.06652074 0.1050228 0.1577113
2 aec.highTRUE 1.10111327 9.5217391 82.4629942
```

```
glm(formula = ae.steroid ~ aec.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.4745 -0.4745 -0.4745 -0.4745  2.3272
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    -2.1272      0.2206   -9.643  <2e-16 ***
aec.halfTRUE    -0.5119      0.7644   -0.670   0.503
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(Dispersion parameter for binomial family taken to be 1)
```

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.18 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 165.18
```

```
Number of Fisher Scoring iterations: 5
```

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.07530383 0.1191710 0.1795231
2 aec.halfTRUE 0.09303842 0.5993789 2.1822227
```

```
glm(formula = ae.steroid ~ aec.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.482 -0.446 -0.446 -0.446  2.171
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    -2.2581      0.2191  -10.304  <2e-16 ***
aec.singleTRUE  2.9513      1.2442   2.372   0.0177 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(Dispersion parameter for binomial family taken to be 1)
```

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 156.02 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 160.02
```

```
Number of Fisher Scoring iterations: 5
```

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.06622367 0.1045455 0.1569777
2 aec.singleTRUE 1.76842388 19.1304348 421.0954641
```

```
glm(formula = ae.steroid ~ aec.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.464 -0.464 -0.464 -0.464  2.137
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    -2.1748      0.2111  -10.304  <2e-16 ***
aec.doubleTRUE -13.3913    1455.3975  -0.009   0.993
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(Dispersion parameter for binomial family taken to be 1)
```

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.48 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 165.48
```

```
Number of Fisher Scoring iterations: 14
```

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.07513827 1.136364e-01 0.1718595
2 aec.doubleTRUE 0.00000000 1.528358e-06 Inf
```

```
glm(formula = ae.steroid ~ aec.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.463 -0.463 -0.463 -0.463  2.138
```

```
Coefficients: (1 not defined because of singularities)
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    -2.179      0.211  -10.33  <2e-16 ***
aec.tripleTRUE      NA           NA      NA      NA
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
(Dispersion parameter for binomial family taken to be 1)
```

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.69 on 245 degrees of freedom
(8 observations deleted due to missingness)
AIC: 163.69
```

Number of Fisher Scoring iterations: 4

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) NA NA NA
```

- [LC]

```
glm(formula = ae.steroid ~ lc.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.6231 -0.4495 -0.4495 -0.4495  2.1646
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.2417     0.2242   -9.977 <2e-16 ***
lc.highTRUE    0.7012     0.6746    1.040  0.299
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 160.74 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 164.74
```

Number of Fisher Scoring iterations: 5

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.06657043 0.1062802 0.1610324
2 lc.highTRUE 0.44072762 2.0162338 6.7847370
```

AIC: 164.54

Number of Fisher Scoring iterations: 5

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.06625616 0.1057692 0.1602394
2 lc.singleTRUE 0.47439888 2.1818182 7.4237909
```

```
glm(formula = ae.steroid ~ lc.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.463 -0.463 -0.463 -0.463  2.138
```

```
Coefficients: (1 not defined because of singularities)
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.179     0.211   -10.33 <2e-16 ***
lc.doubleTRUE    NA         NA      NA      NA
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.69 on 245 degrees of freedom
(8 observations deleted due to missingness)
AIC: 163.69
```

Number of Fisher Scoring iterations: 4

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) NA NA NA
```

```
glm(formula = ae.steroid ~ lc.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.4788 -0.4788 -0.4788 -0.4340  2.1951
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.3150     0.3706   -6.247 4.19e-10 ***
lc.halfTRUE    0.2066     0.4509    0.458  0.647
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.48 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 165.48
```

Number of Fisher Scoring iterations: 5

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.04396984 0.09876543 0.1916779
2 lc.halfTRUE 0.52210121 1.22946429 3.1294195
```

```
glm(formula = ae.steroid ~ lc.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.464 -0.464 -0.464 -0.464  2.137
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.1748     0.2111   -10.304 <2e-16 ***
lc.tripleTRUE -13.3913  1455.3975   -0.009  0.993
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 161.48 on 244 degrees of freedom
(8 observations deleted due to missingness)
AIC: 165.48
```

Number of Fisher Scoring iterations: 14

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept) 0.07513827 1.136364e-01 0.1718595
2 lc.tripleTRUE 0.00000000 1.528358e-06 Inf
```

- [LDH]

```
glm(formula = ae.steroid ~ lc.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.6444 -0.4484 -0.4484 -0.4484  2.1666
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.2465     0.2242   -10.02 <2e-16 ***
lc.singleTRUE  0.7802     0.6786    1.15  0.25
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 161.69 on 245 degrees of freedom
Residual deviance: 160.54 on 244 degrees of freedom
(8 observations deleted due to missingness)
```

```
glm(formula = ae.steroid ~ ldh.weide, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.5553 -0.4663 -0.4663 -0.4663  2.1321
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.1643     0.2155   -10.042 <2e-16 ***
ldh.weideTRUE  0.3725     0.7936    0.469  0.639
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 166.02 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 170.02

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.07336292 0.1148325 0.1714137
2 ldh.weideTRUE 0.21762589 1.4513889 5.7482684

```

```

glm(formula = ae.steroid ~ ldh.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.5003	-0.5003	-0.4506	-0.4506	2.1623

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.2361	0.2811	-7.954	1.81e-15 ***
ldh.highTRUE	0.2212	0.4165	0.531	0.595

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 165.95 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 169.95

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.05885435 0.1068702 0.1787149
2 ldh.highTRUE 0.54330421 1.2476190 2.8267478

```

```

glm(formula = ae.steroid ~ ldh.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.5350	-0.5350	-0.4202	-0.4202	2.2230

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.8718	0.2871	-6.520	7.03e-11 ***
ldh.halfTRUE	0.5108	0.4165	-1.227	0.22

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 164.72 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 168.72

Number of Fisher Scoring iterations: 5

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.08391883 0.1538462 0.2608635
2 ldh.halfTRUE 0.26120945 0.6000000 1.3586065

```

```

glm(formula = ae.steroid ~ ldh.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.5067	-0.5067	-0.4531	-0.4531	2.1574

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.2246	0.2631	-8.454	<2e-16 ***
ldh.singleTRUE	0.2367	0.4277	0.554	0.58

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 165.93 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 169.93

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.06204694 0.1081081 0.1752944
2 ldh.singleTRUE 0.53154378 1.2671233 2.8945510

```

```

glm(formula = ae.steroid ~ ldh.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.5780	-0.4652	-0.4652	-0.4652	2.1341

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.1691	0.2155	-10.067	<2e-16 ***
ldh.doubleTRUE	0.4643	0.7983	0.582	0.561

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 165.92 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 169.92

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.07302012 0.1142857 0.1705771
2 ldh.doubleTRUE 0.23718905 1.5909091 6.3899588

```

```

glm(formula = ae.steroid ~ ldh.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.5553	-0.4690	-0.4690	-0.4690	2.1269

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.1518	0.2113	-10.184	<2e-16 ***
ldh.tripleTRUE	0.3600	1.1006	0.327	0.744

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 166.13 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 170.13

Number of Fisher Scoring iterations: 4

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.07498638 0.1162791 0.1722956
2 ldh.tripleTRUE 0.07431049 1.4333333 8.8685231

```

- [CRP]

```

glm(formula = ae.steroid ~ crp.high, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)

```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.5214	-0.5214	-0.4222	-0.4222	2.2190

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.3728	0.3153	-7.527	5.21e-14 ***
crp.highTRUE	0.4461	0.4192	1.064	0.287

```
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 165.08 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 169.08
```

Number of Fisher Scoring iterations: 5

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.04735657 0.09322034 0.1649411
2 crp.highTRUE 0.69084055 1.56222418 3.6351296
```

```
glm(formula = ae.steroid ~ crp.half, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.4807  -0.4807  -0.4807  -0.4807   2.2815
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.1001     0.2163  -9.711  <2e-16 ***
crp.halfTRUE  -0.4257     0.7660  -0.556   0.578
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 165.89 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 169.89
```

Number of Fisher Scoring iterations: 5

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.07813144 0.1224490 0.1830856
2 crp.halfTRUE 0.10122260 0.6533333 2.3891423
```

```
glm(formula = ae.steroid ~ crp.single, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.4741  -0.4741  -0.4741  -0.4666   2.1460
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -2.12931     0.22551  -9.442  <2e-16 ***
crp.singleTRUE -0.06791     0.57323  -0.118   0.906
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 166.21 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 170.21
```

Number of Fisher Scoring iterations: 4

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.07432681 0.1189189 0.1807038
2 crp.singleTRUE 0.26172748 0.9343434 2.6219044
```

```
glm(formula = ae.steroid ~ crp.double, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.4831  -0.4831  -0.4831  -0.4831   2.4478
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.089     0.212  -9.855  <2e-16 ***
crp.doubleTRUE -0.855     1.048  -0.816   0.414
```

```
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 165.38 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 169.38
```

Number of Fisher Scoring iterations: 5

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.07971636 0.1237624 0.1836752
2 crp.doubleTRUE 0.02317875 0.4252632 2.1920864
```

```
glm(formula = ae.steroid ~ crp.triple, family = binomial("logit"),
     data = nb.data, na.action = na.exclude)
```

```
Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.6095  -0.4218  -0.4218  -0.4218   2.2198
```

```
Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -2.3749     0.2614  -9.086  <2e-16 ***
crp.tripleTRUE  0.7857     0.4344   1.809   0.0705 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

(Dispersion parameter for binomial family taken to be 1)

