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Peripheral neuropathy among people treated with immune checkpoint inhibitors: systematic review and network meta-analysis

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ABSTRACT

Objective

Immune checkpoint inhibitors (ICI) have revolutionized the treatment of cancer, though uncertainty persists regarding their neurological safety. We sought to estimate the frequency of peripheral neuropathy in cancer patients receiving ICIs, as well as their comparative safety profile regarding other neurological adverse effects.

Methods

We searched CENTRAL, MEDLINE, Embase, and ClinicalTrials.gov for randomized controlled trials (RCTs) from inception to February 2021. We included RCTs investigating any ICI for any type of cancer. The primary outcome was serious peripheral neuropathy, as defined in the individual trials. The secondary endpoints were non-serious peripheral neuropathy, symptomatic neurological adverse events, central syndromic and peripheral syndromic neurological adverse events. Screening, data extraction, and bias assessment were conducted independently. We conducted a Bayesian network meta-analysis, ranked the treatment options (using SUCRA), and estimated the absolute event rate for each outcome.

Results

We included 96 trials with a combined 52,811 participants, with a median trial sample size of 559 participants. The median participant age was 62.1 years, and 37.0% of the overall trial participants were female. 34 trials (35.4%) used a double-blind design. 28 trials were conducted in patients with non-small cell lung cancer (17,014 combined participants) and 15 trials were conducted in patients with melanoma (8,008 combined participants).

When the interventions were combined into their treatment modality, the most frequently studied were anti-PD-1 or anti-PD-L1 inhibitors or anti-PD-1 or anti-PD-L1 inhibitors plus conventional therapy, with 25,106 and 11,924 combined participants, respectively. For serious peripheral neuropathy, the worst-ranked treatment modality was

anti-CTLA-4 plus conventional (SUCRA 24%), and the best-ranked treatment modality was ICI combination plus conventional (SUCRA 89%). The estimated incidence of serious peripheral neuropathy ranges from 0,01% (placebo) to 0,58% (anti-CTLA4 plus conventional). For non-serious peripheral neuropathy, the worst-ranked treatment modality was anti-anti-PD-1/PD-L1 plus conventional (SUCRA 11%). Anti-PD-1/anti-PD-L1 plus conventional therapy has increased odds of non-serious peripheral neuropathy when compared to conventional therapy. The estimated incidence of non-serious peripheral neuropathy ranges from 2,32% (anti-PD-1/PD-L1) to 19,26% (anti-PD-1/PD-L1 plus conventional).

Conclusions

The findings of this systematic review with network meta-analysis, highlight the need of monitor the development of peripheral neuropathy and other neurological toxicities among patients exposed to ICI type treatments. This condition, which is likely clinically relevant and can severely impair the quality of life of patients and trigger a painful disorder, should be considered in the management of individual cancer patients.

Key words

Systematic review; Network meta-analysis; Clinical Trials; Immune Checkpoint Inhibitors; Cancer.

The following work is the author's full responsibility.

RESUMO

Objetivo

Os inibidores de *checkpoint* imunitário (ICI) revolucionaram o tratamento oncológico, embora exista alguma incerteza em relação à sua neurotoxicidade. Procuramos estimar a frequência de neuropatia periférica em doentes com cancro expostos a ICIs, bem como o seu perfil de segurança em relação a outros efeitos adversos neurológicos.

Métodos

A pesquisa foi realizada nas bases de dados CENTRAL, MEDLINE, Embase, e ClinicalTrials.gov, até fevereiro de 2021. Foram incluídos ensaios clínicos aleatorizados e controlados, com qualquer ICI como intervenção, para qualquer tipo de cancro. O objetivo primário é estimar a frequência de neuropatia periférica, os objectivos secundários foram neuropatia periférica não grave, eventos adversos neurológicos sintomáticos, eventos adversos neurológicos sindrómicos centrais e periféricos. A revisão foi realizada de forma independente nas várias fases, nomeadamente de seleção, avaliação do risco de viés e extração de dados. Realizou-se meta-análise em rede Bayesiana, com comparação entre classes de ICI e entre ICI em monoterapia. Realizou-se ranking das modalidades terapêuticas (usando a superfície da curva cumulativa de *ranking* [SUCRA]) e estimou-se a frequência mediana para cada *outcome*.

Resultados

Foram incluídos 96 ensaios com um total de 52,811 participantes, publicados entre 2011 e 2021. O tamanho amostral mediano foi de 559, sendo a idade mediana dos participantes 62 anos com 37% do sexo feminino. Apenas 35.4% dos ensaios utilizaram ocultação dupla e 82% tiveram elevado risco de viés. O cancro do pulmão de não-pequenas-células (28 ensaios, 17,014 participantes) e o melanoma (15 ensaios, 8,808 doentes) foram os mais frequentemente analisados. Quando as intervenções foram combinadas em modalidades de tratamento, as mais frequentemente estudadas foram inibidores anti-PD-1 ou anti-PD-L1 ou inibidores anti-PD-1 ou anti-PD-L1 mais terapia convencional, com 25.106 e 11.924 participantes, respetivamente. Para neuropatia

periférica grave, a modalidade anti-CTLA-4 mais convencional apresenta a maior probabilidade global (SUCRA 24%), e a modalidade de tratamento com menor probabilidade global (SUCRA 89%) é a combinação de ICI mais convencional. A incidência estimada de neuropatia periférica grave varia de 0,01% (placebo) a 0,58% (anti-CTLA4 mais convencional). Para neuropatia periférica não grave, a modalidade anti-PD-1/PD-L1 mais convencional apresenta a maior probabilidade global (SUCRA 11%). Anti-PD-1/anti-PD-L1 mais terapia convencional apresentam *odds* aumentados de neuropatia periférica não grave quando comparada à terapia convencional. A incidência estimada de neuropatia periférica não grave varia de 2,32% (anti-PD-1/PD-L1) a 19,26% (anti-PD-1/PD-L1 mais convencional).

Conclusão

Considerando os resultados desta revisão sistemática com meta-análise em rede salienta-se a necessidade de monitorizar o desenvolvimento de neuropatia periférica e outros efeitos neurotóxicos em doentes expostos a tratamentos do tipo ICI. Esta condição, que é clinicamente relevante e pode afetar seriamente a qualidade de vida do doente e desencadear um distúrbio doloroso, deve, portanto, ser considerada na gestão individual de doentes com cancro.

Palavras-chave

Revisão sistemática; Meta-análise network; ensaios clínicos; inibidores de *checkpoint* imunitário; cancro.

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To António and José Maria, my kids,

To Francisco, my partner, for keep me going,

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I thank you all for the unconditional support and for the opportunity to grow and learn with you.

To my mother, for the person I´m today.

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ABBREVIATIONS

CI- Confidence interval

CIPN – Chemotherapy-induced peripheral neuropathy

CrI- Credible interval

CTLA-4- cytotoxic T-lymphocyte–associated antigen 4

DIC- deviance information criterion

nAE- neurological-related adverse events

ICI- immune-checkpoint inhibitors

ICSRs – Individual case safety reports

NMA- network meta-analysis

OR- odds ratio

PD-1- programmed-death 1

PD-L1- programmed death-ligand 1

PFS- progression-free survival

PN - Peripheral neuropathy

RCT – Randomized Clinical Trial

SUCRA- surface under the cumulative ranking curve

SD- standard deviation

INTRODUCTION

The progress made in oncologic treatments in recent decades combined with earlier diagnoses have made it possible to considerably lessen mortality for most cancer types.[1] Despite the advancements, peripheral neuropathy remains a challenging side effect associated with several commonly used antineoplastic agents. The prevalence of chemotherapy-induced peripheral neuropathy (CIPN) is rather high with approximately 68% of patients exhibiting symptoms one month after the end of their treatment, and 30% at six months post-treatment. The development of CIPN may require chemotherapy dose reduction or cessation, which may increase cancer-related morbidity and mortality. CIPN is characterized by predominantly sensory manifestations that may be accompanied by motor and autonomic changes.[2] Platinum salts such as cisplatin, carboplatin and oxaliplatin, along with taxanes like paclitaxel and docetaxel, are the chemotherapy agents most commonly associated with CIPN.[3]

Immune-checkpoint inhibitors (ICIs) have recently emerged as a core pillar of cancer therapy, shifting the focus of therapies from the tumor to the tumor microenvironment. This groundbreaking approach, awarded the Nobel Prize for Physiology or Medicine in 2018, works by blocking intrinsic downregulators of immunity, resulting in an increase in antitumor immunity.[4] The first antibody blocking an immune checkpoint, ipilimumab (a CTLA-4 inhibitor), was authorized in 2011. This was rapidly followed by the development of monoclonal antibodies targeting PD-1 (pembrolizumab and nivolumab) and PDL-1 (atezolizumab and durvalumab), which have become some of the most widely prescribed anticancer therapies.[5] Nearly half of all patients with metastatic cancer in economically developed countries are eligible to receive ICIs, with eight approved agents available for 17 different malignancies as of December 2021, with increasing use of these agents seen in several (neo)adjuvant and maintenance settings. ICIs are also often being used in combination regimens, including those involving other classes of ICI, cytotoxic chemotherapy, and biological and/or targeted therapies. [6]

The complexity of the nervous system and the potential for long-term morbidity make neurologic immune-related adverse events (nEAs) an emerging area of interest.[7,8] A variety of neurological side effects have been reported with ICIs, implicating both peripheral and central nervous systems. Although these are considered rare, affecting up to 3% of patients, some pose severe, potentially life-threatening consequences. [9]

A recent review on nEAs associated with ICI treatments described an extremely broad spectrum of possible syndromes, potentially involving any area of the nervous system. The overall incidence of nAEs was estimated at 3.8% with anti-CTLA-4 antibodies, 6.1% with anti-PD-1 antibodies, and 12.0% with the combination of both. Severe nAEs (grade 3 and 4) appeared to be less common than other organs AEs, with an incidence slightly higher with anti-CTLA-4 treatments (0.7%) than with anti-PD-1 antibodies (0.4%).[10] Management of these side effects typically involves discontinuation of the immune-enhancing chemotherapy and institution of immunosuppressant therapies.[9]

In an observational, retrospective, pharmacovigilance study based on adverse drug reactions reported in VigiBase, the WHO database, a total of 48,653 adverse events were reported with ICI drugs, from a total number of 18,518,994 ICSRs reported in the full VigiBase dataset. Five broad categories of neurologic events were associated with ICI treatment compared with reporting from the full database. ICIs were associated with higher reporting of neuromuscular junction dysfunction, non-infectious encephalitis and/or myelitis, cerebral artery vasculitis, peripheral neuropathy, and non-infectious meningitis. Myasthenia gravis and encephalitis were associated with anti-PD-1 whereas other nAEs were associated with anti-CTLA-4. Myasthenia gravis was characterized by high fatality rates (~ 20%), early onset (median 29 days), whereas other nAEs had lower fatality rates (6–12%) and later onset (median 61–80 days). [11]

Regarding peripheral neuropathy, a systematic review with meta-analysis comparing ICIs with chemotherapy, which included 12 trials, found a significantly lower risk of peripheral neuropathy in the ICI arms (1.9% vs 6.5%; RR, 0.42; 95% CI, 0.21-0.85; I2 = 68%; P = .02).[12]

Taking into consideration the neurological toxicity of classic antineoplastic agents, it is important to determine the frequency of peripheral neuropathy, as well as other nAEs, induced by ICIs. By adding to the body of evidence, we hope to improve peripheral neuropathy early recognition and management, contributing to the better care to cancer patients.

In this systematic review and network meta-analysis, we aimed to estimate the frequency of peripheral neuropathy associated with different treatment modalities of ICIs, as well as their comparative safety profile, regarding other nAEs such as aseptic meningitis, transverse myelitis, posterior reversible leukoencephalopathy, encephalitis, Guillain-Barré, myasthenia, facial nerve palsy, paraesthesia, headache, dysgeusia, dizziness/vertigo, insomnia and seizures.

METHODS

This systematic review is reported according to the PRISMA guidelines. [13]

Inclusion criteria

We included randomized controlled trials conducted in a population of adult (i.e., >18 years of age) patients with any type of cancer treated with any type of ICI. We compared ICI with the following:

1) other ICI;

2) conventional therapy (namely, chemotherapy, targeted therapy, or their combination);

3) placebo or no intervention; or

4) combinations of the previous interventions.

