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A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors

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Novelty and impact

- Immune related adverse events are frequent, but heterogeneous according to treatment type
- Grade≥ 3 adverse events are frequent when immune checkpoint inhibitors are used in combination with chemotherapy or with another immunotherapy.
- The overall quality of AEs reporting is satisfactory, but items pertaining to methods of data collection and analysis are infrequently reported

- An increasing number of patients presenting with immune related AEs are expected in the future.

ABSTRACT

The advent of immune checkpoint-inhibitors (CPI) has transformed treatment for several cancer types. This review was performed to assess the rate of adverse events (AEs) associated with the use of CPI, alone or in combinations. A review of AEs reporting quality was also performed.

All publications of Randomized Clinical Trials (RCTs) assessing CPI published before December 2017 were included. To investigate the quality of AEs reporting, a set of items was defined based on the 2004 CONSORT harms extension statement.

Rates of Grade 5, serious, and study-withdrawal related AEs were collected in each treatment category. Specific immune related AEs (irAEs) were also collected when available. Pooled estimates of adverse event rates were calculated by using generalized linear mixed model.

A total of 35 RCTs including 16485 patients were included. The overall quality of AEs reporting was satisfactory, but items pertaining to methods of data collection and analysis were infrequently reported. Grade ≥ 3 AEs were reported for 14% (95% CI 12-16) of patients treated with PD(L)-1 inhibitors, 34% (95% CI 27-42) of patients treated with CTLA-4 inhibitors, 55% (95% CI 51-59) of patients on CPI combinations and 46% (95% CI 40-53) of patients on immunotherapy-chemotherapy combination. The profile of irAEs was different among the treatment categories.

The use of CPI, especially in combination, is associated with significant rates of Grade ≥3 AEs. Healthcare planning should anticipate the expected high number of patients presenting with irAEs in the future.

KEY WORDS

Adverse event, immune checkpoint inhibitors, systematic review, quality control, immune toxicity

INTRODUCTION

A careful balance between toxicity and efficacy is necessary to evaluate the overall effect of a treatment, especially in oncology. Both US Food and Drug Administration (1) and the European Medicines Agency (2) have stressed out the importance of a structured and transparent approach to benefit–risk assessment concerning the evaluation of new therapies.

During the last decade, anti-tumoral immunotherapies (3), based historically on interleukins, interferon alpha, or vaccines (4–8), have presented a major breakthrough with the advent of immune checkpoint-inhibitors (CPI). Monoclonal antibodies and especially those targeting Cytotoxic T-Lymphocyte–Associated antigen 4 (CTLA-4) (9), Programmed Death - Ligand 1 (PD-L1), and Programmed-cell-Death 1 (PD-1) (10–12), used alone or in combination with another CPI or a cytotoxic chemotherapy , have shown a significant improvement in overall survival (OS) and/or progression-free survival (PFS) in several clinical settings (13–15).

Toxicity profiles of CPI are different in comparison to toxicities seen with chemotherapies or targeted therapies comprised of immune mediated disorders (16–18). Thus many investigators involved in immuno-oncological trials faced difficulties to properly assess and report this new type of AEs (19). Upcoming trial-development strategies of combined therapies based on CPI in combination with cytotoxic agents such as chemotherapy; targeted therapy or even local therapy treatments such as radiation therapy might further increase the rate of toxicities and therefore make benefit-risk assessment of new treatment combinations even more challenging.

Since the first publication of the Consolidated Standards of Reporting Trials (CONSORT) Statement, reporting in Randomized Clinical Trials (RCTs) has improved (20–22). The CONSORT Statement was completed in 2004 (23) with a set of 10 specific recommendations on AEs reporting. However, the reporting of treatments toxicities remained challenging. A substantial heterogeneity in AEs data collection, analysis, and reporting has been identified in several studies (24,25). This may affect the number and severity of reported AEs (26).

This review was performed to assess the rate of key AEs (namely grade 5 AEs, AEs leading to study withdrawal, and serious AEs) and several AEs of special interest such as immune related AEs associated with the use of CPI alone or in a combination setting. A quality assessment review of AEs-report in immuno-oncology RCTs was also performed in order to determinate the reliability of available evidence on AEs.

METHODS

Trial Selection

We searched MEDLINE via PubMed (http://www.pubmed.gov) in order to identify all publications of RCTs assessing immune checkpoint inhibitors.

The search was performed in December 2017, for CTLA-4 inhibitors (Ipilimumab and Tremelimumab), PD-1 inhibitors (Nivolumab and Pembrolizumab) and PD-L1 inhibitors (Atezolizumab, Avelumab and Durvalumab) using the drug name and the term “randomized” as keywords. “English”, “clinical trials”, or “randomized controlled trial” were used as limits. Exclusion

criteria were as follows: hematology trials; phase I or IV trials; overviews, and secondary reports on previously published trials.

Definition of Trial Characteristics

Trials were considered as industry funded if a RCT received any form of industry funding with the exception of studies where only drug(s) was provided but without any funding.

A positive trial was defined as one in which the experimental arm was deemed to be superior to the standard arm for the primary endpoint by the authors. A negative study was defined as one in which the experimental arm was deemed not superior to the standard arm for the primary endpoint. The trial positivity status was considered as not stated when there was no formal statistical testing.

The authors' assessment of the overall toxicity profile of the experimental arm was based on conclusions in the abstract or in the discussion section of articles. The toxicity of experimental arms was categorized as more toxic, less toxic, acceptable, or not stated according to author's conclusions.

Neoadjuvant and adjuvant setting was defined based on the administration schedule of the experimental CPI before or after a curative local treatment for a localized tumor, whereas metastatic stage included patients with metastasis or locally advanced unresectable disease.

Phase II studies were defined as comparative if patients were randomized and a statistical comparison between the different arms was planned by the trial investigators.

Quality assessment of adverse events reports

Similar to previous studies investigating the quality of AE reporting in clinical trials (19,24) a set of items was defined by three of the authors (J.P., D.M., and B.Y.) based on the 2004 CONSORT harms extension statement (23). A total of 16 items were derived from the 10 recommendations (Table A in the appendix). These items were chosen because they all refered to objectively measurable, different, and important aspects of AE reporting. For these recommendations with several subcomponents, a score was provided for each of them. The ninth recommendation of the 2004 CONSORT extension was excluded because subgroup analysis for AEs was rarely performed.