```
Null deviance: 166.23 on 246 degrees of freedom
Residual deviance: 163.14 on 245 degrees of freedom
(7 observations deleted due to missingness)
AIC: 167.14
```

Number of Fisher Scoring iterations: 5

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.05354701 0.09302326 0.1502081
2 crp.tripleTRUE 0.90983009 2.19387755 5.0835785
```

Excluding baseline

any AE

- [REC]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.weide + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
973.1	988.4	-483.5	967.1	1234

Scaled residuals:
Min 1Q Median 3Q Max
-0.6353 -0.3922 -0.3458 -0.3031 3.5179

Random effects:
Groups Name Variance Std.Dev.
pid (Intercept) 0.4926 0.7019
Number of obs: 1237, groups: pid, 234

Fixed effects:
Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.9174 0.1137 -16.856 <2e-16 ***
rec.weideTRUE 0.3244 0.2925 1.109 0.267

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
(Intr)
rec.wedTRUE -0.287

- Odds Ratios
row.labels or.l or or.u
1 (Intercept) 0.1158170 0.1469945 0.182112
2 rec.weideTRUE 0.7599496 1.3831925 2.408167

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.high + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
974.2	989.5	-484.1	968.2	1234

Scaled residuals:
Min 1Q Median 3Q Max
-0.5922 -0.3836 -0.3490 -0.3073 3.5265

Random effects:
Groups Name Variance Std.Dev.
pid (Intercept) 0.495 0.7036
Number of obs: 1237, groups: pid, 234

Fixed effects:
Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.8903 0.1107 -17.076 <2e-16 ***
rec.highTRUE 0.1125 0.3812 0.295 0.768

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
(Intr)
rec.hghTRUE -0.181

- Odds Ratios
row.labels or.l or or.u
1 (Intercept) 0.1198085 0.1510293 0.1861497
2 rec.highTRUE 0.5021812 1.1191202 2.2684540

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.half + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
972.4	987.8	-483.2	966.4	1234

Scaled residuals:
Min 1Q Median 3Q Max
-0.6818 -0.3907 -0.3470 -0.3041 3.5375

Random effects:
Groups Name Variance Std.Dev.

pid (Intercept) 0.4726 0.6875
Number of obs: 1237, groups: pid, 234

Fixed effects:
Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.9246 0.1129 -17.050 <2e-16 ***
rec.halfTRUE 0.3820 0.2754 1.387 0.165

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
(Intr)
rec.hlfTRUE -0.287

- Odds Ratios
row.labels or.l or or.u
1 (Intercept) 0.1152617 0.1459411 0.1806312
2 rec.halfTRUE 0.8353044 1.4651607 2.4710755

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.single + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
974.2	989.6	-484.1	968.2	1234

Scaled residuals:
Min 1Q Median 3Q Max
-0.5950 -0.3840 -0.3492 -0.3071 3.5122

Random effects:
Groups Name Variance Std.Dev.
pid (Intercept) 0.5009 0.7077
Number of obs: 1237, groups: pid, 234

Fixed effects:
Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.88647 0.11075 -17.03 <2e-16 ***
rec.singleTRUE 0.03977 0.39758 0.10 0.92

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
(Intr)
rc.snglTRUE -0.172

- Odds Ratios
row.labels or.l or or.u
1 (Intercept) 0.1202383 0.1516056 0.1868685
2 rec.singleTRUE 0.4489133 1.0405752 2.1674295

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.double + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
973.9	989.2	-483.9	967.9	1234

Scaled residuals:
Min 1Q Median 3Q Max
-0.6999 -0.3837 -0.3482 -0.3075 3.4995

Random effects:
Groups Name Variance Std.Dev.
pid (Intercept) 0.4946 0.7033
Number of obs: 1237, groups: pid, 234

Fixed effects:
Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.8890 0.1092 -17.306 <2e-16 ***
rec.doubleTRUE 0.5643 0.8793 0.642 0.521

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
(Intr)
rec.dblTRUE -0.076

- Odds Ratios
row.labels or.l or or.u
1 (Intercept) 0.1202414 0.1512247 0.1857262
2 rec.doubleTRUE 0.2342216 1.7581485 8.6403604

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ rec.triple + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
974.2	989.6	-484.1	968.2	1234

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5970	-0.3840	-0.3487	-0.3065	3.5081

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5067	0.7118

Number of obs: 1237, groups: pid, 234

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.8862	0.1097	-17.201	<2e-16 ***
rec.tripleTRUE	0.2365	1.1397	0.207	0.836

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
rc.trplTRUE -0.077

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.12039599	0.1516469	0.1863496
2 rec.tripleTRUE	0.06321155	1.2667704	8.7515097

- [AEC]

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.high + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
970.9	986.2	-482.4	964.9	1234

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.7158	-0.3874	-0.3470	-0.3080	3.6334

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4551	0.6746

Number of obs: 1237, groups: pid, 234

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.9213	0.1099	-17.483	<2e-16 ***
aec.highTRUE	0.6837	0.3545	1.929	0.0538 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
aec.hghTRUE -0.214

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1163507	0.1464234	0.1801893
2 aec.highTRUE	0.9543985	1.9811116	3.8736151

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.half + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
974.2	989.6	-484.1	968.2	1234

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5981	-0.3782	-0.3496	-0.3070	3.5022

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.5071	0.7121

Number of obs: 1237, groups: pid, 234

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.88132	0.11236	-16.743	<2e-16 ***
aec.halfTRUE	-0.03875	0.30926	-0.125	0.9

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
aec.hlfTRUE -0.230

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1205142	0.1523887	0.1884738
2 aec.halfTRUE	0.5066601	0.9619949	1.7154024

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.single + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
971.7	987.1	-482.9	965.7	1234

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.7073	-0.3812	-0.3467	-0.3067	3.6352

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.475	0.6892

Number of obs: 1237, groups: pid, 234

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.9147	0.1104	-17.345	<2e-16 ***
aec.singleTRUE	0.6303	0.3802	1.658	0.0973 .

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ac.snglTRUE -0.200

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1169549	0.1473911	0.1814838
2 aec.singleTRUE	0.8546710	1.8780947	3.8469075

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.double + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
972.3	987.6	-483.1	966.3	1234

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.9122	-0.3831	-0.3445	-0.3076	3.4967

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4859	0.6971

Number of obs: 1237, groups: pid, 234

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.8958	0.1090	-17.389	<2e-16 ***
aec.doubleTRUE	1.1616	0.7787	1.492	0.136

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
aec.dblTRUE -0.096

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.1194530	0.1501974	0.1844204
2 aec.doubleTRUE	0.5986886	3.1951390	14.0094190

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ aec.triple + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
973.5	988.9	-483.8	967.5	1234

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5951	-0.3845	-0.3501	-0.3079	3.4978

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4986	0.7061

Number of obs: 1237, groups: pid, 234

Fixed effects:

```

      Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.881e+00 1.058e-01 -17.79 <2e-16 ***
aec.tripleTRUE -2.431e+01 3.136e+05 0.00 1
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
ac.trplTRUE 0.000
convergence code: 0
unable to evaluate scaled gradient
Hessian is numerically singular: parameters are not
uniquely determined

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.1238272 1.523552e-01 0.1874557
2 aec.tripleTRUE 0.0000000 2.760653e-11      Inf

- [LC]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ lc.high + (1 | pid)
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
974.2    989.6   -484.1    968.2    1234

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.5993 -0.3781 -0.3493 -0.3066  3.5082

Random effects:
      Groups Name      Variance Std.Dev.
pid (Intercept) 0.5107  0.7146
Number of obs: 1237, groups: pid, 234

Fixed effects:
      Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.88142 0.11060 -17.012 <2e-16 ***
lc.highTRUE -0.09467 0.48301 -0.196 0.845
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.snglTRUE -0.142

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.1208678 0.1523743 0.1877609
2 lc.singleTRUE 0.3205346 0.9096716 2.1886435

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ lc.double + (1 | pid)
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
973.6    989.0   -483.8    967.6    1234

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.6029 -0.3772 -0.3481 -0.3050  3.5211

Random effects:
      Groups Name      Variance Std.Dev.
pid (Intercept) 0.5234  0.7234
Number of obs: 1237, groups: pid, 234

Fixed effects:
      Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.885e+00 1.066e-01 -17.68 <2e-16 ***
lc.doubleTRUE -2.803e+01 2.111e+06 0.00 1
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.doblTRUE 0.000
convergence code: 0
unable to evaluate scaled gradient
Hessian is numerically singular: parameters are not
uniquely determined

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.1232618 1.518988e-01 0.1871889
2 lc.doubleTRUE 0.0000000 6.739625e-13      Inf

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ lc.triple + (1 | pid)
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
972.3    982.5   -484.1    968.3    1235

Scaled residuals:
      Min       1Q   Median       3Q      Max
-0.5963 -0.3841 -0.3493 -0.3070  3.5044

Random effects:
      Groups Name      Variance Std.Dev.
pid (Intercept) 0.5037  0.7097
Number of obs: 1237, groups: pid, 234

Fixed effects:
      Estimate Std. Error z value Pr(>|z|)
(Intercept) -1.8846 0.1092 -17.26 <2e-16 ***
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
fit warnings:

```

fixed-effect model matrix is rank deficient so dropping 1 column / coefficient

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept)  NA NA  NA
```

- [LDH]

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.weide + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
964.9	980.3	-479.5	958.9	1230

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5880	-0.3786	-0.3463	-0.3012	3.6119

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4784	0.6916

Number of obs: 1233, groups: pid, 236

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.8824	0.1091	-17.257	<2e-16 ***
ldh.weideTRUE	-1.1303	1.0545	-1.072	0.284

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ldh.wedTRUE -0.081

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.1209354 0.1522187 0.1868964
2 ldh.weideTRUE 0.01748508 0.3229294 1.6960268
```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.high + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
966.4	981.8	-480.2	960.4	1230

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5813	-0.3812	-0.3494	-0.3079	3.4678

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4725	0.6874

Number of obs: 1233, groups: pid, 236

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.90579	0.11281	-16.894	<2e-16 ***
ldh.highTRUE	0.07857	0.29901	0.263	0.793

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ldh.hghTRUE -0.267

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.1173320 0.1487054 0.183864
2 ldh.highTRUE 0.5834795 1.0817415 1.897865
```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.half + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
964.5	974.7	-480.2	960.5	1231

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5836	-0.3765	-0.3492	-0.3085	3.4622

Random effects:

Groups Name	Variance	Std.Dev.
-------------	----------	----------

pid (Intercept) 0.4746 0.6889
Number of obs: 1233, groups: pid, 236

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.8981	0.1088	-17.45	<2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

fit warnings:
fixed-effect model matrix is rank deficient so dropping 1 column / coefficient

```
- Odds Ratios
  row.labels or.l or or.u
1 (Intercept)  NA NA  NA
```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.single + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
966.3	981.7	-480.2	960.3	1230

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5803	-0.3805	-0.3487	-0.3076	3.4703

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4715	0.6866

Number of obs: 1233, groups: pid, 236

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.9092	0.1127	-16.937	<2e-16 ***
ldh.singleTRUE	0.1159	0.2997	0.387	0.699

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ldh.sngTRUE -0.265

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.1169494 0.1481974 0.1832007
2 ldh.singleTRUE 0.6049772 1.1228773 1.9730756
```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.double + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
966.5	981.8	-480.2	960.5	1230

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5843	-0.3767	-0.3493	-0.3086	3.4623

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4759	0.6899

Number of obs: 1233, groups: pid, 236

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.89664	0.10970	-17.290	<2e-16 ***
ldh.doubleTRUE	-0.06692	0.66143	-0.101	0.919

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ldh.dblTRUE -0.127

```
- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.1191008 0.1500722 0.1844223
2 ldh.doubleTRUE 0.2071825 0.9352665 3.0162378
```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.triple + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
965.5	980.8	-479.7	959.5	1230


```

Scaled residuals:
  Min       1Q   Median       3Q      Max
-0.5871 -0.3779 -0.3506 -0.3008  3.5032

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.4782  0.6915
Number of obs: 1233, groups: pid, 236

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.8869    0.1091  -17.293  <2e-16 ***
ldh.tripleTRUE -0.9438    1.0653   -0.886    0.376
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
              (Intr)
ldh.trpTRUE -0.077

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1204321 0.1515475 0.1860456
2 ldh.tripleTRUE 0.0208396 0.3891458 2.1097172

- [CRP]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.high + (1 | pid)
Data: excl.b.data

              AIC      BIC    logLik deviance df.resid
          972.5    987.9   -483.3    966.5     1240

Scaled residuals:
  Min       1Q   Median       3Q      Max
-0.5895 -0.3705 -0.3438 -0.3043  3.7410

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.4845  0.696
Number of obs: 1243, groups: pid, 237

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.8856    0.1136  -16.600  <2e-16 ***
crp.highTRUE  -0.1476    0.2854   -0.517    0.605
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
              (Intr)
crp.hghTRUE -0.278

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1195293 0.1517359 0.1878727
2 crp.highTRUE 0.4784084 0.8627435 1.4745599

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.half + (1 | pid)
Data: excl.b.data

              AIC      BIC    logLik deviance df.resid
          972.4    987.8   -483.2    966.4     1240

Scaled residuals:
  Min       1Q   Median       3Q      Max
-0.6373 -0.3809 -0.3460 -0.3058  3.5132

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.4813  0.6938
Number of obs: 1243, groups: pid, 237

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.9169    0.1117  -17.167  <2e-16 ***
crp.halfTRUE   0.2080    0.3306    0.629    0.529
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
              (Intr)
crp.hlfTRUE -0.216

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1195293 0.1517359 0.1878727
2 crp.halfTRUE 0.4784084 0.8627435 1.4745599

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.single + (1 | pid)
Data: excl.b.data

              AIC      BIC    logLik deviance df.resid
          971.9    987.3   -483.0    965.9     1240

Scaled residuals:
  Min       1Q   Median       3Q      Max
-0.5880 -0.3721 -0.3466 -0.3027  3.6829

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.477  0.6907
Number of obs: 1243, groups: pid, 237

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.8803    0.1110  -16.937  <2e-16 ***
crp.singleTRUE -0.3547    0.3956   -0.897    0.37
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
              (Intr)
crp.sngTRUE -0.197

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1207292 0.1525469 0.1878723
2 crp.singleTRUE 0.3000765 0.7014065 1.4433914

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.double + (1 | pid)
Data: excl.b.data

              AIC      BIC    logLik deviance df.resid
          970.0    985.4   -482.0    964.0     1240

Scaled residuals:
  Min       1Q   Median       3Q      Max
-0.7657 -0.3745 -0.3461 -0.3063  3.5240

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.4615  0.6793
Number of obs: 1243, groups: pid, 237

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.9313    0.1103  -17.503  <2e-16 ***
crp.doubleTRUE  0.7350    0.4203    1.749    0.0803 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
              (Intr)
crp.dblTRUE -0.186

- Odds Ratios
 row.labels      or.l      or      or.u
1 (Intercept) 0.1148560 0.1449535 0.1782853
2 crp.doubleTRUE 0.8698594 2.0854101 4.6040794

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.triple + (1 | pid)
Data: excl.b.data

              AIC      BIC    logLik deviance df.resid
          969.7    985.1   -481.9    963.7     1240

Scaled residuals:
  Min       1Q   Median       3Q      Max
-0.5659 -0.3862 -0.3456 -0.3049  3.5827

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 0.4513  0.6718
Number of obs: 1243, groups: pid, 237

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -1.9529    0.1130  -17.279  <2e-16 ***
crp.tripleTRUE  0.5245    0.2899    1.809    0.0704 .

```

```

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '
' 1
Correlation of Fixed Effects:
(Intr)
crp.trpTRUE -0.288

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.1118163 0.1418565 0.1753762
2 crp.tripleTRUE 0.9347769 1.6896393 2.9317338

```

AE with steroid intervention

- [REC]

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ rec.weide + (1 | pid)
Data: excl.b.data

```

	AIC	BIC	logLik	deviance	df.resid
	428.9	444.3	-211.4	422.9	1234

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.5244 -0.1387 -0.1266 -0.1091  6.5547

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 3.192    1.787
Number of obs: 1237, groups: pid, 234

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.8303    0.3933   -9.738  <2e-16 ***
rec.weideTRUE  0.4941    0.7934    1.031    0.303
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '
' 1

```

```

Correlation of Fixed Effects:
(Intr)
rec.wedTRUE -0.073

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.002048941 0.02170211 0.03984618
2 rec.weideTRUE 0.583341614 1.63900714 3.98029954

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ rec.high + (1 | pid)
Data: excl.b.data

```

	AIC	BIC	logLik	deviance	df.resid
	428.6	444.0	-211.3	422.6	1234

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.5450 -0.1319 -0.1153 -0.1025  6.7084

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 4.034    2.009
Number of obs: 1237, groups: pid, 234

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.8849    0.5120   -7.588 3.25e-14 ***
rec.highTRUE  -0.8877    0.8687   -1.022    0.307
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '
' 1

```

```

Correlation of Fixed Effects:
(Intr)
rec.hghTRUE 0.185

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.0007038044 0.02055057 0.04079227
2 rec.highTRUE 0.0208465776 0.41159545 1.76368788

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ rec.half + (1 | pid)

```

Data: excl.b.data

	AIC	BIC	logLik	deviance	df.resid
	429.9	445.2	-211.9	423.9	1234

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.4635 -0.1379 -0.1228 -0.1071  6.5530

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 3.506    1.872
Number of obs: 1237, groups: pid, 234

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.83083    0.42561   -9.001  <2e-16 ***
rec.halfTRUE    0.01758    0.54002    0.033    0.974
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '
' 1

```

```

Correlation of Fixed Effects:
(Intr)
rec.hlfTRUE 0.011

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.0007166873 0.02169154 0.04079983
2 rec.halfTRUE 0.2327076704 1.01774047 2.69127775

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ rec.single + (1 | pid)
Data: excl.b.data

```

	AIC	BIC	logLik	deviance	df.resid
	428.7	444.1	-211.4	422.7	1234

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.5433 -0.1317 -0.1148 -0.1024  6.6214

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 4.036    2.009
Number of obs: 1237, groups: pid, 234

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.8876    0.5128   -7.581 3.43e-14 ***
rec.singleTRUE -0.8598    0.8744   -0.983    0.325
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '
' 1

```