We only included trials published in English. We imposed no restrictions on the number of recruitment centers, regional area, or year of publication.

Trials had to report quantitative data on at least one of the following endpoints:

Primary endpoints: serious peripheral neuropathy, as defined in the individual trials.

Secondary endpoints: non-serious peripheral neuropathy, symptomatic neurological adverse events, central syndromic and peripheral syndromic adverse events. Due to the scarcity of individual CNS and peripheral nervous syndromes (with 0 events in many trials) we have decided to group them. The definitions used can be found in the following table:

Table 1 Symptomatic neurological adverse events, central syndromic and peripheral syndromic adverse events

Central syndromic
Aseptic Meningitis Transverse Myelitis Posterior Reversible Leukoencephalopathy Encephalitis
Peripheral syndromic
Guillain-Barré Myasthenia Facial Nerve Palsy
Symptomatic
Paraesthesia Headache Dysgeusia Dizziness/vertigo Insomnia Seizures

Literature search and trial selection

We searched MEDLINE, Embase, and CENTRAL databases, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov, from inception to February 2021 (Appendix 1: Search strategy, via Ovid). Two reviewers independently screened the search results and resolved disagreements by consensus. The reasons for exclusion were recorded at the full-text screening stage.

Data extraction and risk of bias assessment

Two reviewers independently extracted study data following a pre-established data collection form. Disagreements were resolved by adjudication with a third reviewer. Additionally, we used R (version 4.1.0) to retrieve publicly available information on trial char-

acteristics and data on safety results from the Access to Aggregate Content of ClinicalTrials.gov database. [14] This allowed us to validate the manually-extracted data, and enabled automatic updates to the result data anytime updates were made in the ClinicalTrials.gov database.

Risk of bias was independently evaluated by two authors using the Cochrane risk of bias tool, where seven domains were qualitatively classified as at high, unclear, or low risk of bias.[15] Disagreements were resolved by consensus. The overall risk of bias for each RCT was divided as high or low risk, with high risk being those RCTs in which at least one domain was assessed at a high risk of bias, or more than three domains had a rating of unclear.[15]

Data analysis

We summarized the key clinical and methodological characteristics that could potentially modify the treatment effects across trials. We tabulated and presented them to compare the characteristics and identify possible sources of clinical and methodological heterogeneity.

All outcomes were dichotomous, and therefore we analyzed these data based on the number of events and the number of participants at risk in the intervention arms. We used these data to calculate the odds ratio (OR), where an OR lower than one corresponds to a safety benefit associated with the control group.

Network meta-analysis

We conducted NMAs of clinical trials to compare all interventions- ICIs, chemotherapy, and placebo- in patients with any type of cancer. We used a Markov Chain Monte Carlo method in R using the *gemtc* package.[16] We analyzed data using log ORs and used a binomial likelihood and cloglog link.

Prior distributions

For all models, vague prior distributions were used for all trial baselines and for relative treatment or class effects (normal $(0,100^2)$). For random treatment effects models, a

minimally informative uniform prior distribution was used for the between-study heterogeneity parameter. For exchangeable-class models, a uniform (0, 5) prior distribution was used for the within-class standard deviation. [17]

Where the number of studies per comparison is small (usually less than 5), empirically informative prior distributions for the heterogeneity parameter are recommended. Therefore, we conducted these analyses using the empirically estimated meta-epidemiological distributions log normal (-3.23, 1.79).[18,19]

Model fit and choice

We chose a model and considering it as the primary analysis for NMA using the following strategy:

1. Begin with consistency models (with random and fixed treatment effects). If both fit well (i.e., posterior mean of residual deviance is close to the number of data points), choose the model with the lowest deviance information criterion (DIC) (if the difference is less than 3, choose the fixed effect model) and stop. In this review we did not proceed past this point.
2. If the fixed treatment effect-fixed class model does not fit well, try the fixed treatment effect-random class model – assess fit, compare to models in the first step here, and choose the model with the lowest DIC.
3. If neither of the models in the first or second step fit well, try also random treatment effects with random class model. Choose a final model based on DIC but interpret with caution if model fit is poor.
4. Compare results of random class models to the equivalent treatment level model (i.e., no class), if networks are connected.
5.

Unit of analysis issues

Our unit of analysis is study-level data, preferability from intention-to-treat analyses. Participants were used as the unit of analysis to eliminate the risk of multiple participants counting (i.e., number of participants with at least one event).

Dealing with missing data

Where data were missing, we used the available information (e.g., standard error, 95% confidence interval, or exact P value) to algebraically recover the missing data.[20]

Assessment of transitivity We summarized the key clinical and methodological characteristics that could potentially modify the treatment effects across trials. We tabulated and presented them to compare the characteristics and identify possible sources of clinical and methodological heterogeneity.

Assessment of inconsistency and statistical consistency

We assessed consistency by comparing the model fit and between-trial heterogeneity from NMA models versus those from an unrelated mean effects (inconsistency) model.[21] This was used as an omnibus test for inconsistency. We further created nodesplit models for each outcome.

Assessment of reporting biases

Pairwise meta-analysis

We planned to assess the possibility of reporting bias through visual inspection of funnel plot asymmetry, and Peter's test, provided that 10 or more studies per outcome were available.[22]

Network meta-analysis

We aimed to minimize reporting bias from unpublished trials or selective outcome reporting by using a broad search strategy, and by checking references of included trials and relevant systematic reviews. For each outcome, we estimated and presented the proportion of trials that contributed to the NMA.

Data synthesis

We performed statistical analysis using R (version 4.1.0).[23]

Pairwise meta-analysis

We pooled data in situations where two or more trials provided data for the same comparison by applying the Sidik-Jonkman method. [24,25] We conducted data synthesis using a random-effects model by default, independently of the presence or lack of considerable statistical heterogeneity, owing to the variety of disease subtypes that we intended to analyze.

Network meta-analysis

The model selection for the network meta-analysis was based on the following strategy, in sequence:

1. The selection process started with consistency models, with fixed and random treatment effects. In the case where there is an adequate fit with both, that is, where the subsequent *posterior mean of the residual deviance* is close to the number of data points, the model-mode was selected based on the receipt of deviance information (*deviance information criterion*, DIC).
2. In case the DIC differs by a value of less than 3 between the models (minimum value referred to in the literature [20, 23] for the difference between models to be considered relevant – principle of parsimony), the model of fixed effects was selected by default.
3. If the fixed effects model does not show an adequate fit, evaluate the fit of the *unrelated mean effects* model, compare it with the models in the first step and choose the model with the lowest DIC.

For each outcome, we constructed a network diagram to display the treatment comparisons for which direct evidence was available. We used this network diagram to examine the symmetry and geometry of the data, with node sizes corresponding to the number of participants receiving an intervention and connection sizes corresponding to the number of trials within a given comparison. When performing a network meta-analysis, we relied on the assumptions of transitivity (i.e., if drug B is superior to drug A, and drug C is superior to drug B, it is assumed that drug C is superior to drug A). [17]We performed all analyses using 100,000 iterations after a burn-in of 50,000. To assess model convergence, we assessed Gelman-Rubin-Brooks plots and the potential scale reduction factors. In case of convergence, the potential scale reduction factor should gradually shrink

down to zero with increasing numbers of interactions and should at least be below 1.05 in the end.[26] To rank the treatments for each outcome, we used the surface under the cumulative ranking curve (SUCRA).[27]

We synthetized our results by comparing the effect of each intervention with conventional therapy. Additionally, we assessed the absolute rate of each outcome, as rates per 10,000 patients. These estimates were calculated in accordance with the GRADE methodology. [28]

RESULTS

General results

Search results and characteristics of included trials

The results of the search are shown in **Error! Reference source not found.**. We included 96 trials with a combined 52,811 participants, published between 2011 and 2021. Trial references and characteristics are summarized in Appendix 2: List of included trials and Appendix 3: Characteristics of included trials, respectively. The median trial sample size was 559 (interquartile range [IQR] 75 to 763). The median participant age was 62.1 years (IQR 60.3 to 74.3), and 37.0% of the overall trial participants were female (19,540 of 52,811). 34 trials (35.4%) used a double-blind design. Nine trials were not published (9.4%).

The forms of cancer for which participants were treated are summarized in Appendix 3: Characteristics of included trials. Of note, 28 trials were conducted in patients with non-small cell lung cancer (17,014 combined participants) and 15 trials were conducted in patients with melanoma (8,008 combined participants).

The treatment modalities used across trials are summarized in Appendix 3: Characteristics of included trials. Of note, 15 trials assessed pembrolizumab alone (9,322 combined participants) and 14 trials assessed nivolumab alone (5,779 combined participants). When the interventions were combined into their treatment modality, the most frequently studied were anti-PD-1 or anti-PD-L1 inhibitors or anti-PD-1 or anti-PD-L1 inhibitors plus conventional therapy, with 25,106 and 11,924 combined participants, respectively.

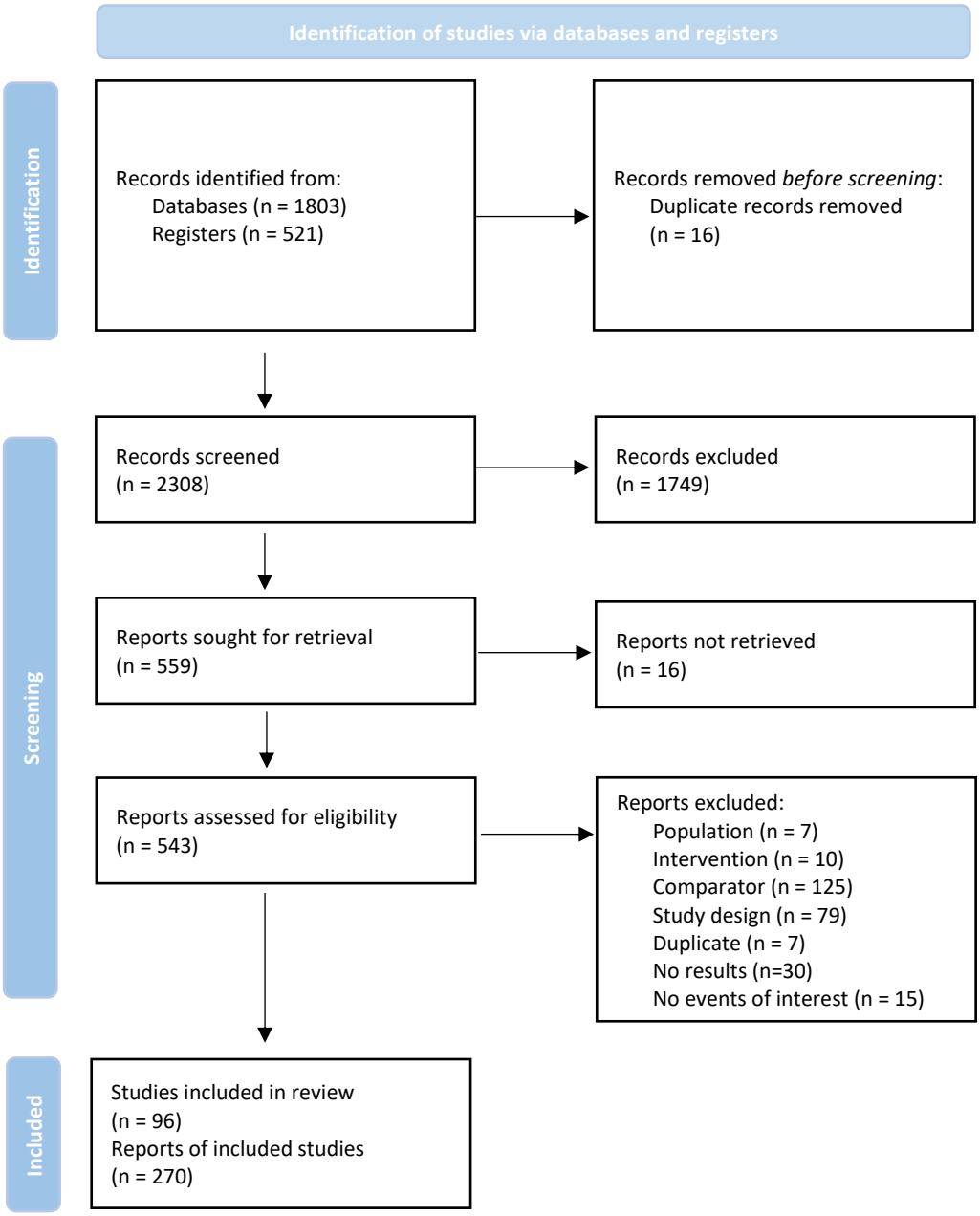


Figure 1 Flowchart of study selection and design

Risk of bias

Regarding the overall risk of bias, 17 trials (17.7%) had a low risk of bias, and 79 trials (82.3%) had a high risk of bias. The risk of bias in individual trials is available in

Appendix 5: Risk of bias assessment.