A standardized data extraction form had been previously tested by two investigators (J.P. and D.M.)(24). This included the following guidelines to ensure homogenous data extraction for those recommendations potentially at risk for interpretation: AEs were defined by the authors as "adequately" (item 3b) if relevant AEs were formally defined or if AEs were collected according to a commonly accepted standard (such as National Cancer Institute Common Toxicity Criteria or WHO criteria). An adequate reporting of "how harms data were collected" (item 4a) required at least a description of the collection circumstances (e.g., during periodic physical examination, phone interviews or using diaries); and for the requirement of a separate reporting of serious AEs (item 8b), frequencies of grade 3 and 4 AEs that were provided separately or in aggregate were considered as adequate.

The attribution of treatment causality for AEs was defined as clear when the methods used to attribute causality were explained in the methods section.

Adverse events rate

The absolute number of grade 5 AEs, AEs leading to study withdrawal, and serious AEs (SAEs) was collected in accordance to the treatment arm for all included trials when available. The rates of several adverse events of special interest for this review were also collected when available including: adrenal insufficiency, anorexia, arthralgia, AST or ALT elevation, colitis, diarrhea, dyspnea, fatigue, hyperthyroidism, hypothyroidism, hypophysitis, mucositis, myositis, nausea, neuropathy, pneumonitis, pruritus, rash, thyroiditis. The rate of adverse events was collected for all grade, and then limited to grade ≥3.

Immune-related adverse events (irAEs) were defined as AEs at least possibly related to the study drugs and that were consistent with an immune phenomenon, such as hyperthyroidism, hypothyroidism, hypophysitis, adrenal insufficiency, colitis and pneumonitis. The timing of immune adverse event occurrence was defined as the time between the beginning of the drug study and the occurrence of an immune AE, whereas the timing of immune adverse event resolution was the time until the resolution of immune AE after its occurrence.

Statistical Analysis

Most analyses were descriptive. Proportions were calculated for categorical data, whereas median and interquartile ranges were calculated for continuous data. Trial treatments were grouped in 5 treatment categories: CTLA-4 inhibitors; PD (L)-1 inhibitors; immunotherapies combination; immunotherapy and chemotherapy combination and cytotoxic chemotherapy. Due to the fact that the trials included were conducted across different clinical settings with various experimental treatments and various procedures for data collection and analysis, the rate of immune adverse events was expected to be heterogeneous even in a given treatment category. Pooled estimates

of adverse event rates were then calculated by using generalized linear mixed model. Heterogeneity was assessed by inspection of the forest plots, Cochran's chi-squared tests, and I^2 statistic percentage. In order to reduce the heterogeneity between trials, the analyses were also performed among specific subgroups defined by type of therapy, tumor site, year of publication, and trial positivity. Random effect models were always used, independently of the statistical assessment of the heterogeneity. Pooled estimates were not performed when data from less than 2 trial arms were available. Statistical analyses were performed using R Software v3.3.2 (http://www.R-project.org/), and pooled estimates were calculated using the metaprop function of the metafor package.

RESULTS

Characteristics of Selected RCTs

From the 386 trials initially screened, 41 were assessed for eligibility and a total of 35 RCTs investigating 79 trial arms were included in this analysis (Figure 1, Appendix 2). Most screened trials were excluded because there were not randomized controlled trials. Six trials were then rejected because of exclusion criteria: hematology trials (n=1) phase I or IV trials (n=2), overviews (n=1), and secondary reports on previously published trials (n=2). PD(L)-1 inhibition was assessed in 24 RCTs arms, while 19 arms investigated CTLA-4 inhibitors alone, 8 investigated CPI in combination with a chemotherapy, and only 4 trial arms investigated a combination of different CPI. Chemotherapy was the most frequent control arm (n=17). Most trials were at least partially industry funded (n=34, 97%) and published in journals with Impact Factor superior than 20 (n=33, 94%) (Table 1). The median sample size of trials was 542, with an interquartile range of 231-810.

Most trials were phase III RCTs (n=23, 66%) and were positive based on the authors' conclusions for the primary endpoints (n=24, 69%).

CPI have been most frequently assessed in melanoma (n=17, 49%) and lung cancer patients (n=11, 31%). Thirty-two (91%) RCTs were performed in the metastatic or locally advanced stage, whereas only three (9%) trials were performed on neoadjuvant or adjuvant settings.

Adherence to CONSORT Statement

All RCTs used the Common Terminology Criteria for Adverse Events (CTCAE) to report AEs nature and severity.

Items pertaining to methods of data collection and analysis (items 4 to 5, Table A in the appendix) were infrequently reported. Especially, no trial reports described how AEs were collected (item 4a), and only 23% of RCTs gave a description of the timing of AEs data collection (item 4b). An adequate description of methods for presenting and analyzing AEs was present in 21% of articles (item 5), while the attribution to trial interventions of reported AEs was clear in 29% (item 4c). The number of treatment withdrawals was reported in 91% of the trials (item 6a). The number of grade 5 AEs was reported in 34 RCTs (97%), whereas description of AEs leading to death (nature of the grade 5 AE) was mentioned in 30 RCTs (86%) (Table 2, and item 6c of Table A).

Reporting of Immune Adverse Events

The management of immune related AEs was present in eighteen RCTs (51%), whereas the timing of immune AEs occurrence was reported in nine RCTs (26%) and the timing of immune

AEs resolution in eleven RCTs (31%). Immune-Related AEs frequency was reported separately in twenty-seven RCTs (77%), with a clear definition provided in twelve RCTs (44%) (Table 2).

Toxicity Profile

The analysis of AEs included 5879 patients from 24 trial arms for PD(L)-1 inhibitors; 4762 patients from 19 trial arms for CTLA-4 inhibitors alone; 545 patients from 4 trial arms for immunotherapy combination; 1370 patients from 8 trial arms for immunotherapy plus chemotherapy combination; and 3929 patients from 17 trial arms for cytotoxic chemotherapy (Table 3).