```

Correlation of Fixed Effects:
(Intr)
rc.snglTRUE 0.193

```

```

- Odds Ratios
  row.labels      or.l      or      or.u
1 (Intercept) 0.0006978931 0.02049388 0.04069074
2 rec.singleTRUE 0.0206596231 0.42326361 1.83199186

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ rec.double + (1 | pid)
Data: excl.b.data

```

	AIC	BIC	logLik	deviance	df.resid
	426.9	442.2	-210.4	420.9	1234

```

Scaled residuals:
  Min      1Q  Median      3Q      Max
-0.4661 -0.1380 -0.1232 -0.1078  6.5554

```

```

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 3.365    1.834
Number of obs: 1237, groups: pid, 234

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.8351    0.4078   -9.404  <2e-16 ***
rec.doubleTRUE  2.1173    1.1313    1.872    0.0613 .
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '
' 1

```

```

Correlation of Fixed Effects:
(Intr)
rec.dblTRUE -0.127

```

```

- Odds Ratios

```

```

      row.labels      or.l      or      or.u
1 (Intercept) 0.001956498 0.02159884 0.04007065
2 rec.doubleTRUE 0.729689484 8.30830372 77.81586194

```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ rec.triple + (1 | pid)
 Data: excl.b.data

```

      AIC      BIC      logLik deviance df.resid
429.4      444.8      -211.7      423.4      1234

```

Scaled residuals:

```

      Min      1Q  Median      3Q      Max
-0.4589 -0.1390 -0.1237 -0.1079  6.5389

```

Random effects:

```

Groups Name      Variance Std.Dev.
pid (Intercept) 3.462      1.861
Number of obs: 1237, groups: pid, 234

```

Fixed effects:

```

      Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.816e+00  2.359e-01 -16.18 <2e-16 ***
rec.tripleTRUE -3.612e+01  2.536e+07   0.00  1

```

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

```

      (Intr)
rc.trplTRUE 0.000
convergence code: 0
unable to evaluate scaled gradient
Hessian is numerically singular: parameters are not
uniquely determined

```

- Odds Ratios

```

      row.labels      or.l      or      or.u
1 (Intercept) 0.01387396 2.202758e-02 0.034973
2 rec.tripleTRUE 0.00000000 2.067288e-16      Inf

```

- [AEC]

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ aec.high + (1 | pid)
 Data: excl.b.data

```

      AIC      BIC      logLik deviance df.resid
429.6      444.9      -211.8      423.6      1234

```

Scaled residuals:

```

      Min      1Q  Median      3Q      Max
-0.5066 -0.1319 -0.1169 -0.1041  6.4319

```

Random effects:

```

Groups Name      Variance Std.Dev.
pid (Intercept) 3.87      1.967
Number of obs: 1237, groups: pid, 234

```

Fixed effects:

```

      Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.8752      0.4880  -7.941  2e-15 ***
aec.highTRUE -0.4067      0.7793  -0.522   0.602

```

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

```

      (Intr)
aec.hghTRUE 0.228

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 1.045895e+05 0.02074926 0.04047793
2 aec.highTRUE 2.561193e-01 0.66583065 2.51962094

```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ aec.half + (1 | pid)
 Data: excl.b.data

```

      AIC      BIC      logLik deviance df.resid
427.4      442.8      -210.7      421.4      1234

```

Scaled residuals:

```

      Min      1Q  Median      3Q      Max
-0.6168 -0.1234 -0.1073 -0.0888  6.5060

```

Random effects:

```

Groups Name      Variance Std.Dev.
pid (Intercept) 4.975      2.23
Number of obs: 1237, groups: pid, 234

```

Fixed effects:

```

      Estimate Std. Error z value Pr(>|z|)
(Intercept) -4.0112      0.8353  -4.802 1.57e-06 ***
aec.halfTRUE -1.1006      0.8742  -1.259   0.208

```

Correlation of Fixed Effects:

```

      (Intr)
aec.hlfTRUE 0.493

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.003523635 0.01811252 0.09310371
2 aec.halfTRUE 0.059970614 0.33268765 1.84558845

```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ aec.single + (1 | pid)
 Data: excl.b.data

```

      AIC      BIC      logLik deviance df.resid
429.7      445.1      -211.9      423.7      1234

```

Scaled residuals:

```

      Min      1Q  Median      3Q      Max
-0.4963 -0.1322 -0.1176 -0.1046  6.4570

```

Random effects:

```

Groups Name      Variance Std.Dev.
pid (Intercept) 3.795      1.948
Number of obs: 1237, groups: pid, 234

```

Fixed effects:

```

      Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.8678      0.4777  -8.097 5.64e-16 ***
aec.singleTRUE -0.3140      0.7921  -0.396   0.692

```

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

```

      (Intr)
ac.snglTRUE 0.236

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 2.951304e+10 0.02090451 0.04048823
2 aec.singleTRUE 2.673216e-02 0.73053025 2.83706016

```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ aec.double + (1 | pid)
 Data: excl.b.data

```

      AIC      BIC      logLik deviance df.resid
428.7      444.1      -211.4      422.7      1234

```

Scaled residuals:

```

      Min      1Q  Median      3Q      Max
-0.4699 -0.1339 -0.1191 -0.1040  6.5891

```

Random effects:

```

Groups Name      Variance Std.Dev.
pid (Intercept) 3.728      1.931
Number of obs: 1237, groups: pid, 234

```

Fixed effects:

```

      Estimate Std. Error z value Pr(>|z|)
(Intercept) -3.8898      0.4632  -8.397 <2e-16 ***
aec.doubleTRUE 1.4740      1.2614   1.168   0.243

```

Correlation of Fixed Effects:

```

      (Intr)
aec.dblTRUE -0.189

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.0004590448 0.02045008 0.03957937
2 aec.doubleTRUE 0.1940957206 4.36652076 60.76882889

```

Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ aec.triple + (1 | pid)

```
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
429.7    445.0   -211.8    423.7    1234

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.4605 -0.1383 -0.1230 -0.1074  6.5458

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 3.499    1.871
Number of obs: 1237, groups: pid, 234

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -3.825e+00  2.366e-01 -16.17  <2e-16 ***
aec.tripleTRUE -3.535e+01  3.875e+07   0.00      1
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
ac.trplTRUE 0.000
convergence code: 0
unable to evaluate scaled gradient
Model failed to converge: degenerate Hessian with 1 negative eigenvalues

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.01371862 2.181268e-02 0.03468227
2 aec.tripleTRUE 0.00000000 4.425988e-16      Inf

- [LC]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.high + (1 | pid)
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
429.7    445.1   -211.8    423.7    1234

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.4898 -0.1345 -0.1195 -0.1061  6.5532

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 3.638    1.907
Number of obs: 1237, groups: pid, 234

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -3.8381    0.4418  -8.688  <2e-16 ***
lc.highTRUE  -0.3551    0.8814  -0.403   0.687
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.highTRUE 0.068

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.0006832067 0.02153393 0.04089018
2 lc.highTRUE 0.0835137885 0.70110422 3.14071083

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.half + (1 | pid)
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
427.4    442.7   -210.7    421.4    1234

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.4783 -0.1382 -0.1189 -0.1030  6.2722

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 3.699    1.923
Number of obs: 1237, groups: pid, 234

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -3.7966    0.4545  -8.354  <2e-16 ***
lc.halfTRUE  -1.1234    0.8121  -1.383   0.167
---
```

```
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.halfTRUE 0.056

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.0004334092 0.02244589 0.04311111
2 lc.halfTRUE 0.0291002849 0.32518010 1.25637078

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.single + (1 | pid)
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
429.7    445.1   -211.8    423.7    1234

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.4898 -0.1345 -0.1195 -0.1061  6.5532

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 3.638    1.907
Number of obs: 1237, groups: pid, 234

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -3.8381    0.4418  -8.688  <2e-16 ***
lc.singleTRUE -0.3551    0.8814  -0.403   0.687
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.snglTRUE 0.068

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.0006832067 0.02153393 0.04089018
2 lc.singleTRUE 0.0835137885 0.70110422 3.14071083

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.double + (1 | pid)
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
429.4    444.8   -211.7    423.4    1234

Scaled residuals:
    Min      1Q  Median      3Q      Max
-0.4684 -0.1363 -0.1211 -0.1056  6.5641

Random effects:
 Groups Name      Variance Std.Dev.
 pid      (Intercept) 3.65    1.911
Number of obs: 1237, groups: pid, 234

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -3.853e+00  2.396e-01 -16.08  <2e-16 ***
lc.doubleTRUE -3.665e+01  6.711e+07   0.00      1
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
lc.doblTRUE 0.000
convergence code: 0
unable to evaluate scaled gradient
Hessian is numerically singular: parameters are not uniquely determined

- Odds Ratios
      row.labels      or.l      or      or.u
1 (Intercept) 0.01326156 2.121145e-02 0.03392705
2 lc.doubleTRUE 0.00000000 1.206625e-16      Inf

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ lc.triple + (1 | pid)
Data: excl.b.data