Feasibility assessment

Model fit, heterogeneity, and inconsistency assessment

For all outcomes, the analysis of treatment modalities, only the random-effect models had similar total residual deviances, when compared with the total number of data points, indicating an adequate fit of the results. Therefore, the results presented throughout pertain exclusively to the random-effects models.

For all outcomes, the analysis of treatment modalities, the between-study SD, interpreted as a measure of heterogeneity in the random-effects model, was deemed to be acceptably low. Additional evidence regarding inconsistency can be seen in the nodesplit models. Regarding evidence of statistical inconsistency, across most outcomes, only the comparisons including placebo/no intervention showed evidence of statistical inconsistency.

Regarding statistical evidence of publication bias, we did not find evidence of small-study effects in any of the outcomes assessed.

Table 2 Publication Bias

Outcome	Peters Test – P Value
Serious peripheral neuropathy	0,21
Non serious peripheral neuropathy	0,91
Central syndromic	0,60
Peripheral syndromic	0,47
Syndromic adverse	0,92

Serious peripheral neuropathy

Overall, 43 trials were used to pool data for this combined outcome, with a combined population of 25,727 participants. Figure 2 shows the network plot of all included trials according with treatment modalities.

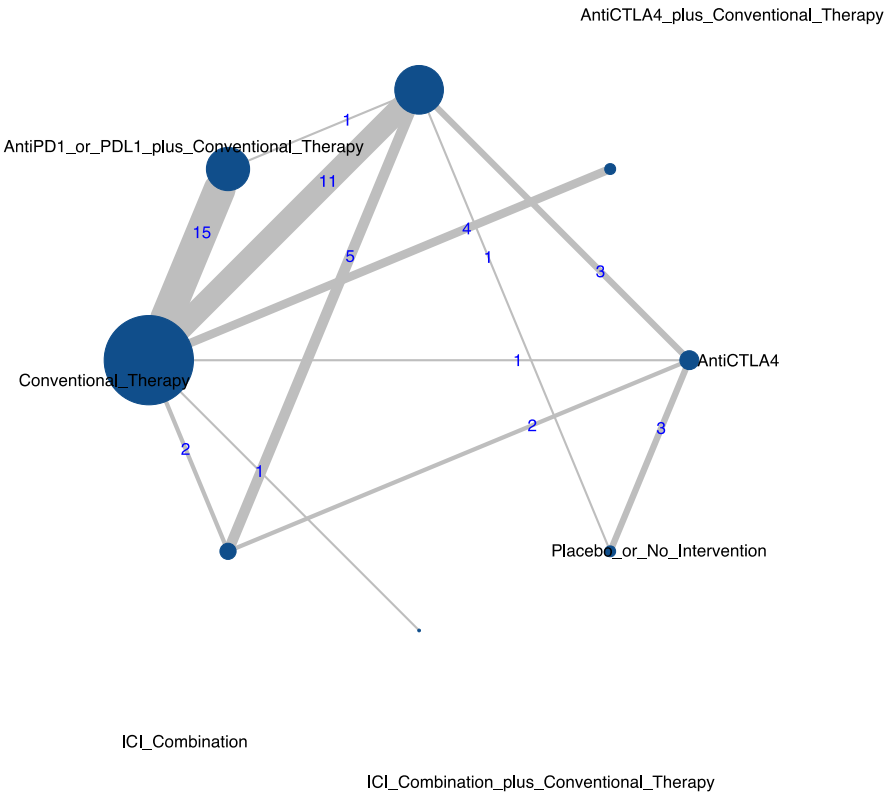


Figure 2 Network plot, serious peripheral neuropathy.

Pairwise meta-analysis

We found no evidence of statistical heterogeneity among any of the comparisons (figure 3). We also found no evidence of publication bias (t = -1,25; p = 0,21).

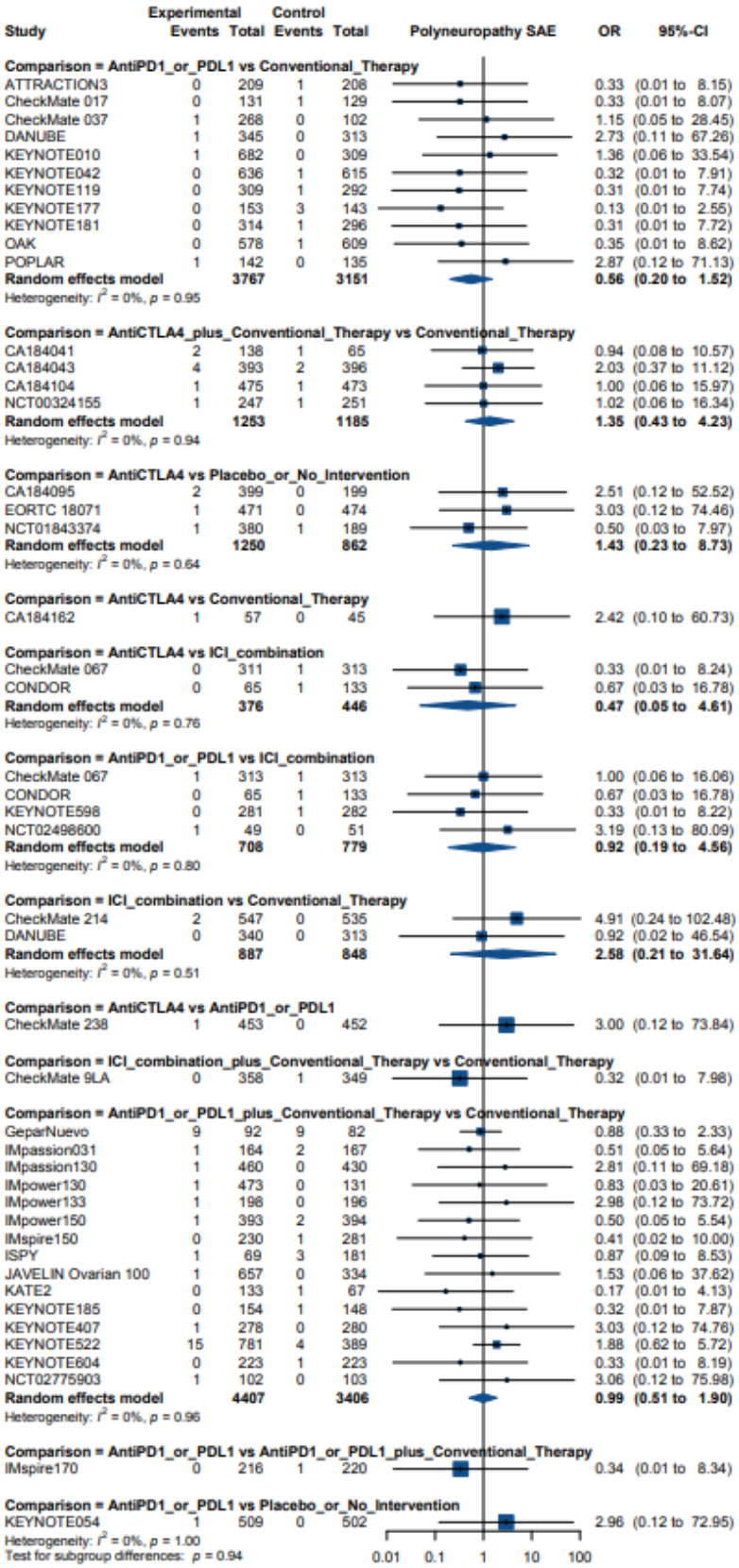


Figure 3 Forest plot, serious peripheral neuropathy

Network meta-analysis

Random effect model was chosen according to our previously described model selection criteria.

With regards to consistency, the comparison of the DIC values between the random effects (consistency) model and the inconsistency model do not suggest that the consistency assumption was violated. The standard deviation between studies in the inconsistency model, interpreted as a measure of heterogeneity, was also similar to the corresponding value in the random effect model (consistency model).

Table 3 Deviance Statistics, serious peripheral neuropathy

	Fixed effects model	Random effects model	Unrelated mean effect model	OS regression model	PFS regression model	Bias regression model
Data points	89	89	89	52	59	89
Dbar	99.92	92,29	88,55	58,12	66,74	97,59
pD	53.95	44,31	47,03	34,16	40,82	58,72
DIC	153.87	136,6	135,58	92,29	107,55	156,31
Tau	-	0,21	0,38	0,58	0,93	0,62
SD	-	0,17	0,32	0,58	0,96	0,52
SD95%CrILB	-	0,03	0,01	0,03	0,04	0,02
SD95%CrIUB	-	0,61	1,16	1,13	1,76	1,77
Beta	-	-	-	-0,39	-0,12	-0,02
Beta95%CrILB	-	-	-	-3,57	-2,14	-1,41
Beta95%CrIUB	-	-	-	1,77	1,78	1,18

As shown in the league table below, none of the comparisons of treatment modalities had a statistically significant difference between them. The best-ranked treatment modality was ICI combination plus conventional therapy (SUCRA 89%), while the worst-ranked treatment modality was anti-CTLA-4 plus conventional (SUCRA 24%).

In absolute terms, the mean event rate of serious peripheral neuropathy was 1 per 10,000 patients (95% CI: 0 to 17) and 58 per 10,000 patients (95% CI: 20 to 117) among placebo treated patient and Anti-CTLA-4 plus conventional treated patients, respectively.

Table 4 Serious peripheral neuropathy. League table of NMA estimations. Results in bold indicates statistical significance. Comparisons should be read from up to right in the lower-left corner or from down to left in the upper-right corner.

AntiCTLA4	1.31 (0.15 to 11.26)	0.65 (0.11 to 3.99)	1.09 (0.14 to 6.93)	0.87 (0.12 to 5.16)	1.12 (0.17 to 8.71)	0.02 (0 to 4.59)	0.17 (0.01 to 1.35)
0.77 (0.09 to 6.86)	AntiCTLA4 plus Conventional Therapy	0.5 (0.11 to 2.28)	0.83 (0.21 to 3.05)	0.66 (0.19 to 2.11)	0.86 (0.13 to 5.96)	0.02 (0 to 2.48)	0.13 (0 to 2.01)
1.55 (0.25 to 9.52)	2.00 (0.44 to 9.38)	AntiPD1 or PDL1	1.66 (0.55 to 4.99)	1.32 (0.5 to 3.33)	1.76 (0.4 to 7.4)	0.04 (0 to 4.06)	0.27 (0.01 to 2.89)
0.92 (0.14 to 7.18)	1.20 (0.33 to 4.78)	0.60 (0.20 to 1.81)	AntiPD1 or PDL1 plus Conventional Therapy	0.8 (0.44 to 1.41)	1.07 (0.21 to 5.57)	0.02 (0 to 2.48)	0.16 (0.01 to 2.06)
1.15 (0.19 to 8.21)	1.51 (0.47 to 5.2)	0.76 (0.30 to 1.98)	1.25 (0.71 to 2.27)	Conventional Therapy	1.33 (0.3 to 6.21)	0.03 (0 to 2.97)	0.2 (0.01 to 2.45)
0.89 (0.11 to 5.94)	1.16 (0.17 to 7.71)	0.57 (0.14 to 2.50)	0.94 (0.18 to 4.70)	0.75 (0.16 to 3.38)	ICI combination	0.02 (0 to 3.16)	0.15 (0 to 1.95)
41.43 (0.22 to 117673.41)	53 (0.4 to 112838.51)	24.93 (0.25 to 62685.4)	42.07 (0.40 to 101962.06)	33.32 (0.34 to 80642.68)	46.57 (0.32 to 140222.91)	ICI combination plus Conventional Therapy	6.62 (0.02 to 21899.56)
5.78 (0.74 to 128.55)	7.85 (0.50 to 236.79)	3.76 (0.35 to 103.52)	6.32 (0.49 to 177.88)	4.99 (0.41 to 138.37)	6.73 (0.51 to 208.51)	0.15 (0.00 to 48.76)	Placebo or No Intervention

Non-serious peripheral neuropathy

Overall, 43 trials were used to pool data for this combined outcome, with a combined population of 25,727 participants. Figure 4 shows the network plot of all included trials according to treatment modalities.