Grade ≥ 3 AEs were reported on 14% (95% CI 12-16) of patients treated with PD(L)-1 inhibitors alone, 34% (95% CI 27-42) of patients treated with an CTLA-4 inhibitor alone, 38% (95% CI 33-43) of patients treated with a cytotoxic chemotherapy, 55% (95% CI 51-59) of patients on immunotherapy combinations and 46% (95% CI 40-53) of patients on immunotherapy plus chemotherapy combination (Table 3 and Figure 2).

The rate of AEs leading to treatment withdrawal was 6% (95% CI 5-8) for PD(L)-1 inhibitors, 21% (95% CI 15-28) CTLA-4 inhibitors, 8% (95% CI 6-11) chemotherapy group, 38% (95% CI 34-42) for immunotherapy, and 13% for immunotherapy plus chemotherapy combination but with substantial heterogeneity across trials (Table 3). The rates of deaths related to treatment were below 1.5% in all treatment categories (Table 3, and Figure A in the appendix).

The most frequent AEs of any grade with PD(L)-1 inhibitors and CTLA-4 inhibitors alone were respectively diarrhea (11% and 36%), fatigue (21% and 25%) pruritus (15% and 25%), and rash (10% and 23%), whereas we noted 8% of grade 3-4 diarrhea for CTLA-4 inhibitors alone (Table 3 and Appendix 1).

For immunotherapy combinations, the rate of any grade diarrhea was 44% (10% grade 3-4), 41% of rash (5% grade 3-4) and 34% of pruritus (2% grade 3-4). Combination of immune checkpoint inhibitors and chemotherapy was associated with a high rate of AST or ALT elevation (31% any grade, 5% grade 3-4) (Table 3 and Appendix 1).

The profile of Immune mediated AEs was different for PD (L)-1 inhibitors and CTLA-4 inhibitors. Hypothyroidism, hyperthyroidism, and pneumonitis were more frequent with PD (L)-1 inhibitors, while colitis and hypophysitis were more frequent with CTLA-4 inhibitors. Combination of immune checkpoint inhibitors was associated with a substantial increase of colitis and hypothyroidism compared to PD (L)-1 inhibitors or CTLA-4 inhibitors alone (Table 3).

Among patients receiving a PD(L)-1 inhibitor, 4653 received a PD-1 inhibitor (Nivolumab or Pembrolizumab) and 1226 a PDL-1 inhibitor (Atezolizumab, Avelumab, or Durvalumab). Six percent of patients receiving a PD-1 inhibitor withdrew from the treatment whereas this rate was 10% with PDL-1 inhibitors. Patients treated with PDL-1 inhibitors had also more serious AEs (31% vs 8% for PD-1 inhibitors) and more grade 3-4 AEs (18% and 13%). Among the 3 trials investigating a PDL-1 inhibitor as a single agent, all included lung cancer patients and all were published after 2015 (Appendix 1). In the group of patients receiving a PD(L)-1 inhibitor, lung cancer patients had more serious AEs (19% vs 8%) and more grade 3-4 AEs (15% vs 12%) than melanoma patients. Trials published after 2015 were associated with an increased rate of serious AEs (14% vs 4% for PD(L)-1 inhibitors, and 36% vs 14% for CTLA-4 inhibitors), but there was no relevant increase of grade 3-4 AEs (14% vs 11% for PD(L)-1 inhibitors, and 32% vs 37% for CTLA-4 inhibitors) (Appendix 1).

Several organ specific AE rates varied among tumor site. For example, the rate of any grade rash was 16% among melanoma patients treated with a PD(L)-1 inhibitor versus 9% among lung

cancer patients in the same treatment group. On the opposite, the rate of any grade pneumonitis was 5% among lung cancer patients vs 1% among melanoma patients receiving a PD(L)-1 inhibitor.

DISCUSSION

The use of monoclonal antibodies targeting CTLA-4 or PD(L)-1, alone or in combination, was associated with a significant improvement in overall survival or progression-free survival in several RCTs (13–15) with a benefit-risk assessment commonly considered as favorable (27). In this review, we investigated the quality of AE reporting as a surrogate of the reliability of AE rates reported in RCTs manuscripts. The final objective was to describe toxicity of CPI by reporting pooled estimates of several important measures of treatment toxicity, as well as pooled estimates of specific adverse events rates by treatment categories.

The overall quality of AEs reporting was acceptable according to the 2004 CONSORT harms extension statement. The reporting quality was higher than the quality observed in a similar review conducted among all oncology RCTs (24), but AEs report remains suboptimal for several methodological items. However, key measures of treatment overall toxicity, such as number of withdrawals due to AEs or number of toxic deaths, were usually adequately reported. Some parameters of immune-checkpoint inhibitors toxicity were often missing. For example the timing of immune adverse events occurrence or resolution was reported in only one-third of articles included in our review. The timing of immune adverse events is a relevant information for clinical practice, as for example skin and gastro-intestinal events have been described to occur

precociously with a rapid resolution of about five to six weeks, while endocrine disorders appear later, with a frequent need of prolonged substitutive endocrine therapies (28).

This is the first systematic pooled analysis of adverse events rates reported with the use of checkpoint inhibitors in RCTs. Overall, CTLA-4 inhibitors had a higher rate of serious adverse events and treatment withdrawal compared to cytotoxic chemotherapy; PD (L)-1 inhibitors were less toxic. The toxicity profiles were widely different for these three treatment groups. Skin AEs were common to both anti CTLA-4 and PD (L)-1 inhibitors but were more frequent in the CTLA-4 inhibitor treatment group, while they were infrequent for cytotoxic chemotherapies. PD (L)-1 inhibitors were more frequently associated with thyroid adverse events, dyspnea and pneumonitis, as CTLA-4 inhibitors were associated with an increased rate of hypophysitis and gastro-intestinal toxicities.