      AIC      BIC    logLik deviance df.resid
427.9    438.1   -211.9    423.9    1235
```

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.4612 -0.1379 -0.1227 -0.1071 6.5498

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 3.517 1.875
 Number of obs: 1237, groups: pid, 234

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.831 0.427 -8.973 <2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '
 ' 1
 fit warnings:
 fixed-effect model matrix is rank deficient so dropping 1
 column / coefficient

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) NA NA NA

- [LDH]

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ ldh.weide + (1 | pid)
 Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
421.7	437.1	-207.9	415.7	1230

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.4666 -0.1362 -0.1211 -0.1056 6.5047

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 3.628 1.905
 Number of obs: 1233, groups: pid, 236

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.855e+00 2.414e-01 -15.97 <2e-16 ***
 ldh.weideTRUE -3.848e+01 1.540e+07 0.00 1

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '
 ' 1

Correlation of Fixed Effects:
 (Intr)
 ldh.wedTRUE 0.000
 convergence code: 0
 unable to evaluate scaled gradient
 Hessian is numerically singular: parameters are not
 uniquely determined

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.01319355 2.117684e-02 0.03399075
 2 ldh.weideTRUE 0.00000000 1.933779e-17 Inf

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ ldh.high + (1 | pid)
 Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
423.5	438.9	-208.8	417.5	1230

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.4734 -0.1292 -0.1181 -0.1031 6.5386

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 3.777 1.943
 Number of obs: 1233, groups: pid, 236

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.90984 0.48426 -8.074 6.81e-16 ***
 ldh.highTRUE -0.03673 0.54714 -0.067 0.946

 Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '
 ' 1

Correlation of Fixed Effects:
 (Intr)
 ldh.hghTRUE -0.100

- Odds Ratios
 row.labels or.l or or.u

1 (Intercept) 0.0003809718 0.02004378 0.03958038
 2 ldh.highTRUE 0.2920060040 0.96393425 2.59633157

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ ldh.half + (1 | pid)
 Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
421.5	431.7	-208.8	417.5	1231

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.4707 -0.1289 -0.1179 -0.1030 6.5433

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 3.775 1.943
 Number of obs: 1233, groups: pid, 236

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.9132 0.4818 -8.122 4.59e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '
 ' 1
 fit warnings:
 fixed-effect model matrix is rank deficient so dropping 1
 column / coefficient

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) NA NA NA

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ ldh.single + (1 | pid)
 Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
423.5	438.9	-208.8	417.5	1230

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.4711 -0.1289 -0.1179 -0.1030 6.5426

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 3.775 1.943
 Number of obs: 1233, groups: pid, 236

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.912766 0.484149 -8.082 6.38e-16 ***
 ldh.singleTRUE -0.005336 0.548525 -0.010 0.992

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '
 ' 1

Correlation of Fixed Effects:
 (Intr)
 ldh.sngTRUE -0.098

- Odds Ratios
 row.labels or.l or or.u
 1 (Intercept) 0.0003809361 0.01998515 0.03945898
 2 ldh.singleTRUE 0.3004565143 0.99467843 2.69148208

Generalized linear mixed model fit by maximum likelihood
 (Laplace Approximation) ['glmerMod']
 Family: binomial (logit)
 Formula: ae.steroid ~ ldh.double + (1 | pid)
 Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
423.5	438.8	-208.7	417.5	1230

Scaled residuals:
 Min 1Q Median 3Q Max
 -0.4716 -0.1295 -0.1180 -0.1032 6.5409

Random effects:
 Groups Name Variance Std.Dev.
 pid (Intercept) 3.785 1.945
 Number of obs: 1233, groups: pid, 236

Fixed effects:
 Estimate Std. Error z value Pr(>|z|)
 (Intercept) -3.9104 0.4826 -8.103 5.34e-16 ***
 ldh.doubleTRUE -0.1616 1.2173 -0.133 0.894

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '
 ' 1

Correlation of Fixed Effects:

(Intr)
ldh.dblTRUE -0.032

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.0003867051	0.02003331	0.03933744
2 ldh.doubleTRUE	0.0326574454	0.85081011	6.32407824

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ ldh.triple + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
422.0	437.4	-208.0	416.0	1230

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.4674	-0.1354	-0.1204	-0.1051	6.5131

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	3.658	1.913

Number of obs: 1233, groups: pid, 236

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.867e+00	2.419e-01	-15.98	<2e-16 ***
ldh.tripleTRUE	-3.801e+01	1.678e+07	0.00	1

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
ldh.trpTRUE 0.000

convergence code: 0

unable to evaluate scaled gradient

Hessian is numerically singular: parameters are not uniquely determined

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.01301774	2.091612e-02	0.03360677
2 ldh.tripleTRUE	0.00000000	3.112462e-17	Inf

- [CRP]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.high + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
423.7	439.1	-208.8	417.7	1240

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5136	-0.1296	-0.1193	-0.1019	5.9175

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	3.792	1.947

Number of obs: 1243, groups: pid, 237

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.9606	0.4903	-8.079	6.55e-16 ***
crp.highTRUE	0.2655	0.4584	0.579	0.563

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
crp.hghTRUE -0.122

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.0003567709	0.01905238	0.03791312
2 crp.highTRUE	0.4923395125	1.30403271	3.05384398

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.half + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
423.1	438.4	-208.5	417.1	1240

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.4883	-0.1286	-0.1136	-0.1001	6.5821

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	4.073	2.018

Number of obs: 1243, groups: pid, 237

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.9387	0.5402	-7.292	3.06e-13 ***
crp.halfTRUE	-0.7591	0.8526	-0.890	0.373

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
crp.hlfTRUE 0.087

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.0002427659	0.01947392	0.03960878
2 crp.halfTRUE	0.0067011752	0.46810026	1.91126856

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.single + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
424.0	439.4	-209.0	418.0	1240

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.4849	-0.1307	-0.1164	-0.1017	6.6302

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	3.854	1.963

Number of obs: 1243, groups: pid, 237

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.93972	0.49579	-7.946	1.92e-15 ***
crp.singleTRUE	0.06663	0.62014	0.107	0.914

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
crp.sngTRUE -0.053

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.0003731992	0.0194537	0.03864051
2 crp.singleTRUE	0.2717626458	1.0688996	3.24918077

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.double + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
424.0	439.4	-209.0	418.0	1240

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.4786	-0.1271	-0.1159	-0.1011	6.6151

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	3.94	1.985

Number of obs: 1243, groups: pid, 237

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.9455	0.5136	-7.682	1.57e-14 ***
crp.doubleTRUE	-0.1476	0.9274	-0.159	0.874

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)
crp.dblTRUE 0.116

- Odds Ratios

row.labels	or.l	or	or.u
1 (Intercept)	0.00000000	0.01934129	0.03862553
2 crp.doubleTRUE	0.01686142	0.86278401	4.13443513

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.triple + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
415.9	431.3	-205.0	409.9	1240

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.7111	-0.1197	-0.1101	-0.0921	5.9482

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	3.857	1.964

Number of obs: 1243, groups: pid, 237

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-4.1366	0.5526	-7.486	7.08e-14 ***
crp.tripleTRUE	1.3427	0.4541	2.957	0.00311 **

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)
crp.trpTRUE	-0.335

- Odds Ratios

	row.labels	or.l	or	or.u
1	(Intercept)	0.005409201	0.01597647	0.04718766
2	crp.tripleTRUE	1.572447598	3.82941509	9.32585606

2. Main analysis

Including Baseline

Incl. Baseline – Any AE

- [incl. baseline – any AE]

- Multicollinearity
VIF

ldh.half	rec.weide	crp.triple	sex	age
1.280694	1.280133	1.004751	1.003851	1.003857

1/VIF

ldh.half	rec.weide	crp.triple	sex	age
0.7808268	0.7811686	0.9952716	0.9961639	0.9961574

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.half + rec.weide + crp.triple + sex
+ (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
1253.9	1285.6	-620.9	1241.9	1456

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.0978	-0.4177	-0.3467	-0.2978	3.6835

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.4043	0.6358

Number of obs: 1462, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.0422	0.1438	-14.198	< 2e-16 ***
ldh.halfTRUE	0.8725	0.2351	3.711	0.000206 ***
rec.weideTRUE	0.4953	0.1971	2.513	0.011965 *
crp.tripleTRUE	0.6789	0.2187	3.104	0.001911 **
sexf	0.1622	0.1785	0.909	0.363355

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

	(Intr)	l.TRUE	r.TRUE	c.TRUE
ldh.hlfTRUE	-0.127			
rec.wedTRUE	-0.237	-0.459		
crp.trpTRUE	-0.256	0.055	-0.029	
sexf	-0.644	-0.010	0.009	0.011

- [combination therapy – incl. baseline – any AE]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.half + rec.weide + crp.triple + sex
+ (1 | pid) + age
Data: subset(final.data, med.group == "Combi")

AIC	BIC	logLik	deviance	df.resid
85.1	99.2	-35.5	71.1	49

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.3863	-0.7836	-0.6084	0.9449	1.9129

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.922e-14	1.386e-07

Number of obs: 56, groups: pid, 19

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.14065	1.15246	-0.122	0.903
ldh.halfTRUE	1.18511	0.94860	1.249	0.212
rec.weideTRUE	-0.01190	0.70794	-0.017	0.987
crp.tripleTRUE	0.96225	0.66805	1.440	0.150
sexf	0.67697	0.67362	1.005	0.315
age	-0.01896	0.02461	-0.770	0.441

Correlation of Fixed Effects:

	(Intr)	l.TRUE	r.TRUE	c.TRUE	sexf
ldh.hlfTRUE	-0.056				
rec.wedTRUE	-0.043	-0.399			
crp.trpTRUE	-0.138	0.179	0.041		