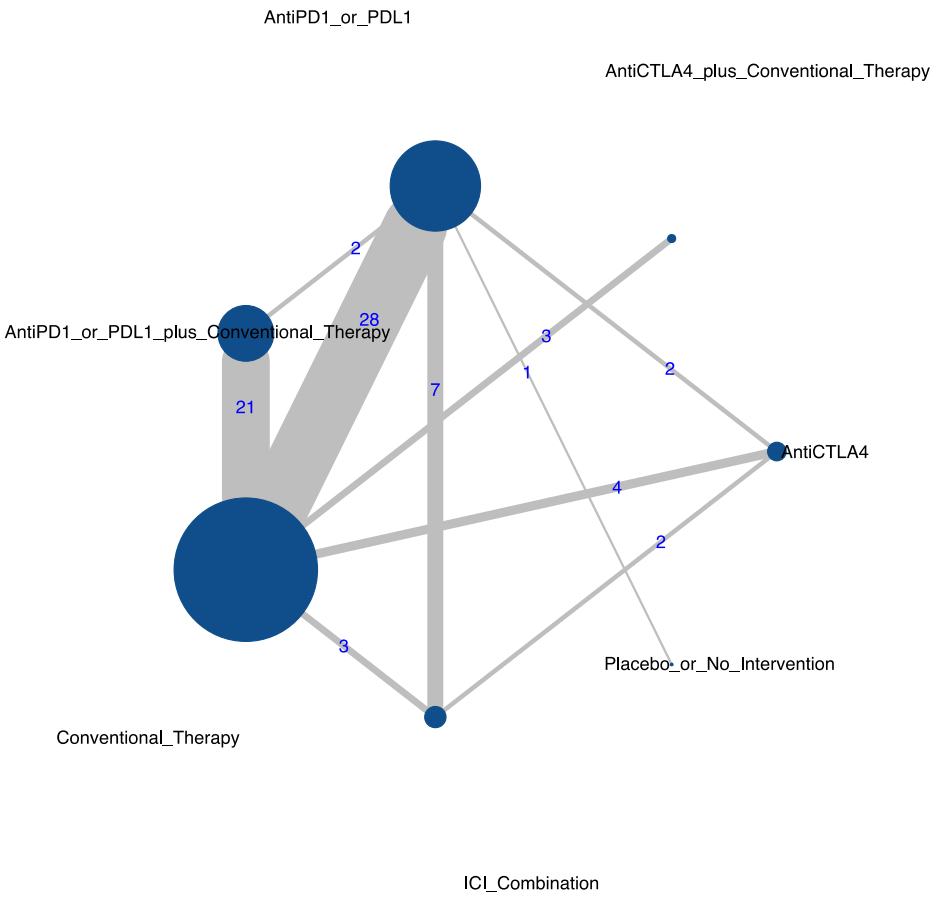
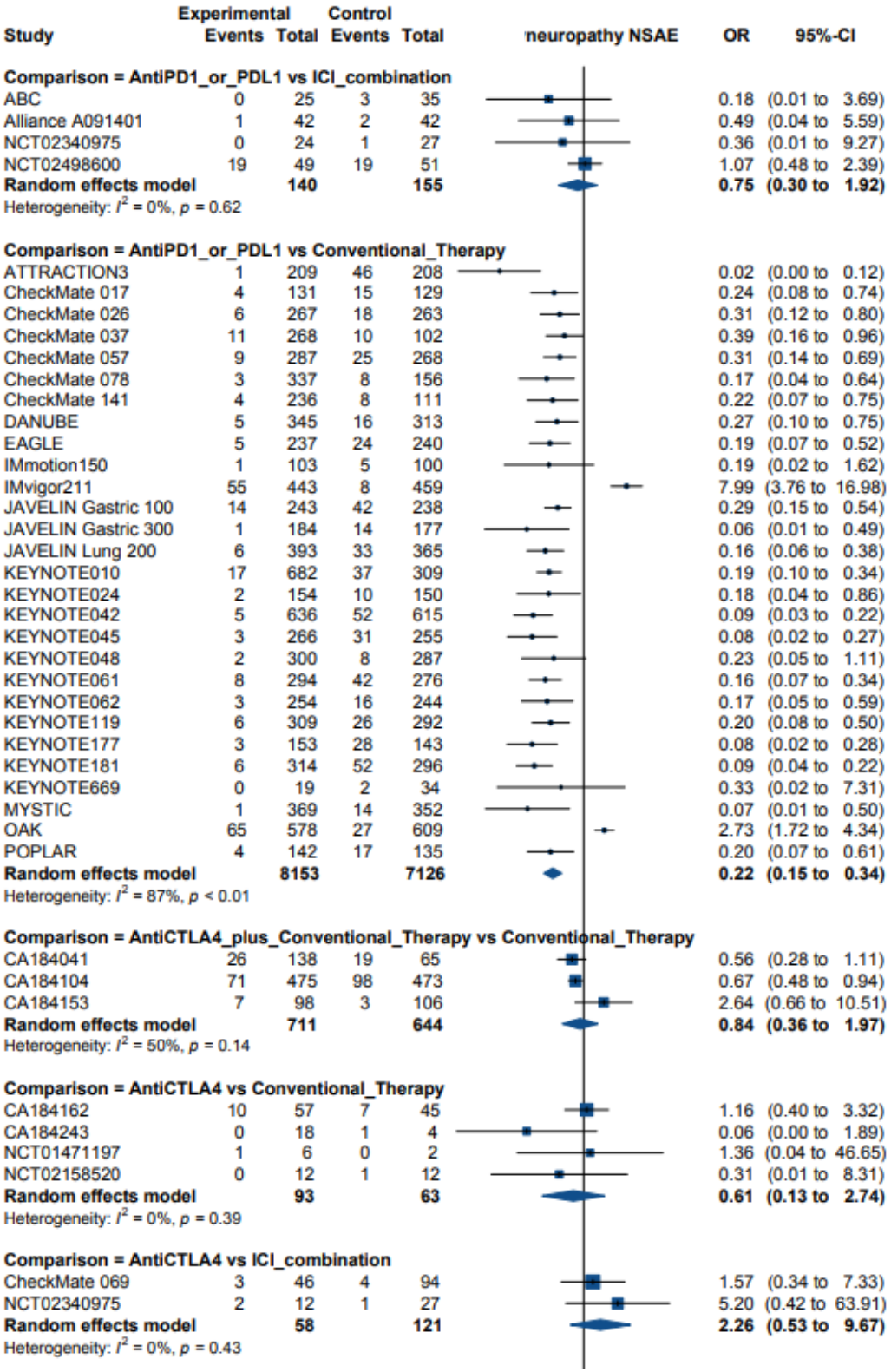


Figure 4 Network plot, non-serious peripheral neuropathy

Pairwise meta-analysis

Regarding pairwise meta-analysis, we only found evidence of statistical heterogeneity among anti-PD-1 or anti-PD-L1 versus conventional (I^2= 87%), and anti-CTLA-4 plus conventional therapy versus conventional therapy (I^2= 50%) with all other comparisons in the network displaying low values of I^2. We also found no evidence of publication bias (t = 0,10; p = 0,91).


Study
Experimental Events Total
Control Events Total
neuropathy NSAE
OR 95%-CI
Comparison = AntiPD1_or_PDL1 vs ICI_combination
ABC 0 25 3 35 0.18 (0.01 to 3.69)
Alliance A091401 1 42 2 42 0.49 (0.04 to 5.59)
NCT02340975 0 24 1 27 0.36 (0.01 to 9.27)
NCT02498600 19 49 19 51 1.07 (0.48 to 2.39)
Random effects model 140 155 0.75 (0.30 to 1.92)
Heterogeneity: I^2 = 0%, p = 0.62
Comparison = AntiPD1_or_PDL1 vs Conventional_Therapy
ATTRACTION3 1 209 46 208 0.02 (0.00 to 0.12)
CheckMate 017 4 131 15 129 0.24 (0.08 to 0.74)
CheckMate 026 6 267 18 263 0.31 (0.12 to 0.80)
CheckMate 037 11 268 10 102 0.39 (0.16 to 0.96)
CheckMate 057 9 287 25 268 0.31 (0.14 to 0.69)
CheckMate 078 3 337 8 156 0.17 (0.04 to 0.64)
CheckMate 141 4 236 8 111 0.22 (0.07 to 0.75)
DANUBE 5 345 16 313 0.27 (0.10 to 0.75)
EAGLE 5 237 24 240 0.19 (0.07 to 0.52)
IMmotion150 1 103 5 100 0.19 (0.02 to 1.62)
IMvigor211 55 443 8 459 7.99 (3.76 to 16.98)
JAVELIN Gastric 100 14 243 42 238 0.29 (0.15 to 0.54)
JAVELIN Gastric 300 1 184 14 177 0.06 (0.01 to 0.49)
JAVELIN Lung 200 6 393 33 365 0.16 (0.06 to 0.38)
KEYNOTE010 17 682 37 309 0.19 (0.10 to 0.34)
KEYNOTE024 2 154 10 150 0.18 (0.04 to 0.86)
KEYNOTE042 5 636 52 615 0.09 (0.03 to 0.22)
KEYNOTE045 3 266 31 255 0.08 (0.02 to 0.27)
KEYNOTE048 2 300 8 287 0.23 (0.05 to 1.11)
KEYNOTE061 8 294 42 276 0.16 (0.07 to 0.34)
KEYNOTE062 3 254 16 244 0.17 (0.05 to 0.59)
KEYNOTE119 6 309 26 292 0.20 (0.08 to 0.50)
KEYNOTE177 3 153 28 143 0.08 (0.02 to 0.28)
KEYNOTE181 6 314 52 296 0.09 (0.04 to 0.22)
KEYNOTE669 0 19 2 34 0.33 (0.02 to 7.31)
MYSTIC 1 369 14 352 0.07 (0.01 to 0.50)
OAK 65 578 27 609 2.73 (1.72 to 4.34)
POPLAR 4 142 17 135 0.20 (0.07 to 0.61)
Random effects model 8153 7126 0.22 (0.15 to 0.34)
Heterogeneity: I^2 = 87%, p < 0.01
Comparison = AntiCTLA4_plus_Conventional_Therapy vs Conventional_Therapy
CA184041 26 138 19 65 0.56 (0.28 to 1.11)
CA184104 71 475 98 473 0.67 (0.48 to 0.94)
CA184153 7 98 3 106 2.64 (0.66 to 10.51)
Random effects model 711 644 0.84 (0.36 to 1.97)
Heterogeneity: I^2 = 50%, p = 0.14
Comparison = AntiCTLA4 vs Conventional_Therapy
CA184162 10 57 7 45 1.16 (0.40 to 3.32)
CA184243 0 18 1 4 0.06 (0.00 to 1.89)
NCT01471197 1 6 0 2 1.36 (0.04 to 46.65)
NCT02158520 0 12 1 12 0.31 (0.01 to 8.31)
Random effects model 93 63 0.61 (0.13 to 2.74)
Heterogeneity: I^2 = 0%, p = 0.39
Comparison = AntiCTLA4 vs ICI_combination
CheckMate 069 3 46 4 94 1.57 (0.34 to 7.33)
NCT02340975 2 12 1 27 5.20 (0.42 to 63.91)
Random effects model 58 121 2.26 (0.53 to 9.67)
Heterogeneity: I^2 = 0%, p = 0.43