We also found differences between PD-1 and PDL-1 inhibitors, with less grade 3-4 AEs, less SAEs, and less AEs leading to treatment withdrawal for patients receiving a PD-1 inhibitor. However these results have to be balanced with the fact that PDL-1 inhibitors were investigated in only 3 trials included in this study, all of them in the setting of lung cancer, and all of them published after 2015. These differences in trial characteristics might explain the observed differences in AE rates. Heterogeneous procedures for AE data collection and analysis between pharmaceutical companies might also explain such differences. Different types of immunotherapy may cause different adverse events, and the timing of adverse events is also different according to the type of immunotherapy (28,29). As a consequence, patients who have been recently treated with a checkpoint inhibitor and who present an adverse event that can be suspected to be

immune-related should ideally be managed in a multi-disciplinary way between oncologists, organ specialists, and emergency care specialists if appropriate (30).

The combination of two immune checkpoint inhibitors or their combination with cytotoxic chemotherapy was associated with substantially higher toxicity, with for example more than one third of treatment withdrawal for immune-checkpoint inhibitors combinations. The combination of several checkpoint inhibitors increased not only the rate but also intensity of several immune related AEs. As an example, the rate of grade ≥ 3 diarrhea reached 10% for CPI combination, the rate of grade ≥ 3 colitis reached 11%, and the rate of grade ≥ 3 AST or ALT elevation reached 9%. The synergistic effect of combining immunotherapies in inducing immune toxicity was not seen when CPI were combined with cytotoxic chemotherapy. However, in the chemotherapy plus immunotherapy group, the adverse events traditionally reported with chemotherapy (notably nausea, neuropathy, arthralgia, and mild AST or ALT elevation) were added to the adverse events reported with checkpoint inhibitors alone. The result is that the overall rate of adverse events in the chemotherapy plus immunotherapy group was higher than the rate observed in chemotherapy alone or in immunotherapy alone groups. This is not surprising given that multi-agent treatments may produce overlapping toxicities. However, the rate of treatment withdrawals with the combination of chemotherapy plus immunotherapy was surprisingly low compared to CTLA-4 inhibitors alone or immunotherapy combination. It may be explained by a wider experience of managing chemotherapy toxicities, by the fact that most chemotherapy adverse events might be managed successfully by a dose reduction, by a different perception of the risk associated with adverse events when related to chemotherapy or to immunotherapy, but also by the fact that long-term response to CPI is believed to be possible even after treatment withdrawal (31). All these reasons might not incite investigators to continue CPI treatment despite of AEs.

Given the increasing number of combinations including at least one CPI assessed in ongoing clinical trials and the development of new CPI, the number of patients having immune adverse events is expected to increase dramatically in the future. The overall organization of cancer units, as well as their collaboration with other medical specialists, emergency care units, and general practitioners has to be rethought to anticipate the careful follow-up of this large cohort of patients with a high risk of immune adverse events.

There are several limitations of our review: The rate and severity of side effects are multifactorial and synergetic and can be affected by patients' characteristics (performance status, age, comorbidities, cancer entities). As patients characteristics vary across trials, differences observed in adverse events rates might not be only related to study drugs. Another limitation is that the conclusions must be interpreted in the context of the relatively small number of trials included. Most RCTs were phase III trials with high sample sizes, only few were phase II studies. The overall sample size was acceptable for PD (L)-1 and CTLA-4 inhibitors alone, as well as for the chemotherapy treatment group. The interpretation of the pooled adverse events rate for the two combination groups is more complex given the heterogeneity of experimental combinations included in these groups, as also the small number of trial arms for these two treatment groups. All AEs were not reported for all trials included in this review. As a consequence, the pooled rates could not be assessed for several adverse events in several treatment groups, and the pooled rate were only calculated from trials for which the information was available. The number of arms and patients included in the calculation of pooled estimates can be found in the Appendix.

The reporting homogeneity of AEs in RCTs assessing immune checkpoint-inhibitors still needs to be improved. The specificities of Immune-mediated AEs, in nature, timing, and consequences should be carefully described. The safety profile of PD (L)-1 inhibitors was acceptable, while the

rate of high grade AEs was increased for CTLA-4 inhibitors. The combination of checkpoint inhibitors had a synergistic effect on the rate of immune-related adverse events. The combination of checkpoint inhibitors with cytotoxic chemotherapy increased the variety of reported adverse events. The use of CPI, especially in a combined treatment strategy implies a high vigilance from all physicians in contact with this patient group, as also a need to reorganize patient's follow-up while under treatment.

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TABLES

Table 1. Trial characteristics (*n* = 35)

Study characteristics		Studies	
		n	%
Year of publication	2010	3	9
	2011	1	3
	2012	2	6
	2013	1	3
	2014	4	11
	2015	9	26
	2016	9	26
	2017	6	17
Tumor site	Lung	11	31
	Skin	17	49
	Urinary System	5	14
	Others	2	6
Sources of trial funding	Government/Foundation	1	3
	Completely funded by industry	33	94
	Partially funded by industry	1	3
Journal impact factor	<10	1	3
	10-20	1	3
	>20	33	94

Trial design	Non-comparative phase II	2	6
	Comparative phase II	9	26
	Phase III	23	66
	Other	1	3
Number of arms	2	26	74
	>2	9	26
Type of therapy (per trial arm)	CTLA-4 inhibitor	19	24
	PD(L)1 inhibitor	24	30
	- PD-L1 inhibitor	3	4
	- PD-1 inhibitor	21	27
	Chemotherapy plus immunotherapy	8	10
	Immunotherapy combination	4	5
	Chemotherapy	17	22
	Best supportive care	5	6
	Molecular targeted therapy	1	1
	Vaccine	1	1
Cancer stage	Adjuvant and/or neoadjuvant	3	9
	Metastatic	32	91
Sample size	Median	542	
	Interquartile range	231-810	
Primary endpoint †	Overall survival	23	56
	Composite survival endpoint	12	29
	Response	5	12
	Toxicity	1	2
Results of the primary outcome	Positive	24	69
	Negative	9	20
	No formal statistical testing	2	6

Toxicity profile conclusions*	Acceptable	10	31
	Investigational arm more toxic	8	25
	Control arm more toxic	13	41
	No Conclusion	1	3

* Conclusion of the trials' authors

† (n= 41 because of coprimary endpoints)