```

sexf      0.227  0.215 -0.219 -0.157
age       -0.919 -0.069 -0.029 -0.002 -0.439

```

- [PD-1 - incl. baseline - any AE]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.half + rec.weide + crp.triple + sex
+ (1 | pid) + age
Data: subset(final.data, med.group == "PD1")

AIC	BIC	logLik	deviance	df.resid
750.9	785.7	-368.5	736.9	1055

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.8382	-0.3492	-0.3044	-0.2648	3.9097

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.3228	0.5682

Number of obs: 1062, groups: pid, 127

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.873409	0.610254	-4.709	2.49e-06 ***
ldh.halfTRUE	1.011824	0.341489	2.963	0.00305 **
rec.weideTRUE	0.637898	0.276126	2.310	0.02088 *
crp.tripleTRUE	0.445029	0.321653	1.384	0.16649
sexf	-0.003486	0.235176	-0.015	0.98817
age	0.007896	0.008835	0.894	0.37148

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	l.TRUE	r.TRUE	c.TRUE	sexf	
ldh.hlfTRUE	-0.073				
rec.wedTRUE	-0.033	-0.498			
crp.trpTRUE	-0.083	0.003	-0.008		
sexf	-0.268	-0.059	0.024	0.030	
age	-0.947	0.051	-0.047	0.010	0.070

- [CTLA-4 - incl. baseline - any AE]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.any ~ ldh.half + rec.weide + crp.triple + sex
+ (1 | pid) + age
Data: subset(final.data, med.group == "CTLA4")

AIC	BIC	logLik	deviance	df.resid
400.6	427.5	-193.3	386.6	337

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.0932	-0.6323	-0.4951	1.1358	2.2691

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0	0

Number of obs: 344, groups: pid, 106

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.897372	0.611705	-3.102	0.00192 **
ldh.halfTRUE	0.533682	0.326402	1.635	0.10204
rec.weideTRUE	0.178159	0.293170	0.608	0.54339
crp.tripleTRUE	0.510283	0.337237	1.513	0.13025
sexf	0.497855	0.249661	1.994	0.04614 *
age	0.006464	0.008984	0.720	0.47181

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	l.TRUE	r.TRUE	c.TRUE	sexf	
ldh.hlfTRUE	-0.070				
rec.wedTRUE	-0.108	-0.392			
crp.trpTRUE	-0.013	0.084	-0.063		
sexf	-0.277	0.005	0.019	0.025	
age	-0.942	0.001	0.010	-0.090	0.080

Incl. Baseline - Steroid AE

- [incl. baseline - steroid AE]

- Multicollinearity
VIF

```

crp.triple  aec.half  ldh.high      sex      age
1.101894    1.006661  1.101082    1.008189  1.006049

```

1/VIF

```

crp.triple  aec.half  ldh.high      sex      age
0.9075280   0.9933832  0.9081976  0.9918779  0.9939877

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.triple + aec.half + ldh.high +
sex + (1 | pid)
Data: final.data

AIC	BIC	logLik	deviance	df.resid
581.9	613.6	-285.0	569.9	1456

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.5859	-0.1915	-0.1614	-0.1413	5.2230

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	1.291	1.136

Number of obs: 1462, groups: pid, 252

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.47335	0.27696	-12.541	< 2e-16 ***
crp.tripleTRUE	1.24275	0.31811	3.907	9.36e-05 ***
aec.halfTRUE	-0.61535	0.50583	-1.217	0.224
ldh.hghTRUE	-0.02386	0.34362	-0.069	0.945
sexf	0.29138	0.30214	0.964	0.335

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	c.TRUE	a.TRUE	l.TRUE	
crp.trpTRUE	-0.209			
aec.hlfTRUE	-0.067	-0.035		
ldh.hghTRUE	-0.105	-0.259	0.011	
sexf	-0.609	0.001	0.030	-0.009

- [combination therapy - incl. baseline - steroid AE]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.triple + aec.half + ldh.high +
sex + (1 | pid) + age
Data: subset(final.data, med.group == "Combi")

AIC	BIC	logLik	deviance	df.resid
70.7	84.8	-28.3	56.7	49

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.6911	-0.5068	-0.4114	-0.3436	2.5288

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0.3429	0.5856

Number of obs: 56, groups: pid, 19

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.18114	1.54012	-1.416	0.157
crp.tripleTRUE	0.59475	0.85774	0.693	0.488
aec.halfTRUE	-0.29397	1.26600	-0.232	0.816
ldh.hghTRUE	0.05510	0.89387	0.062	0.951
sexf	-0.65411	0.90628	-0.722	0.470
age	0.02068	0.03138	0.659	0.510

Correlation of Fixed Effects:

(Intr)	c.TRUE	a.TRUE	l.TRUE	sexf	
crp.trpTRUE	-0.142				
aec.hlfTRUE	-0.205	-0.134			
ldh.hghTRUE	-0.031	-0.385	0.193		
sexf	0.226	-0.213	-0.051	0.070	
age	-0.922	0.099	0.125	-0.117	-0.447

- [PD-1 - incl. baseline - steroid AE]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.triple + aec.half + ldh.high +
sex + (1 | pid) + age
Data: subset(final.data, med.group == "PD1")


```

      AIC      BIC    logLik deviance df.resid
241.3    276.1   -113.6    227.3     1055

Scaled residuals:
    Min       1Q   Median       3Q      Max
-0.4271 -0.1479 -0.1328 -0.1239  9.2001

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 0          0
Number of obs: 1062, groups: pid, 127

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -5.06995    1.12283   -4.515 6.32e-06 ***
crp.tripleTRUE  1.87504    0.44717   4.193 2.75e-05 ***
aec.halfTRUE   -0.90547    1.03981   -0.871  0.384
ldh.highTRUE    0.12245    0.53689    0.228  0.820
sexf           0.13806    0.40704    0.339  0.734
age            0.01540    0.01597    0.965  0.335
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr) c.TRUE a.TRUE l.TRUE sexf
crp.trpTRUE -0.129
aec.hlfTRUE  -0.046 -0.071
ldh.hghTRUE  0.004 -0.259 -0.017
sexf         -0.307  0.049  0.035  0.003
age          -0.953  0.017  0.014 -0.063  0.111

```

- [CTLA-4 - incl. baseline - steroid AE]

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.steroid ~ crp.triple + aec.half + ldh.high +
sex + (1 | pid) +
          age
Data: subset(final.data, med.group == "CTLA4")

```

```

      AIC      BIC    logLik deviance df.resid
242.4    269.3   -114.2    228.4     337

Scaled residuals:
    Min       1Q   Median       3Q      Max
-0.6838 -0.3913 -0.3117 -0.2462  4.5514

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 1.218e-15 3.489e-08
Number of obs: 344, groups: pid, 106

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -3.41897    0.89230   -3.832 0.000127 ***
crp.tripleTRUE  0.61908    0.46275    1.338 0.180953
aec.halfTRUE   -0.75964    0.62933   -1.207 0.227411
ldh.highTRUE   -0.40371    0.49941   -0.808 0.418881
sexf           0.83148    0.35671    2.331 0.019755 *
age            0.01510    0.01293    1.168 0.242969
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr) c.TRUE a.TRUE l.TRUE sexf
crp.trpTRUE  0.004
aec.hlfTRUE  -0.002  0.051
ldh.hghTRUE  -0.020 -0.284 -0.046
sexf         -0.318  0.024  0.027 -0.056
age          -0.944 -0.095 -0.070 -0.027  0.092

```

Baseline only

Only Baseline - AE

- [nb.any AE]

```

- Multicollinearity
VIF

```

```

rec.half ldh.high crp.half      sex      age
1.008834 1.009389 1.000939 1.006440 1.006980

```

1/VIF

```

rec.half ldh.high crp.half      sex      age
0.9912430 0.9906979 0.9990614 0.9936009 0.9930686

```

```

glm(formula = ae.any ~ rec.half + ldh.high + crp.half + sex
+ age, family = binomial("logit"), data = nb.data, na.ac-
tion = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.282   -0.891   -0.734    1.323    1.829

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -0.343757    0.682251   -0.504  0.6144
rec.halfTRUE    0.620875    0.335653    1.850  0.0643 .
ldh.highTRUE   -0.379696    0.301231   -1.260  0.2075
crp.halfTRUE   -0.638441    0.499215   -1.279  0.2009
sexf           0.395333    0.285608    1.384  0.1663
age           -0.008944    0.010288   -0.869  0.3847
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

Null deviance: 299.68 on 239 degrees of freedom
Residual deviance: 290.18 on 234 degrees of freedom
(14 observations deleted due to missingness)
AIC: 302.18

```

Number of Fisher Scoring iterations: 4

- [combination therapy - nb.any AE]

```

glm(formula = ae.any ~ rec.half + ldh.high + crp.half + sex
+ age, family = binomial("logit"), data = subset(nb.data,
med.group == "Combi"), na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.5350 -1.1389  0.7732  0.9755  1.6890

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)    1.55037    1.97980    0.783  0.434
rec.halfTRUE   -0.26599    1.54709   -0.172  0.863
ldh.highTRUE    0.36765    1.11632    0.329  0.742
crp.halfTRUE   17.46556  2399.54534    0.007  0.994
sexf           0.72806    1.11857    0.651  0.515
age           -0.03701    0.03965   -0.933  0.351

```

(Dispersion parameter for binomial family taken to be 1)

```

Null deviance: 25.864 on 18 degrees of freedom
Residual deviance: 23.555 on 13 degrees of freedom
AIC: 35.555

```

Number of Fisher Scoring iterations: 15

- [PD-1 - nb.any AE]