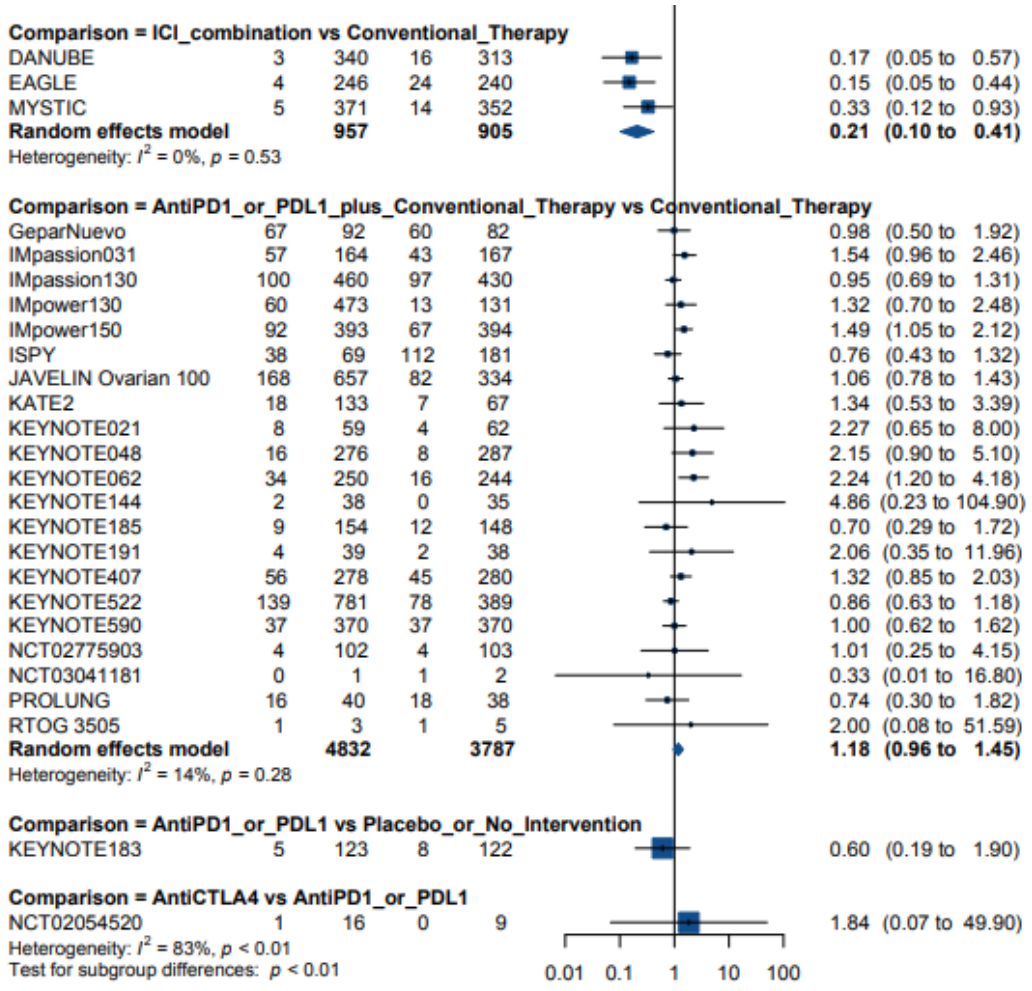


Figure 5 Forest plot, non-serious peripheral neuropathy

Network meta-analysis

Random effect model was chosen according to our previously described model selection criteria.

With regards to consistency, the comparison of the DIC values between the random effects (consistency) model and the inconsistency model does not suggest that the consistency assumption was violated. The standard deviation between studies in the inconsistency model, interpreted as a measure of heterogeneity, was also similar to the corresponding value in the random effect model (consistency model).

Table 5 Deviance Statistics, non-serious peripheral neuropathy.,

	Fixed effects model	Random effects model	Unrelated mean effect model	OS regression model	PFS regression model	Bias regression model
Data points	128	128	128	80	86	128
Dbar	410.73	125,81	124,57	79,63	82,52	125,93
pD	68.5	101,79	103,12	68,98	73,99	105,55
DIC	479.23	227,6	227,69	148,6	156,52	231,49
Tau	-	0,78	0,81	1,03	0,97	0,85
SD	-	0,78	0,8	1,01	0,96	0,84
SD95%CrILB	-	0,61	0,62	0,76	0,73	0,65
SD95%CrIUB	-	1	1,05	1,39	1,3	1,09
Beta				-0,2	-1,56	-0,01
Beta95%CrILB				-1,15	-5,65	-0,74
Beta95%CrIUB				0,72	0,49	0,72

The league table below presents the results of the NMA comparing the odds for non-serious peripheral neuropathy between different treatment modalities. All statistically significant differences are highlighted in bold. Compared with conventional therapy, both ICI combinations (OR 0.26 95% CrI 0.58 to 0.12) and Anti-PD-1 or PD-L1 (OR 0.21, 95% Crl 0.15 to 0.30) have a significantly lower odds of non-serious peripheral neuropathy of non-serious peripheral neuropathy.

Table 6 Non-serious peripheral neuropathy. League table of NMA estimations. Results in bold indicates statistical significance. Comparisons should be read from up to right in the lower-left corner or from down to left in the upper-right corner.

AntiCTLA4	1.11 (0.24 to 5.13)	0.26 (0.08 to 0.86)	1.58 (0.46 to 5.46)	1.25 (0.39 to 4)	0.34 (0.1 to 1.15)	0.43 (0.05 to 3.98)
0.90 (0.20 to 4.18)	AntiCTLA4 plus Conventional Therapy	0.24 (0.08 to 0.68)	1.43 (0.48 to 4.14)	1.13 (0.41 to 3.04)	0.3 (0.08 to 1.06)	0.38 (0.04 to 3.4)
3.80 (1.16 to 12.45)	4.18 (1.48 to 12.26)	AntiPD1 or PDL1	5.99 (3.63 to 10.14)	4.73 (3.36 to 6.73)	1.27 (0.59 to 2.73)	1.63 (0.25 to 11)
0.63 (0.18 to 2.17)	0.70 (0.24 to 2.08)	0.17 (0.10 to 0.28)	AntiPD1 or PDL1 plus Conventional Therapy	0.79 (0.53 to 1.16)	0.21 (0.09 to 0.5)	0.27 (0.04 to 1.95)
0.80 (0.25 to 2.58)	0.88 (0.33 to 2.43)	**0.21 (0.15 to 0.30)**	1.27 (0.86 to 1.89)	Conventional Therapy	0.27 (0.12 to 0.59)	0.34 (0.05 to 2.35)
2.98 (0.87 to 10.38)	3.29 (0.94 to 11.81)	0.79 (0.37 to 1.70)	**4.74 (1.98 to 11.26)**	**3.74 (1.7 to 8.1)**	ICI combination	1.28 (0.17 to 9.84)
2.33 (0.25 to 21.65)	2.60 (0.29 to 23.02)	0.61 (0.09 to 4.06)	3.69 (0.51 to 26.32)	2.9 (0.43 to 20.19)	0.78 (0.1 to 6)	Placebo or No Intervention

The best-ranked treatment modality was anti-PD-1/anti-PDL-1 (SUCRA 90%), while the worst-ranked anti-PD-1 or anti-PDL-1 plus conventional therapy (SUCRA 11%). In absolute terms, the mean event rate of non-serious peripheral neuropathy was 232 per 10,000 patients (95% CI 747 to 2100) among patient treated with anti-PD-1/anti-PD-L1 and 1,926 per 10,000 patients (95% CI 1,260 to 2,694) among patients treated with anti-PD-1 or anti-PD-L1 plus conventional therapy.

Central syndromic adverse events

Overall, 30 trials were used to pool data for this combined outcome, with a combined population of 22,351 participants. Figure 6 shows the network plot of all included trials according with treatment modalities.

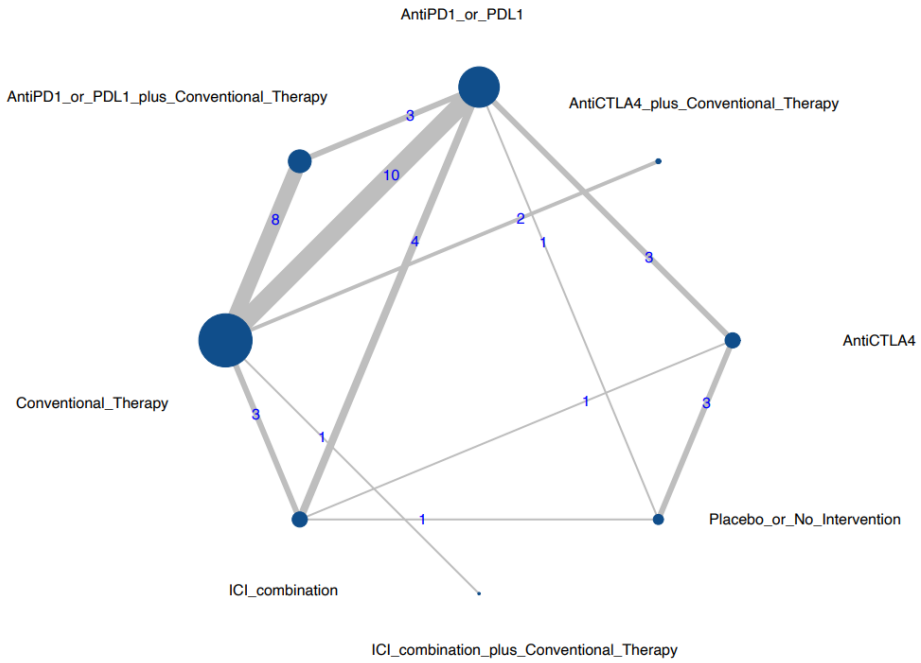


Figure 6 Network plot, central syndromic.

Pairwise meta-analysis

We found no evidence of statistical heterogeneity among any of the comparisons. We also found no evidence of publication bias (t = -0,52; p = 0,60).

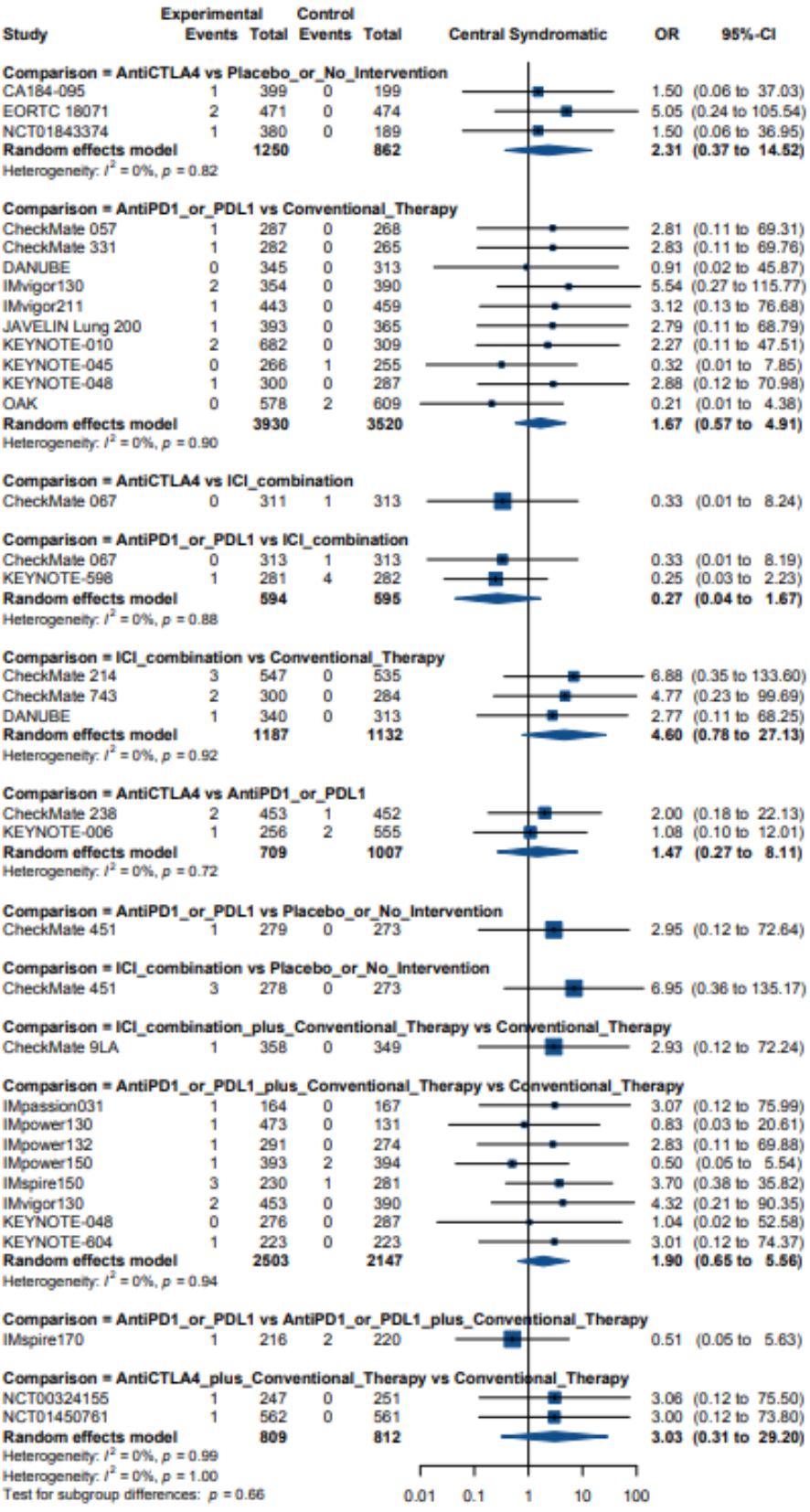


Figure 7 Forest plot, central syndromic adverse events

Network meta-analysis

Random effect model was chosen according to our previously described model selection criteria.