RCT = Randomized controlled trial

Table 2. Description of immune AEs reporting	
	N = 35
Grade 5 AEs	
Number reported	34 (97%)
Nature reported	30 (86%)
AEs leading to study withdrawal	
Number reported	32 (91%)
Nature reported	13 (47%)
Description of any specific treatment of immune adverse events	18 (51%)
Description of the timing of immune adverse events occurence	9 (26%)
Description of the timing of immune adverse events resolution	11 (31%)
Use of at least one aggregate variable of immune adverse events	*N*= 27
Clear definition of which adverse events are included in the variable(s)	12 (44%)
Relation between reported AE and study drugs	*N*=35
Only possibly related AE	30 (85%)

AEs=adverse events

Table 3. Adverse events description and frequency

	PD(L)1 inhibitor		CTLA-4 inhibitor		Immunotherapy combination		Chemotherapy plus immunotherapy		Cytotoxic Chemotherapy	
Number of trial arms	25		18		4		8		17	
Median sample size of trial arms (IQR)	266 (142-339)		283 (83-376)		82 (69-149)		69 (42-282)		205 (129-309)	
Overall sample size	6278		4363		545		1370		3929	
Measure	Random effect model summary proportion (CI)*		Random effect model summary proportion (CI)*		Random effect model summary proportion (CI)*		Random effect model summary proportion (CI)*		Random effect model summary proportion (CI)*	
AEs leading to death rate (%)	0.6% (0.3-1.0)		1.3% (0.8-2.0)		0.1% (0.0-17)		1.1% (0.6-2.0)		1.0% (0.7-1.3)	
AEs leading to treatment withdrawal rate (%)	6% (5-8)		21% (15-28)		38% (34-42)		13% (7-22)		8% (6-11)	
Serious AE rate (%)	12% (7-18)		30% (21-40)		NA		30% (26-34)		17% (12-22)	
	All grade	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**
All nature	74% (69-79)	14% (12-16)	89% (81-93)	34% (27-42)	90% (74-97)	55% (51-59)	89% (81-94)	46% (40-53)	85% (82-88)	38% (33-43)
Adrenal insufficiency	1% (0-2)	0% (0-1)	1% (1-2)	0% (0-1)	NA	NA	NA	NA	0% (0-NA)	0% (0-NA)
Anorexia	9% (8-11)	0% (0-1)	14% (9-21)	1% (1-2)	17% (14-21)	1% (0-3)	16% (12-20)	2% (1-3)	15% (12-18)	1% (0-2)
Arthralgia	8% (7-11)	0% (0-0)	5% (3-9)	0% (0-1)	11% (8-14)	0% (0-2)	18% (9-31)	0% (0-7)	9% (5-16)	0% (0-1)
AST or ALT elevation	5% (4-7)	1% (1-2)	5% (2-9)	2% (1-4)	19% (15-23)	9% (6-12)	31% (18-48)	5% (2-13)	11% (3-36)	1% (0-2)
Colitis	1% (1-2)	1% (0-1)	8% (6-10)	5% (4-6)	16% (10-25)	11% (6-19)	4% (2-7)	2% (1-4)	0% (0-1)	NA

Diarrhea	11% (9-14)	1% (0-1)	36% (31-41)	8% (6-11)	44% (39-49)	10% (7-13)	28% (25-32)	6% (5-8)	15% (13-18)	1% (1-2)
Dyspnea	9% (4-20)	1% (0-2)	6% (2-16)	1% (0-4)	10% (8-13)	1% (0-4)	NA	NA	NA	NA
Fatigue	21% (18-25)	1% (1-1)	25% (20-31)	2% (1-3)	36% (32-41)	4% (3-7)	24% (17-33)	5% (3-7)	25% (20-30)	3% (2-4)
Hyperthyroidism	5% (4-6)	0% (0-0)	4% (2-7)	NA	NA	NA	NA	NA	1% (0-2)	0% (0-NA)
Hypophysitis	1% (0-1)	0% (0-1)	4% (2-7)	2% (1-3)	NA	NA	0% (0-0)	0% (0-0)	0% (0-NA)	0% (0-NA)
Hypothyroidism	8% (7-9)	0% (0-0)	3% (2-5)	0% (0-0)	15% (12-19)	0% (0-2)	NA	NA	1% (0-1)	0% (0-NA)
Mucositis	3% (2-3)	0% (0-1)	NA	NA	NA	NA	NA	NA	12% (10-15)	1% (1-3)
Myositis	0% (0-1)	0% (0-0)	NA	NA	NA	NA	NA	NA	0% (0-1)	0% (0-1)
Nausea	12% (10-14)	0% (0-0)	19 (14-26)	1% (0-2)	25% (21-30)	2% (1-4)	27% (20-36)	1% (0-2)	27% (21-33)	1% (1-2)
Neuropathy	1% (0-1)	0% (0-17)	0% (0-4)	0% (0-4)	NA	NA	18% (12-26)	1% (1-3)	14% (9-20)	1% (1-2)
Pneumonitis	4% (2-6)	1% (1-2)	1% (0-2)	1% (0-1)	NA	NA	NA	NA	1% (0-2)	0% (0-1)
Pruritus	15% (12-17)	0% (0-2)	25% (21-29)	1% (0-1)	34% (29-38)	2% (1-4)	17% (12-22)	1% (1-2)	3% (2-5)	0% (0-0)
Rash	10% (8-13)	0% (0-1)	23% (19-27)	1% (1-2)	41% (36-45)	5% (3-7)	21% (18-26)	2% (1-3)	4% (3-5)	0% (0-1)
Thyroiditis	0% (0-0)	0% (0-0)	0% (0-1)	0% (0-1)	NA	NA	NA	NA	0% (0-NA)	0% (0-NA)

AE=adverse events

* Some adverse events rates were not described in all trial reports. The number of arms with missing data are reported in the appendix.

AE=adverse events

FIGURE LEGENDS

Figure 1. Selection of randomized clinical trials in the systematic review in compliance with PRISMA Statement.

Figure 2. Pooled estimates of grade 3-4 adverse event rates

A) Among trial arms investigating a PD (L)1 inhibitor alone

B) Among trial arms investigating a CTLA4 inhibitor alone

C) Among trial arms investigating a combination of immunotherapies

D) Among trial arms investigating a checkpoint inhibitor in combination with cytotoxic chemotherapy

E) Among trial arms investigating a cytotoxic chemotherapy

Square sizes are proportional to the trials sample sizes.