```

glm(formula = ae.any ~ rec.half + ldh.high + crp.half + sex
+
          age, family = binomial("logit"), data = subset(nb.data,
med.group ==
"PD1"), na.action = na.exclude)

```

```

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.2532 -0.7822 -0.6084    1.1829    2.2189

```

```

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)   -2.23703    1.13246   -1.975  0.0482 *
rec.halfTRUE    0.70161    0.47182    1.487  0.1370
ldh.highTRUE   -1.04579    0.49436   -2.115  0.0344 *
crp.halfTRUE   -0.29228    0.64676   -0.452  0.6513
sexf           -0.06382    0.44201   -0.144  0.8852
age            0.02220    0.01649    1.346  0.1783

```

```

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

(Dispersion parameter for binomial family taken to be 1)

```

Null deviance: 141.01 on 122 degrees of freedom
Residual deviance: 131.96 on 117 degrees of freedom
(5 observations deleted due to missingness)
AIC: 143.96

```

Number of Fisher Scoring iterations: 4

- [CTLA-4 - nb.any AE]

```
glm(formula = ae.any ~ rec.half + ldh.high + crp.half + sex +
+ age, family = binomial("logit"), data = subset(nb.data,
med.group == "CTLA4"), na.action = na.exclude)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-1.5005	-0.9354	-0.6769	1.2188	1.9664

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	0.21651	1.12574	0.192	0.8475
rec.halfTRUE	0.70524	0.54723	1.289	0.1975
ldh.highTRUE	-0.27123	0.48322	-0.561	0.5746
crp.halfTRUE	-1.55019	1.12086	-1.383	0.1667
sexf	0.75430	0.45250	1.667	0.0955
age	-0.01963	0.01684	-1.166	0.2436

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 125.21 on 97 degrees of freedom
Residual deviance: 116.99 on 92 degrees of freedom
(9 observations deleted due to missingness)
AIC: 128.99

Number of Fisher Scoring iterations: 4

Only Baseline - steroid

- [nb.steroid AE]

- Multicollinearity
VIF

crp.triple	rec.weide	ldh.half	sex	age
1.006126	1.261901	1.260114	1.005078	1.002946

1/VIF

crp.triple	rec.weide	ldh.half	sex	age
0.9939113	0.7924552	0.7935792	0.9949478	0.9970631

```
glm(formula = ae.steroid ~ crp.triple + rec.weide +
ldh.half +
sex + age, family = binomial("logit"), data = nb.data,
na.action = na.exclude)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.7485	-0.4900	-0.3848	-0.3547	2.4246

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-1.858783	1.158297	-1.605	0.109
crp.tripleTRUE	0.817979	0.499050	1.639	0.101
rec.weideTRUE	-0.496357	0.447267	-1.110	0.267
ldh.halfTRUE	-0.057597	0.484191	-0.119	0.905
sexf	0.153220	0.441471	0.347	0.729
age	-0.005621	0.015741	-0.357	0.721

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 156.04 on 239 degrees of freedom
Residual deviance: 150.24 on 234 degrees of freedom
(14 observations deleted due to missingness)
AIC: 162.24

Number of Fisher Scoring iterations: 5

- [combination therapy - nb.steroid AE]

```
glm(formula = ae.steroid ~ crp.triple + rec.weide +
ldh.half +
sex + age, family = binomial("logit"), data = sub-
set(nb.data,
med.group == "Combi"), na.action = na.exclude)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-1.750e-05	-2.110e-08	-2.110e-08	-2.110e-08	1.422e-05

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-231.604	285384.239	-0.001	0.999
crp.tripleTRUE	143.378	191560.107	0.001	0.999
rec.weideTRUE	-66.301	101189.151	-0.001	0.999
ldh.halfTRUE	72.865	142102.039	0.001	1.000
sexf	-126.322	162006.770	-0.001	0.999
age	3.398	4273.684	0.001	0.999

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 1.9557e+01 on 18 degrees of freedom
Residual deviance: 1.0851e-09 on 13 degrees of freedom
AIC: 12

Number of Fisher Scoring iterations: 25

- [PD-1 - nb.steroid AE]

```
glm(formula = ae.steroid ~ crp.triple + rec.weide +
ldh.half +
sex + age, family = binomial("logit"), data = sub-
set(nb.data,
med.group == "PD1"), na.action = na.exclude)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-0.5413	-0.4304	-0.3594	-0.3221	2.4712

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.673322	2.095536	-1.276	0.202
crp.tripleTRUE	0.392317	0.836955	0.469	0.639
rec.weideTRUE	-0.002936	0.775192	-0.004	0.997
ldh.halfTRUE	-0.395447	0.771859	-0.512	0.608
sexf	-0.222660	0.714662	-0.312	0.755
age	0.005205	0.026671	0.195	0.845

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 64.394 on 122 degrees of freedom
Residual deviance: 63.382 on 117 degrees of freedom
(5 observations deleted due to missingness)
AIC: 75.382

Number of Fisher Scoring iterations: 5

- [CTLA-4 - nb.steroid AE]

```
glm(formula = ae.steroid ~ crp.triple + rec.weide +
ldh.half +
sex + age, family = binomial("logit"), data = sub-
set(nb.data,
med.group == "CTLA4"), na.action = na.exclude)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-1.0219	-0.5116	-0.3589	-0.2742	2.7537

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.49682	1.78659	-1.398	0.1623
crp.tripleTRUE	1.21197	0.77848	1.557	0.1195
rec.weideTRUE	-0.46049	0.68720	-0.670	0.5028
ldh.halfTRUE	0.41061	0.74372	0.552	0.5809
sexf	1.27690	0.74533	1.713	0.0867
age	-0.01040	0.02417	-0.430	0.6670

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 68.832 on 97 degrees of freedom
Residual deviance: 62.154 on 92 degrees of freedom
(9 observations deleted due to missingness)
AIC: 74.154

Number of Fisher Scoring iterations: 5

Excluding baseline

Excl. Baseline – Any AE

– [excl. baseline – any AE]

```

- Multicollinearity
VIF
crp.triple  aec.high ldh.single      sex      age
1.035446    1.007872  1.038546    1.008314  1.006874

1/VIF

```

```

crp.triple  aec.high ldh.single      sex      age
0.9657670   0.9921891  0.9628847  0.9917546  0.9931732

```

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.triple + aec.high + ldh.single + sex
+ (1 | pid)
Data: excl.b.data

```

```

      AIC      BIC    logLik deviance df.resid
958.2    988.9    -473.1    946.2    1216

```

```

Scaled residuals:
    Min       1Q   Median       3Q      Max
-0.7934 -0.3819 -0.3401 -0.3061  3.1754

```

```

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 0.3979   0.6308
Number of obs: 1222, groups: pid, 234

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  -2.03313    0.15709  -12.943  <2e-16 ***
crp.tripleTRUE  0.54913    0.29001    1.893   0.0583 .
aec.highTRUE   0.75809    0.35395    2.142   0.0322 *
ldh.singleTRUE  0.09212    0.30063    0.306   0.7593
sexf           0.07680    0.20586    0.373   0.7091
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

Correlation of Fixed Effects:
      (Intr) c.TRUE a.TRUE l.TRUE sexf
crp.trpTRUE -0.216
aec.hghTRUE -0.197  0.035
ldh.sngTRUE -0.161 -0.066  0.012
sexf        -0.664  0.018  0.048 -0.027

```

– [combination therapy – excl. baseline – any AE]

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.triple + ldh.single + sex + age + (1
| pid)
Data: subset(excl.b.data, med.group == "Combi")

```

```

      AIC      BIC    logLik deviance df.resid
56.3    66.0    -22.2    44.3     31

```

```

Scaled residuals:
    Min       1Q   Median       3Q      Max
-0.9603 -0.5733 -0.3973  0.8719  1.7356

```

```

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 1.241   1.114
Number of obs: 37, groups: pid, 16

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept)  1.03654    2.32112    0.447   0.655
crp.tripleTRUE -0.34448    1.26986   -0.271   0.786
ldh.singleTRUE -0.30536    1.53756   -0.199   0.843
sexf          0.89555    1.17809    0.760   0.447
age          -0.03934    0.04800   -0.820   0.412

```

```

Correlation of Fixed Effects:
      (Intr) c.TRUE l.TRUE sexf
crp.trpTRUE -0.274
ldh.sngTRUE -0.180  0.184
sexf        0.224 -0.143 -0.056
age        -0.934  0.180  0.116 -0.459

```

– [PD-1 – excl. baseline – any AE]

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.triple + aec.high + ldh.single + sex
+ (1 | pid) + age
Data: subset(excl.b.data, med.group == "PD1")

```

```

      AIC      BIC    logLik deviance df.resid
613.5    647.4    -299.8    599.5    932

```

```

Scaled residuals:
    Min       1Q   Median       3Q      Max
-0.6715 -0.3315 -0.3019 -0.2863  3.4954

```

```

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 0.1841   0.429
Number of obs: 939, groups: pid, 117

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept) -2.724618    0.645420  -4.221 2.43e-05 ***
crp.tripleTRUE  0.376511    0.407043    0.925  0.3550
aec.highTRUE   1.253915    0.514791    2.436  0.0149 *
ldh.singleTRUE  0.248533    0.381966    0.651  0.5153
sexf           0.023109    0.248018    0.093  0.9258
age           0.005623    0.009410    0.598  0.5501
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

Correlation of Fixed Effects:
      (Intr) c.TRUE a.TRUE l.TRUE sexf
crp.trpTRUE -0.041
aec.hghTRUE -0.135  0.012
ldh.sngTRUE -0.018 -0.037  0.040
sexf        -0.291  0.037  0.066 -0.026
age         -0.953 -0.023  0.066 -0.041  0.098