With regards to consistency, the comparison of the DIC values between the random effects (consistency) model and the inconsistency model does not suggest that the consistency assumption was violated. The standard deviation between studies in the inconsistency model, interpreted as a measure of heterogeneity, was higher to the corresponding value in the random effect model (consistency model).

Table 7 Deviance Statistics, central syndromic adverse events

	Fixed effects model	Random effects model	Unrelated mean effect
Data points	65	65	65
Dbar	58.17	54,33	54,82
pD	37.33	31,04	34,38
DIC	95.5	85,36	89,2
Tau	-	0,24	0,74
SD	-	0,18	0,6
SD95%CrILB	-	0,03	0,03
SD95%CrIUB	-	0,71	2,29

The league table below presents the results of the NMA comparing the odds for central syndromic adverse events between different treatment modalities. All statistically significant differences are highlighted in bold. Compared with conventional therapy anti-CTLA-4 plus conventional therapy (OR 72.86, 95% CrI 1.23 to 54682.93), ICI combinations (OR 12,5, 95% CrI 50 to 3,125), anti-PD-1 or anti-PD-L1(OR 3.55, 95% CrI 1.25 to 10.46), anti-PD-1 or anti- PD-L1 plus conventional therapy (OR 3.27, 95% CrI 1.19 to 10.08), were associated with statistically significant increased odds of central syndromic adverse events.

Table 8 Central syndromic adverse events. League table of NMA estimations. Results in bold indicate statistical significance. Comparisons should be read from up to right in the lower-left corner or from down to left in the upper-right corner.

AntiCTLA4	11.66 (0.12 to 8876.03)	0.55 (0.11 to 2.6)	0.51 (0.07 to 3.56)	0.16 (0.02 to 1.04)	1.95 (0.31 to 13.26)	0.63 (0.01 to 81.84)	0.01 (0 to 0.3)
0.09 (0.00 to 8.03)	AntiCTLA4 plus Conventional Therapy	0.05 (0 to 3.24)	0.05 (0 to 3.1)	0.01 (0 to 0.81)	0.17 (0 to 14.19)	0.05 (0 to 33.04)	0 (0 to 0.25)
1.82 (0.39 to 8.90)	19.97 (0.31 to 17850.25)	AntiPD1 or PDL1	0.93 (0.28 to 3.02)	0.28 (0.1 to 0.8)	3.51 (1.07 to 13.07)	1.13 (0.02 to 120.62)	0.01 (0 to 0.59)
1.96 (0.28 to 13.82)	21.98 (0.32 to 17489.95)	1.08 (0.33 to 3.53)	AntiPD1 or PDL1 plus Conventional Therapy	0.31 (0.1 to 0.84)	3.79 (0.81 to 20.07)	1.2 (0.02 to 133.68)	0.01 (0 to 0.9)
6.38 (0.97 to 44.60)	**72.86 (1.23 to 54682.93)**	**3.55 (1.25 to 10.46)**	**3.27 (1.19 to 10.08)**	Conventional Therapy	12.27 (3.11 to 62.6)	3.94 (0.09 to 407.24)	0.04 (0 to 2.73)
0.51 (0.08 to 3.24)	5.93 (0.07 to 5921.17)	**0.29 (0.08 to 0.94)**	0.26 (0.05 to 1.24)	**0.08 (0.02 to 0.32)**	ICI combination	0.32 (0.01 to 40.08)	0 (0 to 0.18)
1.59 (0.01 to 104.51)	19.8 (0.03 to 33915.97)	0.88 (0.01 to 45.09)	0.84 (0.01 to 43.12)	0.25 (0.00 to 11.10)	3.15 (0.02 to 192.23)	ICI combination plus Conventional Therapy	0.01 (0 to 3.64)
139.32 (3.33 to 191176.71)	**2584.99 (3.96 to 56278953.28)**	**80.63 (1.68 to 92992.17)**	**77.23 (1.11 to 107440.81)**	22.74 (0.37 to 32230.24)	**276.30 (5.59 to 427238.48)**	121.46 (0.27 to 417540.10)	Placebo or No Intervention

Regarding the results at the level of treatment modalities, the best-ranked treatment modality was conventional therapy (SUCRA 77%), while the worst-ranked treatment modality was anti-CTLA-4 plus conventional therapy (SUCRA 4%).

In absolute terms, the mean central syndromic adverse events rate was 63 per 10,000 patients (95% CI 34 to 102) among patients treated with ICIs combinations and 2 per 10,000 patients (95% CI 0 to 6) among patients treated conventional therapy.

Peripheral syndromic adverse events

Overall, 29 trials were used to pool data for this combined outcome, with a combined population of 19,825participants. Figure 8 shows the network plot of all included trials according with treatment modalities.

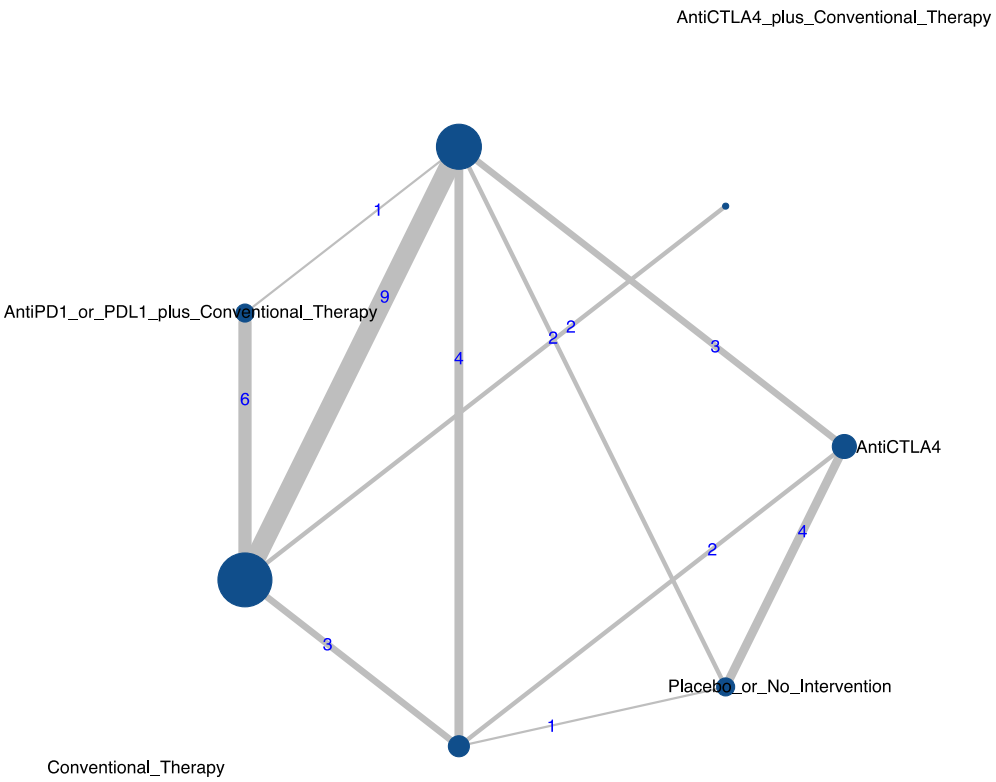


Figure 8 Network plot, peripheral syndromic adverse events

Pairwise meta-analysis

We found no evidence of statistical heterogeneity among any of the comparisons. We also found no evidence of publication bias (t = -0,71; p = 0,47).

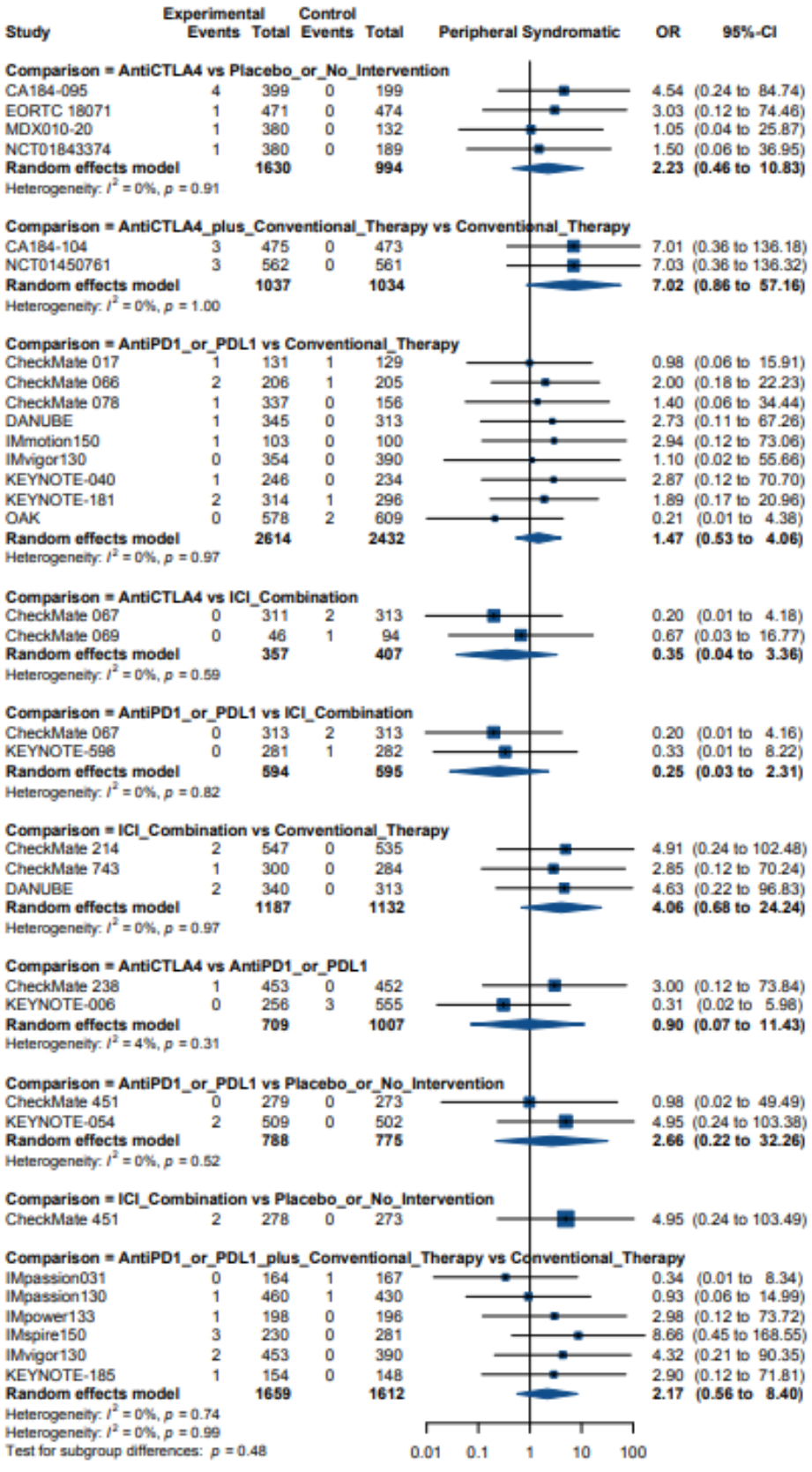


Figure 9 Forest plot, Peripheral syndromic adverse events

Network meta-analysis

Random effect model was chosen according to our previously described model selection criteria.