Figure 3. Pooled estimates of the rate of adverse event leading to treatment withdrawal

A) Among trial arms investigating a PD (L)1 inhibitor alone

B) Among trial arms investigating a CTLA4 inhibitor alone

C) Among trial arms investigating a combination of immunotherapies

D) Among trial arms investigating a checkpoint inhibitor in combination with cytotoxic chemotherapy

E) Among trial arms investigating a cytotoxic chemotherapy

Square sizes are proportional to the trials sample sizes.

Novelty and Impact:

Even the most promising therapies are of little value in the clinic if they're too toxic. With the advent of new immunotherapies, evaluating benefit vs risk has become more complex than for standard chemotherapies. In this analysis, the authors found that treatment with immune checkpoint-inhibitors (CPI) is associated with significant rates of adverse events (AEs) of Grade ≥3, especially when used in combination with other types of therapy. Healthcare planning should anticipate an increased number of patients presenting with immune-related and other AEs in the future.

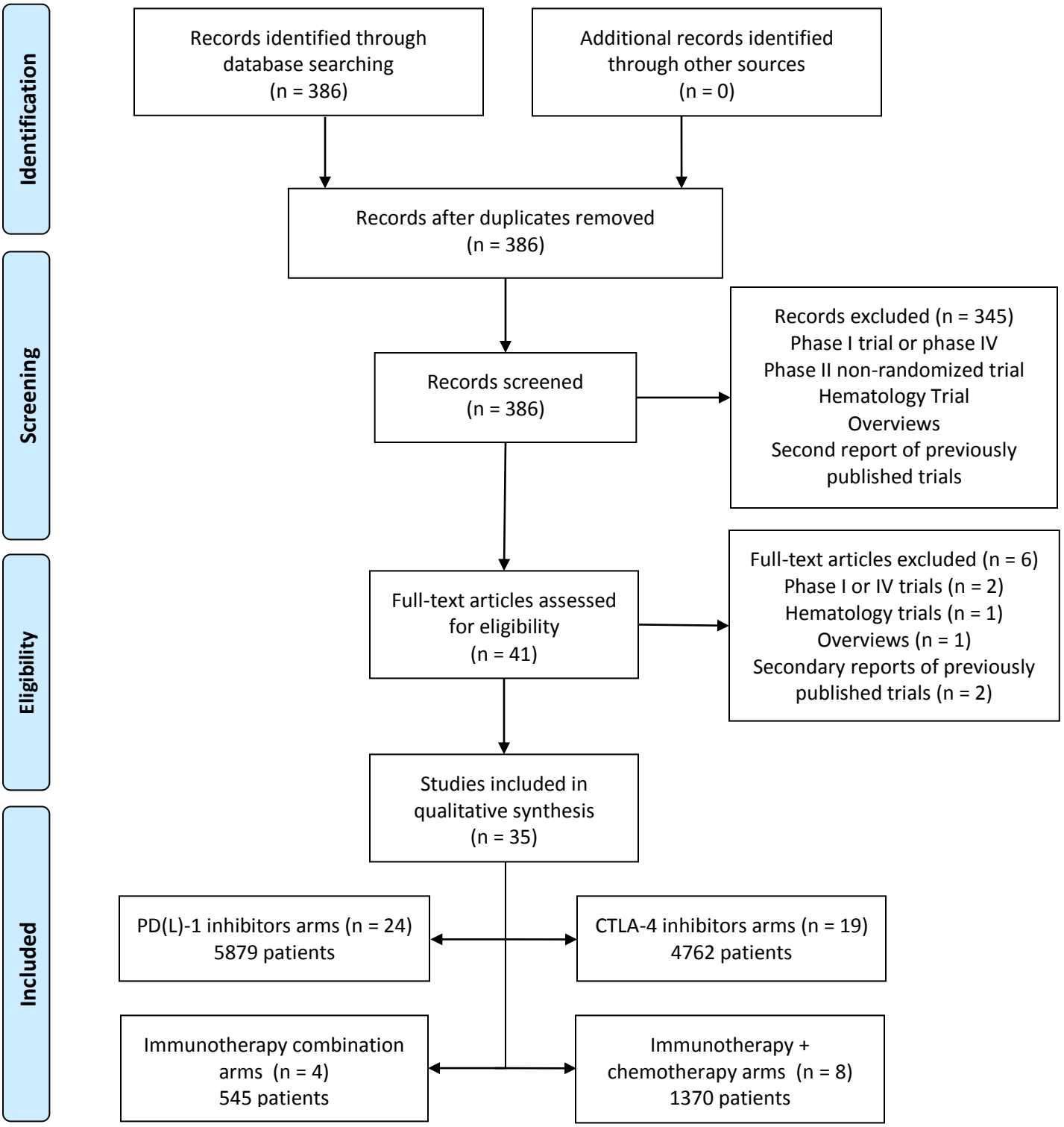
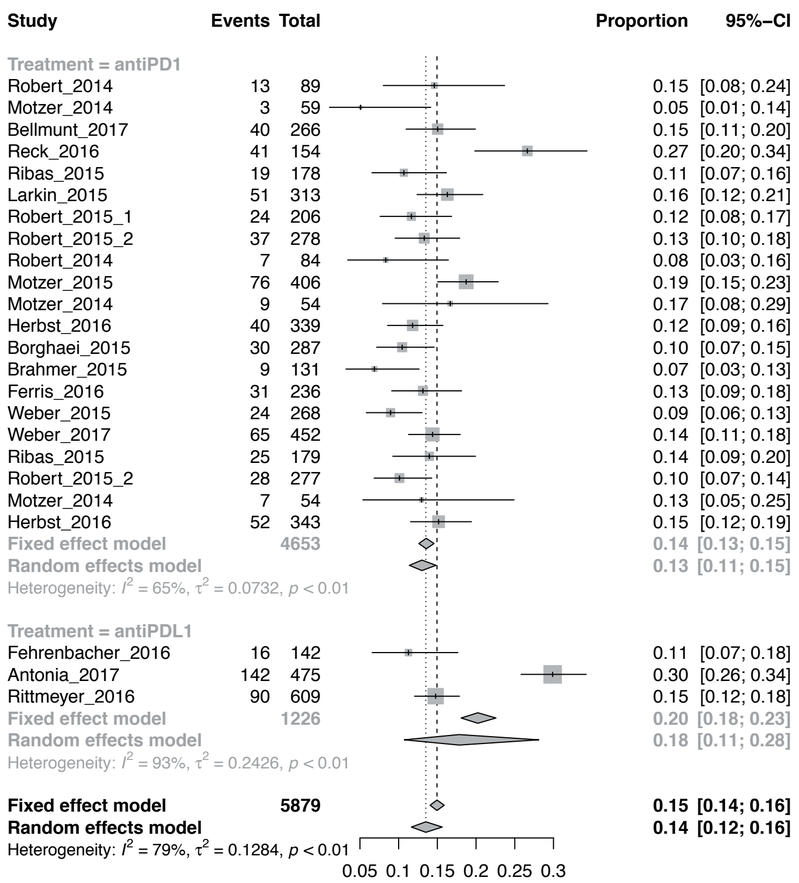
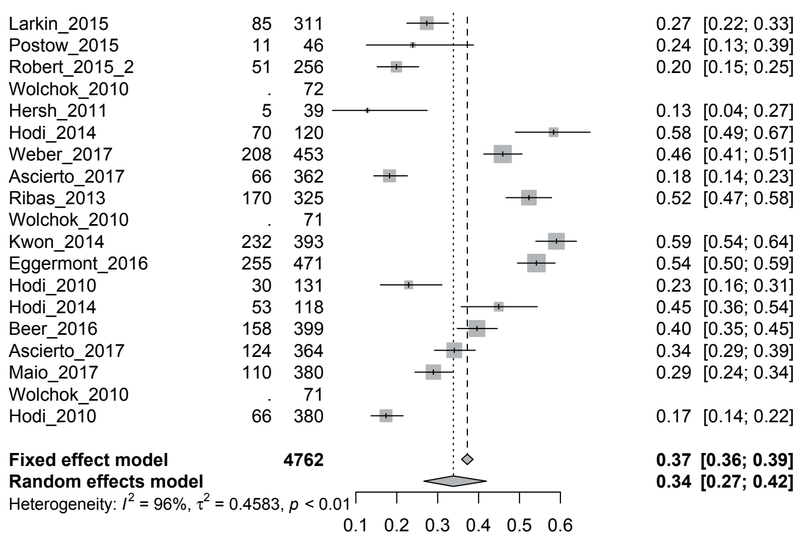