```

– [CTLA-4 – excl. baseline – any AE]

```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.triple + aec.high + ldh.single + sex
+ (1 | pid) + age
Data: subset(excl.b.data, med.group == "CTLA4")

```

```

      AIC      BIC    logLik deviance df.resid
277.6    302.1    -131.8    263.6    239

```

```

Scaled residuals:
    Min       1Q   Median       3Q      Max
-0.8781 -0.5727 -0.4996 -0.3656  2.7182

```

```

Random effects:
  Groups Name      Variance Std.Dev.
pid      (Intercept) 3.799e-14 1.949e-07
Number of obs: 246, groups: pid, 101

```

```

Fixed effects:
              Estimate Std. Error z value Pr(>|z|)
(Intercept) -2.45301    0.75792  -3.237  0.00121 **
crp.tripleTRUE  0.47115    0.44838    1.051  0.29335
aec.highTRUE   0.11706    0.46954    0.249  0.80312
ldh.singleTRUE -0.29991    0.50275   -0.597  0.55082
sexf           0.37931    0.30586    1.240  0.21492
age           0.01678    0.01117    1.502  0.13307
---

```

```

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

```

Correlation of Fixed Effects:
      (Intr) c.TRUE a.TRUE l.TRUE sexf
crp.trpTRUE  0.001
aec.hghTRUE -0.074  0.063
ldh.sngTRUE  0.018 -0.159 -0.019
sexf         -0.254  0.006  0.018 -0.061
age         -0.954 -0.081 -0.007 -0.065  0.073

```

Excl. Baseline – Steroid AE

– [ob. steroid AE]

```

- Multicollinearity
VIF

```

```

crp.triple  lc.half  ldh.half      sex      age
1.054472    1.229245  1.179197    1.005322  1.002902

```

1/VIF

```
crp.triple    lc.half    ldh.half    sex    age
0.9483415    0.8135076    0.8480345    0.9947060    0.9971065
```

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.triple + lc.half + ldh.high + sex
+ age + (1 | pid)
Data: excl.b.data

AIC	BIC	logLik	deviance	df.resid
417.6	453.3	-201.8	403.6	1215

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.8179	-0.1327	-0.1047	-0.0869	5.4850

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	4.084	2.021

Number of obs: 1222, groups: pid, 234

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-4.3419099	1.2116475	-3.583	0.000339 ***
crp.tripleTRUE	1.5223356	0.4812343	3.163	0.001559 **
lc.halfTRUE	-1.5511258	0.9082753	-1.708	0.087679 .
ldh.highTRUE	-0.2241938	0.5770126	-0.389	0.697615
sexf	0.4435773	0.4535402	0.978	0.328058
age	0.0007453	0.0158277	0.047	0.962443

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	c.TRUE	lc.TRUE	ld.TRUE	sexf	
crp.trpTRUE	-0.163				
lc.halfTRUE	0.077	-0.241			
ldh.hghTRUE	0.001	-0.092	0.067		
sexf	-0.287	0.073	-0.087	-0.054	
age	-0.833	-0.048	0.054	-0.028	0.045

- [combination therapy - excl. baseline - steroid AE]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.triple + lc.half + ldh.high + sex
+ age + (1 | pid)
Data: subset(excl.b.data, med.group == "Combi")

AIC	BIC	logLik	deviance	df.resid
50.0	61.3	-18.0	36.0	30

Scaled residuals:

Min	1Q	Median	3Q	Max
-1.1705	-0.3643	-0.2492	-0.1610	1.3935

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	3.912	1.978

Number of obs: 37, groups: pid, 16

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-0.964516	3.069639	-0.314	0.753
crp.tripleTRUE	-0.015347	1.986573	-0.008	0.994
lc.halfTRUE	-1.787607	2.380697	-0.751	0.453
ldh.highTRUE	0.963243	1.946063	0.495	0.621
sexf	0.190586	1.752562	0.109	0.913
age	-0.004335	0.065119	-0.067	0.947

Correlation of Fixed Effects:

(Intr)	c.TRUE	lc.TRUE	ld.TRUE	sexf	
crp.trpTRUE	-0.081				
lc.halfTRUE	-0.184	-0.464			
ldh.hghTRUE	-0.098	0.301	-0.277		
sexf	0.205	-0.182	0.059	-0.093	
age	-0.928	0.047	0.152	0.052	-0.459

- [PD-1 - excl. baseline - steroid AE]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.triple + ldh.high + sex + age +
(1 | pid)
Data: subset(excl.b.data, med.group == "PD1")

AIC	BIC	logLik	deviance	df.resid
167.9	197.1	-78.0	155.9	943

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.4410	-0.1231	-0.1109	-0.0985	12.2963

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	4.114e-14	2.028e-07

Number of obs: 949, groups: pid, 119

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-5.70964	1.39156	-4.103	4.08e-05 ***
crp.tripleTRUE	2.20200	0.53247	4.135	3.54e-05 ***
ldh.highTRUE	0.20499	0.78321	0.262	0.794
sexf	0.40095	0.50892	0.788	0.431
age	0.01685	0.01985	0.849	0.396

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	c.TRUE	ld.TRUE	sexf	
crp.trpTRUE	-0.095			
ldh.hghTRUE	0.010	-0.069		
sexf	-0.310	0.084	-0.042	
age	-0.949	-0.047	-0.061	0.093

- [CTLA-4 - excl. baseline - steroid AE]

Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial (logit)
Formula: ae.steroid ~ crp.triple + lc.half + ldh.high + sex
+ age + (1 | pid)
Data: subset(excl.b.data, med.group == "CTLA4")

AIC	BIC	logLik	deviance	df.resid
177.1	201.6	-81.6	163.1	239

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.6513	-0.3778	-0.3233	-0.2361	4.2076

Random effects:

Groups Name	Variance	Std.Dev.
pid (Intercept)	0	0

Number of obs: 246, groups: pid, 101

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-3.89820	1.10134	-3.540	0.000401 ***
crp.tripleTRUE	0.40397	0.60408	0.669	0.503662
lc.halfTRUE	-0.97310	1.06928	-0.910	0.362796
ldh.highTRUE	-0.84240	0.78917	-1.067	0.285768
sexf	0.73077	0.42016	1.739	0.081986 .
age	0.02382	0.01576	1.512	0.130612

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	c.TRUE	ld.TRUE	sexf		
crp.trpTRUE	0.002				
lc.halfTRUE	-0.026	-0.089			
ldh.hghTRUE	0.048	-0.153	0.070		
sexf	-0.295	0.028	-0.074	-0.099	
age	-0.957	-0.078	0.006	-0.078	0.103

3. Post-hoc analyses

- ldh.half in excl. baseline, pd1, any irAE

```
Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.triple + aec.high + ldh.half + (1 |
pid)
Data: subset(excl.b.data, med.group == "PD1")
```

AIC	BIC	logLik	deviance	df.resid
608.3	627.7	-300.2	600.3	935

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.6770	-0.3272	-0.3038	-0.2872	3.4554

Random effects:

Groups	Name	Variance	Std.Dev.
pid	(Intercept)	0.1927	0.439

Number of obs: 939, groups: pid, 117

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.333859	0.002876	-811.6	<2e-16 ***
crp.tripleTRUE	0.392207	0.002783	140.9	<2e-16 ***
aec.highTRUE	1.226135	0.002783	440.6	<2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	c.TRUE
crp.trpTRUE	0.000
aec.hghTRUE	0.000 0.000

fit warnings:

fixed-effect model matrix is rank deficient so dropping 1 column / coefficient
convergence code: 0
Model failed to converge with max|grad| = 0.0260886 (tol = 0.001, component 1)

- ldh.high in excl. baseline, pd1, any irAE

```
Generalized linear mixed model fit by maximum likelihood
(Laplace Approximation) ['glmerMod']
Family: binomial ( logit )
Formula: ae.any ~ crp.triple + aec.high + ldh.high + (1 |
pid)
Data: subset(excl.b.data, med.group == "PD1")
```

AIC	BIC	logLik	deviance	df.resid
610.0	634.2	-300.0	600.0	934

Scaled residuals:

Min	1Q	Median	3Q	Max
-0.6772	-0.3279	-0.3019	-0.2853	3.4913

Random effects:

Groups	Name	Variance	Std.Dev.
pid	(Intercept)	0.1945	0.441

Number of obs: 939, groups: pid, 117

Fixed effects:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	-2.355292	0.002765	-851.7	<2e-16 ***
crp.tripleTRUE	0.384437	0.002763	139.1	<2e-16 ***
aec.highTRUE	1.236775	0.002763	447.6	<2e-16 ***
ldh.highTRUE	0.227166	0.002763	82.2	<2e-16 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:

(Intr)	c.TRUE	a.TRUE
crp.trpTRUE	0.000	
aec.hghTRUE	0.000 0.000	
ldh.hghTRUE	0.000 0.000 0.000	

convergence code: 0

Model failed to converge with max|grad| = 0.025585 (tol = 0.001, component 1)

10. Lebenslauf

Mein Lebenslauf wird aus Gründen des Datenschutzes in der elektronischen Fassung meiner Arbeit nicht veröffentlicht.