With regards to consistency, the comparison of the DIC values between the random effects (consistency) model and the inconsistency model does not suggest that the consistency assumption was violated. The standard deviation between studies in the inconsistency model, interpreted as a measure of heterogeneity, was also similar to the corresponding value in the random effect model (consistency model).

Table 9 Deviance Statistics, Peripheral syndromic adverse events

	Fixed effects model	Random effects model	Unrelated mean effect model
Data points	62	62	62
Dbar	57.44	53,99	52,76
pD	35.97	29,57	31,77
DIC	93.4	83,55	84,53
Tau	-	0,28	0,83
SD	-	0,21	0,69
SD95%CrILB	-	0,04	0,03
SD95%CrIUB	-	1,02	2,45

The league table below, presents the results of the NMA comparing the odds for peripheral syndromic adverse events between different treatment modalities. All statistically significant differences are highlighted in bold.

Compared with conventional therapy anti-CTLA-4 plus conventional therapy (OR 136.8, 95% CrI 3.39 to 241894.68), ICI combinations (OR 8.33, 95% CrI 50 to2) and Anti-PD-1 or PDL-1 plus conventional therapy (OR 5.61, 95% CrI 1.39 to 37.56) were associated with statistically significant increased odds of peripheral syndromic adverse events.

Table 10 Peripheral syndromic adverse events. League table of NMA estimations. Results in bold indicate statistical significance. Comparisons should be read from up to right in the lower-left corner or from down to left in the upper-right corner.

AntiCTLA4	78.71 (0.87 to 176237.5)	1.04 (0.18 to 6.95)	3.14 (0.29 to 43.55)	0.54 (0.07 to 4.28)	4.5 (0.72 to 34.86)	0.01 (0 to 0.25)
0.01 (0 .00to 1.14)	AntiCTLA4 plus Conventional Therapy	0.01 (0 to 0.71)	0.04 (0 to 2.54)	0.01 (0 to 0.29)	0.06 (0 to 3.53)	0 (0 to 0.03)
0.96 (0.14 to 5.43)	**73.18 (1.40 to 139845.56)**	AntiPD1 or PDL1	2.97 (0.6 to 22.69)	0.52 (0.18 to 1.44)	4.33 (1.15 to 19.39)	0.01 (0 to 0.25)
0.32 (0.02 to 3.46)	22.85 (0.39 to 47480.53)	0.34 (0.04 to 1.66)	AntiPD1 or PDL1 plus Conventional Therapy	0.18 (0.03 to 0.72)	1.45 (0.16 to 11.14)	0 (0 to 0.12)
1.86 (0.23 to 13.70)	**136.8 (3.39 to 241894.68)**	1.93 (0.69 to 5.65)	**5.61 (1.39 to 37.56)**	Conventional Therapy	8.37 (2.01 to 42.78)	0.01 (0 to 0.58)
0.22 (0.03 to 1.39)	16.60 (0.28 to 30261.62)	**0.23 (0.05 to 0.87)**	0.69 (0.09 to 6.24)	**0.12 (0.02 to 0.50)**	ICI Combination	0 (0 to 0.07)
147.01 (4.06 to 157197.21)	**17668.12 (30.27 to 457846167.73)**	**167.28 (4.04 to 130973)**	**525.69 (8.46 to 543246.10)**	**84.55 (1.73 to 71526.23)**	**746.63 (14.90 to 698838.64)**	Placebo or No Intervention

Regarding the results at the level of treatment modalities, the best-ranked treatment modality was conventional therapy (SUCRA 82%), while the worst-ranked treatment modality was Anti-CTLA- 4 plus conventional therapy (SUCRA 13%).

In absolute terms, the mean central syndromic adverse events event rate of was 58 per 10,000 patients (95% CI 21 to 113) among patient treated with Anti-CTLA-4 plus conventional therapy and 4 per 10,000 patients (95% CI 0 to 12) among patients treated conventional therapy.

Symptomatic adverse events

Overall, 77 trials were used to pool data for this combined outcome, with a combined population of 43,843 participants. Figure 10 shows the network plot of all included trials according with treatment modalities.

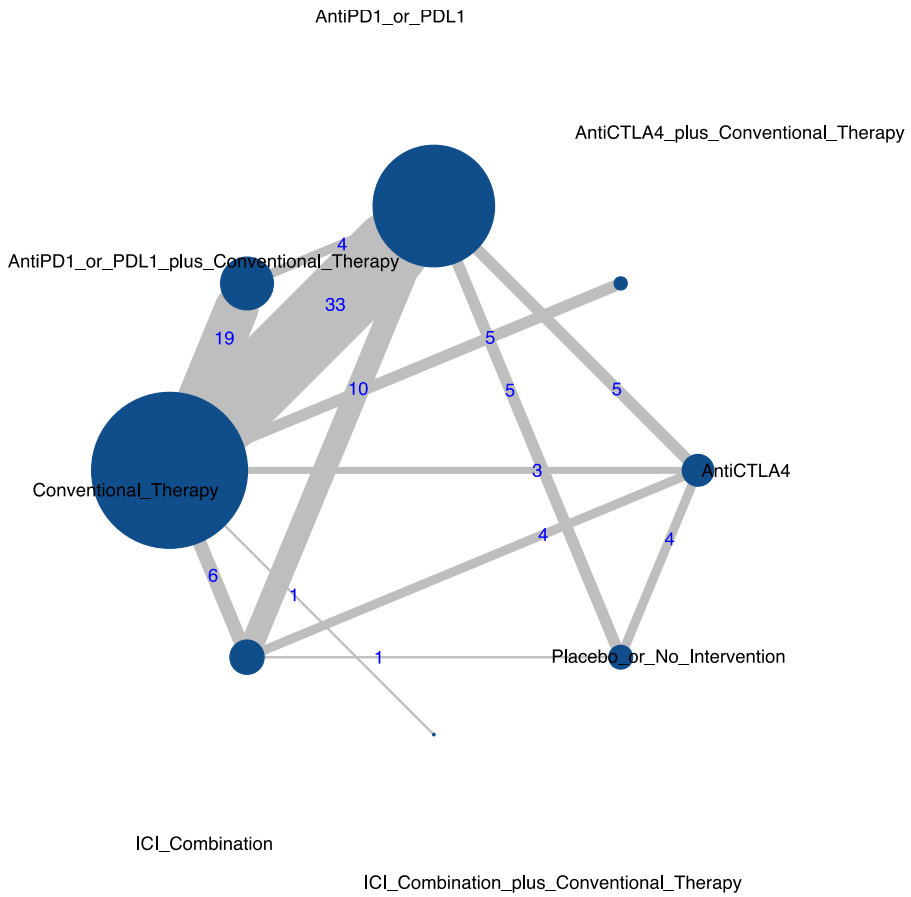
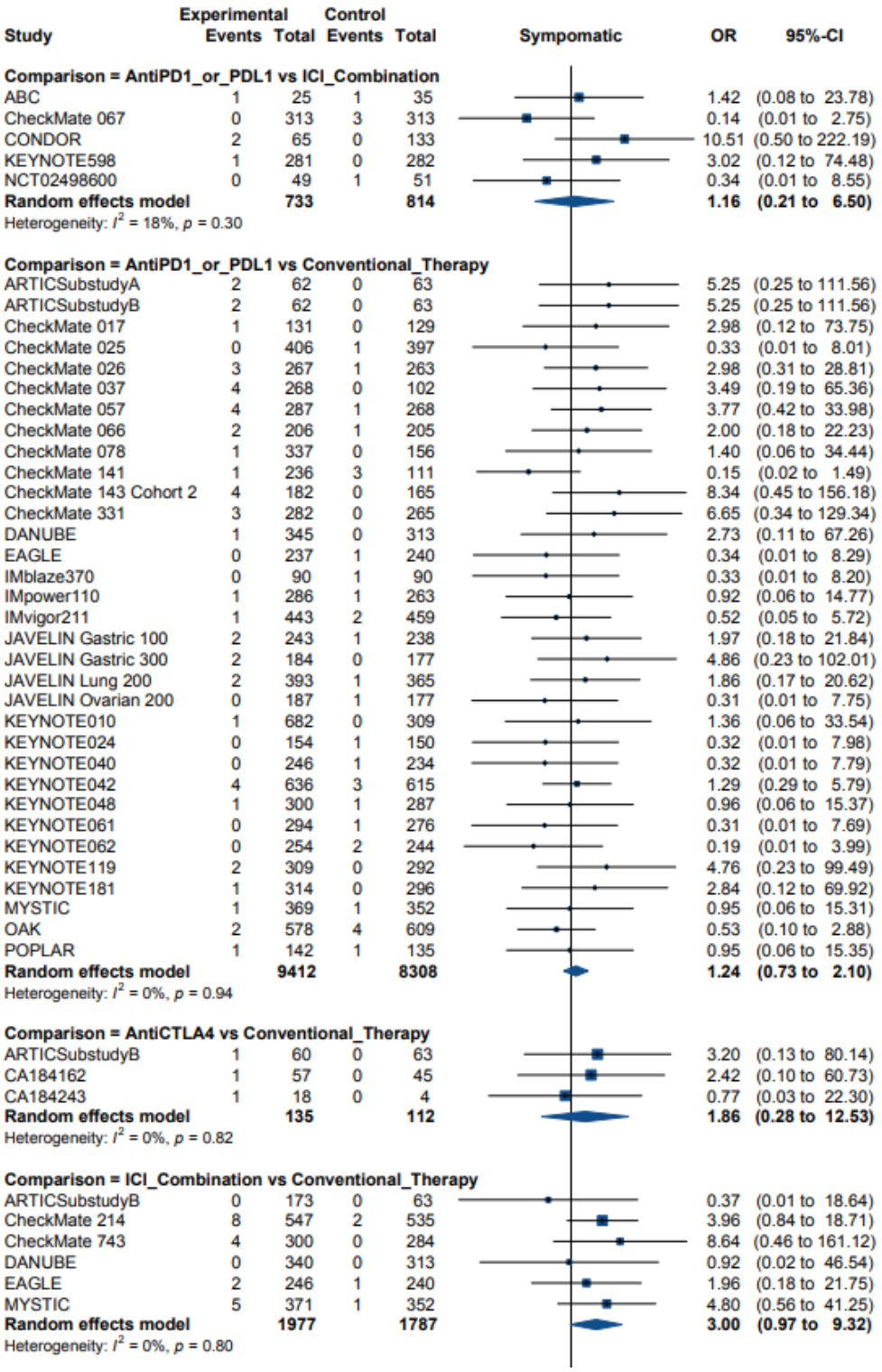


Figure 10 Network plot, Symptomatic adverse events

Pairwise meta-analysis

Regarding pairwise meta-analysis, we only found evidence of statistical heterogeneity among anti-CTLA4 versus placebo or no intervention (I^2= 38%), and anti-CTLA4 plus conventional therapy versus conventional therapy (I^2= 46%) with all other comparisons in the network displaying low values of I^2. Also found no evidence of publication bias (t = -0,09; p = 0,92).