Fig 1. Selection of randomized clinical trials in the systematic review in compliance with PRISMA statement

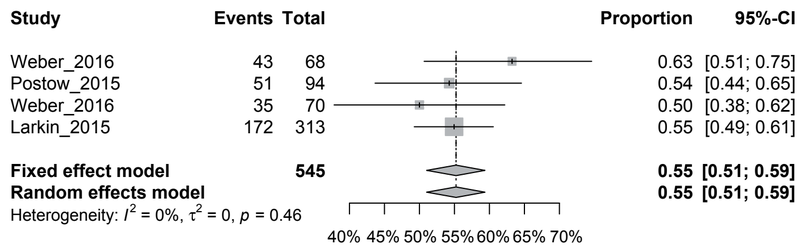
A) PD(L)1 inhibitors



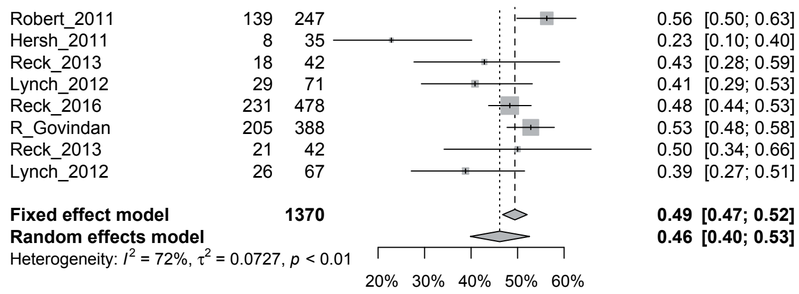
B) CTLA4 inhibitors



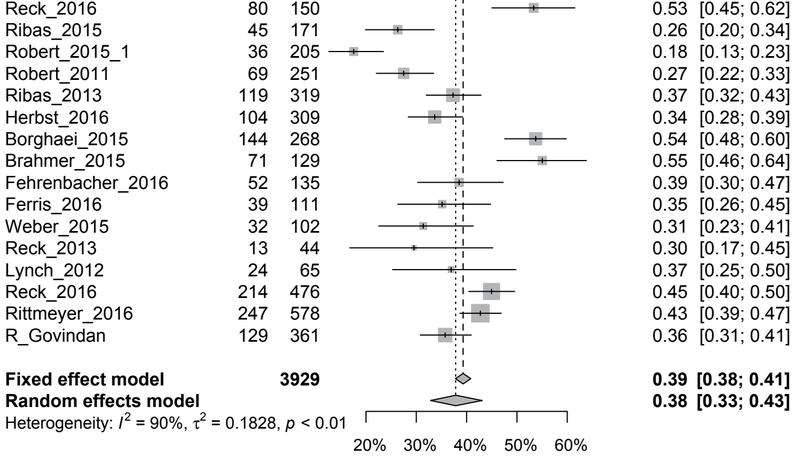
C) Immunotherapy combinations



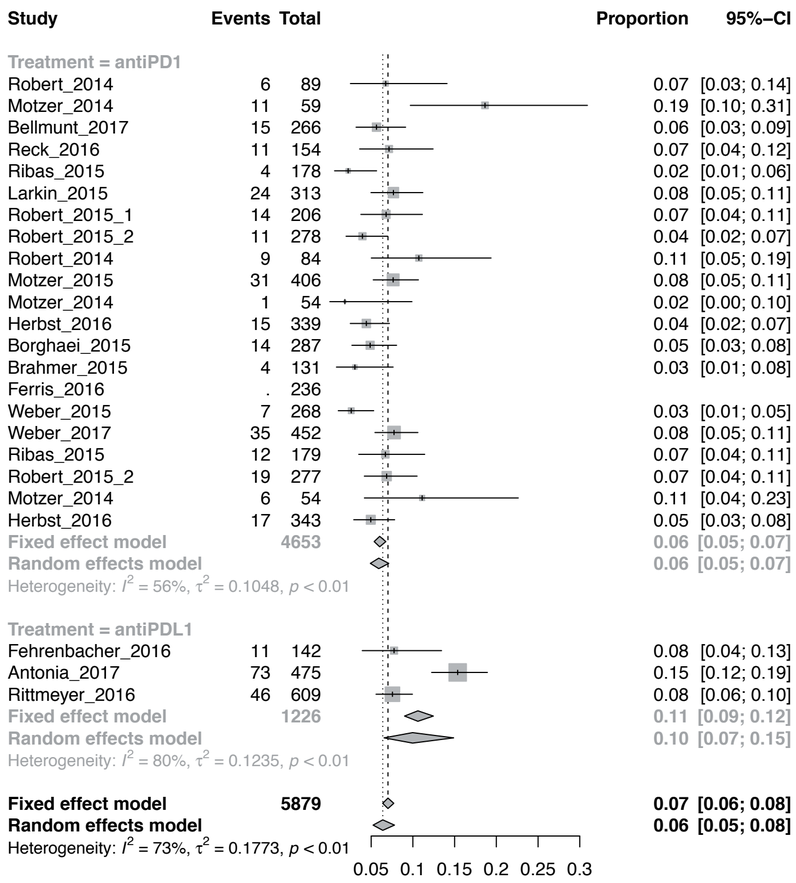
D) Immunotherapy and chemotherapy combinations



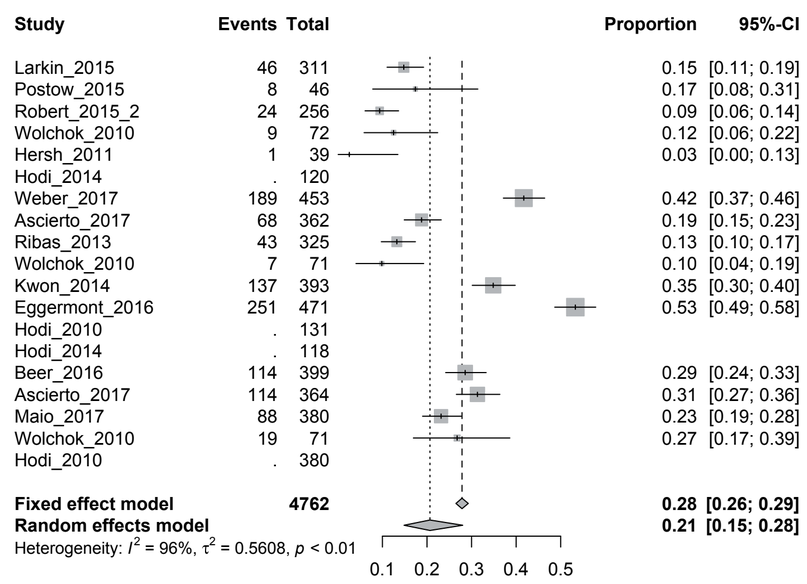
E) Cytotoxic chemotherapy



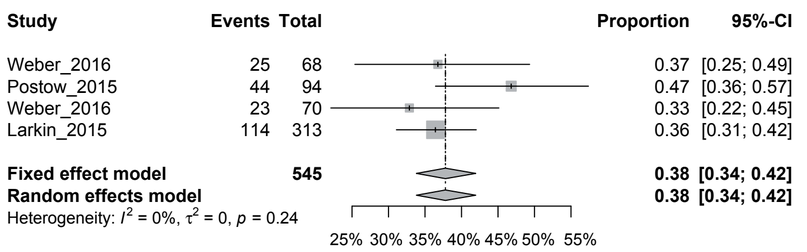
A) PD(L)1 inhibitors



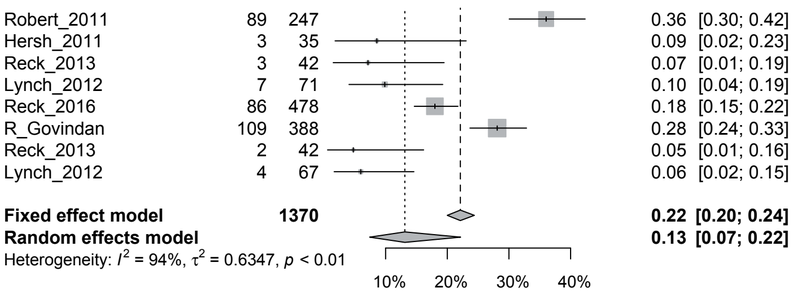
B) CTLA4 inhibitors



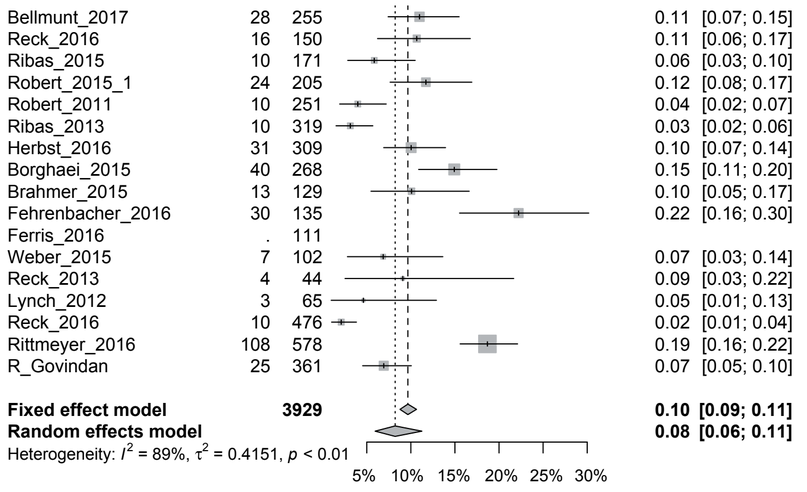
C) Immunotherapy combinations



D) Immunotherapy and chemotherapy combinations



E) Cytotoxic chemotherapy



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Title:
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Date:
2019-08-01

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