Study
Experimental Events Total
Control Events Total
Sympomatic
OR 95%-CI
Comparison = AntiPD1_or_PDL1 vs ICI_Combination
ABC 1 25 1 35 1.42 (0.08 to 23.78)
CheckMate 067 0 313 3 313 0.14 (0.01 to 2.75)
CONDOR 2 65 0 133 10.51 (0.50 to 222.19)
KEYNOTE598 1 281 0 282 3.02 (0.12 to 74.48)
NCT02498600 0 49 1 51 0.34 (0.01 to 8.55)
Random effects model 733 814 1.16 (0.21 to 6.50)
Heterogeneity: I^2 = 18%, p = 0.30
Comparison = AntiPD1_or_PDL1 vs Conventional_Therapy
ARTICSubstudyA 2 62 0 63 5.25 (0.25 to 111.56)
ARTICSubstudyB 2 62 0 63 5.25 (0.25 to 111.56)
CheckMate 017 1 131 0 129 2.98 (0.12 to 73.75)
CheckMate 025 0 406 1 397 0.33 (0.01 to 8.01)
CheckMate 026 3 267 1 263 2.98 (0.31 to 28.81)
CheckMate 037 4 268 0 102 3.49 (0.19 to 65.36)
CheckMate 057 4 287 1 268 3.77 (0.42 to 33.98)
CheckMate 066 2 206 1 205 2.00 (0.18 to 22.23)
CheckMate 078 1 337 0 156 1.40 (0.06 to 34.44)
CheckMate 141 1 236 3 111 0.15 (0.02 to 1.49)
CheckMate 143 Cohort 2 4 182 0 165 8.34 (0.45 to 156.18)
CheckMate 331 3 282 0 265 6.65 (0.34 to 129.34)
DANUBE 1 345 0 313 2.73 (0.11 to 67.26)
EAGLE 0 237 1 240 0.34 (0.01 to 8.29)
IMblaze370 0 90 1 90 0.33 (0.01 to 8.20)
IMpower110 1 286 1 263 0.92 (0.06 to 14.77)
IMvigor211 1 443 2 459 0.52 (0.05 to 5.72)
JAVELIN Gastric 100 2 243 1 238 1.97 (0.18 to 21.84)
JAVELIN Gastric 300 2 184 0 177 4.86 (0.23 to 102.01)
JAVELIN Lung 200 2 393 1 365 1.86 (0.17 to 20.62)
JAVELIN Ovarian 200 0 187 1 177 0.31 (0.01 to 7.75)
KEYNOTE010 1 682 0 309 1.36 (0.06 to 33.54)
KEYNOTE024 0 154 1 150 0.32 (0.01 to 7.98)
KEYNOTE040 0 246 1 234 0.32 (0.01 to 7.79)
KEYNOTE042 4 636 3 615 1.29 (0.29 to 5.79)
KEYNOTE048 1 300 1 287 0.96 (0.06 to 15.37)
KEYNOTE061 0 294 1 276 0.31 (0.01 to 7.69)
KEYNOTE062 0 254 2 244 0.19 (0.01 to 3.99)
KEYNOTE119 2 309 0 292 4.76 (0.23 to 99.49)
KEYNOTE181 1 314 0 296 2.84 (0.12 to 69.92)
MYSTIC 1 369 1 352 0.95 (0.06 to 15.31)
OAK 2 578 4 609 0.53 (0.10 to 2.88)
POPLAR 1 142 1 135 0.95 (0.06 to 15.35)
Random effects model 9412 8308 1.24 (0.73 to 2.10)
Heterogeneity: I^2 = 0%, p = 0.94
Comparison = AntiCTLA4 vs Conventional_Therapy
ARTICSubstudyB 1 60 0 63 3.20 (0.13 to 80.14)
CA184162 1 57 0 45 2.42 (0.10 to 60.73)
CA184243 1 18 0 4 0.77 (0.03 to 22.30)
Random effects model 135 112 1.86 (0.28 to 12.53)
Heterogeneity: I^2 = 0%, p = 0.82
Comparison = ICI_Combination vs Conventional_Therapy
ARTICSubstudyB 0 173 0 63 0.37 (0.01 to 18.64)
CheckMate 214 8 547 2 535 3.96 (0.84 to 18.71)
CheckMate 743 4 300 0 284 8.64 (0.46 to 161.12)
DANUBE 0 340 0 313 0.92 (0.02 to 46.54)
EAGLE 2 246 1 240 1.96 (0.18 to 21.75)
MYSTIC 5 371 1 352 4.80 (0.56 to 41.25)
Random effects model 1977 1787 3.00 (0.97 to 9.32)
Heterogeneity: I^2 = 0%, p = 0.80

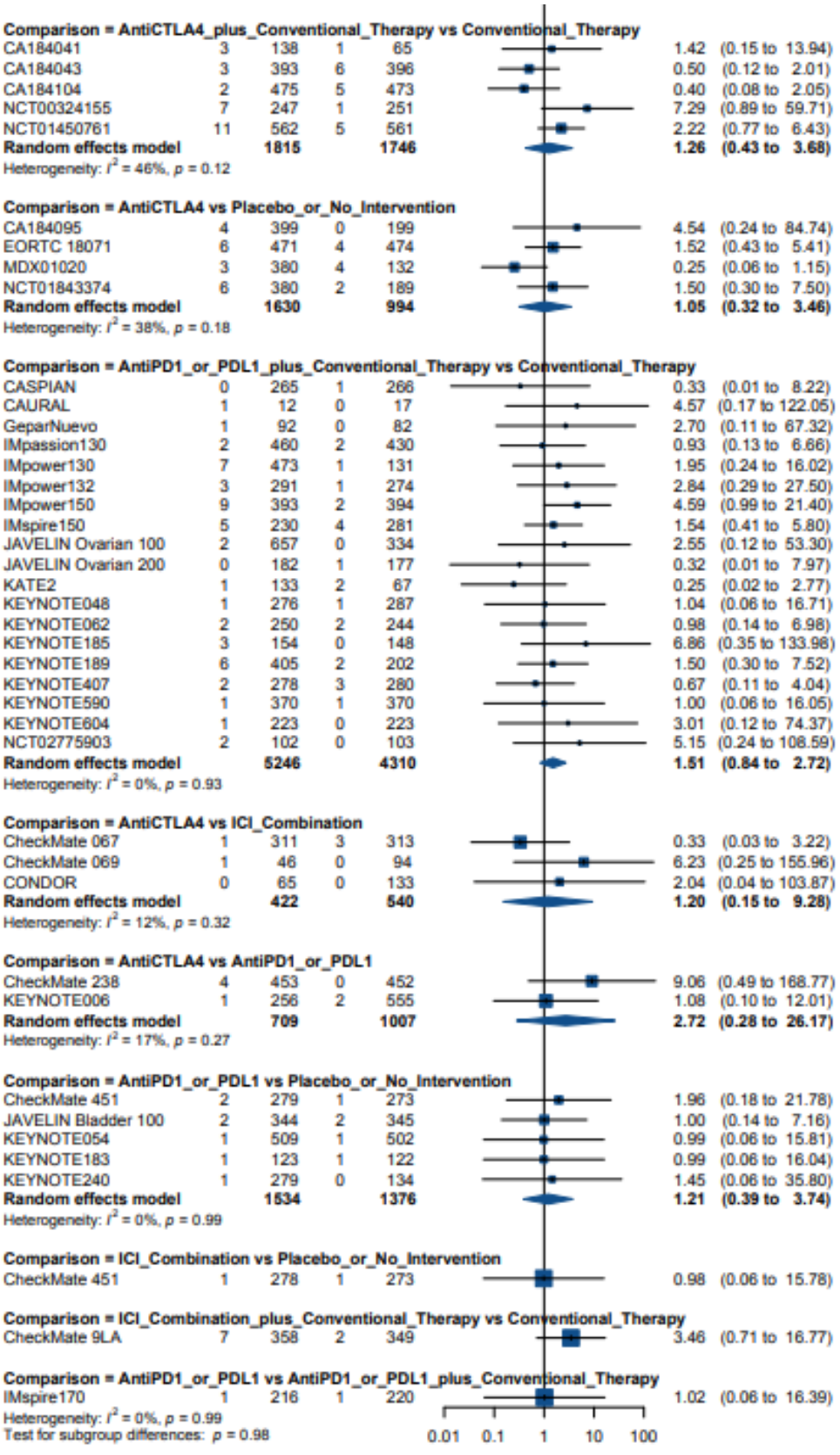


Figure 11 Forest plot, symptomatic adverse events

Network meta-analysis

Random effect model was chosen according to our previously described model selection criteria. With regards to consistency, the comparison of the DIC values between the random effects (consistency) model and the inconsistency model does not suggest that the consistency assumption was violated. The standard deviation between studies in the inconsistency model, interpreted as a measure of heterogeneity, was also similar to the corresponding value in the random effect model (consistency model).

Table 11 Deviance Statistics, symptomatic adverse events

	Fixed.effects.model	Random.effects.model	Unrelated.mean.effect.model
Data points	196	196	196
Dbar	189.04	186,59	176,36
pD	81.3	77,35	86,11
DIC	270.34	263,95	262,46
Tau	-	0,31	0,55
SD	-	0,26	0,55
SD95%CrILB	-	0,04	0,05
SD95%CrIUB	-	0,8	1,14

The league table below, presents the results of the NMA comparing the odds for peripheral syndromic adverse events between different treatment modalities. All statistically significant differences are highlighted in bold.

Compared with conventional therapy, anti-CTLA-4 (OR 2.8, 95% CrI 1.2 to 6.85), Anti-PD-1 or PDL-1 plus conventional therapy (OR 2.19, 95% CrI 1.24 to 4.12) and Anti-PD-1 or PDL-1 (OR 1.94, 95% CrI 1.94 to 3.21) were associated with statistically significant increased odds of symptomatic adverse events.

Table 12 Symptomatic adverse events. League table of NMA estimations. Results in bold indicate statistical significance. Comparisons should be read from up to right in the lower-left corner or from down to left in the upper-right corner.

Anti CTLA4	0.68 (0.2 to 2.31)	0.69 (0.32 to 1.48)	0.79 (0.28 to 2.17)	0.36 (0.15 to 0.84)	0.71 (0.27 to 1.73)	0.75 (0.37 to 1.41)
1.48 (0.43 to 4.99)	Anti CTLA4 plus conventional	1.02 (0.39 to 2.64)	1.17 (0.41 to 3.18)	0.53 (0.23 to 1.17)	1.05 (0.33 to 3.23)	1.1 (0.32 to 3.59)
1.45 (0.68 to 3.12)	0.98 (0.38 to 2.53)	Anti PD1 or PDL1	1.14 (0.55 to 2.31)	0.52 (0.31 to 0.81)	1.02 (0.48 to 2.11)	1.08 (0.5 to 2.23)
1.27 (0.46 to 3.6)	0.86 (0.31 to 2.41)	0.88 (0.43 to 1.81)	Anti PD1 or PDL1 plus conventional	0.46 (0.24 to 0.81)	0.89 (0.33 to 2.41)	0.95 (0.34 to 2.58)
2.8 (1.2 to 6.85)	1.89 (0.86 to 4.42)	**1.94 (1.24 to 3.21)**	**2.19 (1.24 to 4.12)**	Conventional	1.98 (0.88 to 4.46)	2.09 (0.87 to 4.97)
1.41 (0.58 to 3.73)	0.95 (0.31 to 3.07)	0.98 (0.47 to 2.09)	1.12 (0.41 to 3.02)	0.5 (0.22 to 1.14)	ICI combination	1.05 (0.41 to 2.77)
1.34 (0.71 to 2.7)	0.91 (0.28 to 3.09)	0.93 (0.45 to 2.01)	1.05 (0.39 to 2.95)	0.48 (0.2 to 1.14)	0.95 (0.36 to 2.45)	Placebo or no intervention

Regarding the results at the level of treatment modalities, the best-ranked treatment modality was conventional therapy (SUCRA 77%), while the worst-ranked treatment modality was anti-CTLA4 plus conventional therapy (SUCRA 4%). In absolute terms, the mean symptomatic adverse events event rate of was 31 per 10,000 patients (95% CI 20 to 43) among patient treated with conventional therapy and 159 per 10,000 patients (95% CI 64 to 295) among patient treated with Anti-CTLA-4 plus conventional therapy.

DISCUSSION

We conducted a systematic review and network meta-analysis of 96 randomized controlled trials with a combined 52,811 participants, published between 2011 and 2021. To our knowledge, this is the largest network meta-analysis to date on ICI neurological safety. This is particularly relevant considering the broadest overall time period of ICI use in clinical practice, the growing number of indications for treatment of different types of tumors with ICI in monotherapy or in combination and the increase in the number of clinical trials testing new combinations of ICI in settings other than those for which there is already approval for its use.

We included all available trials of ICIs to assess the comparative safety profile of the available interventions with regards to neuro-related adverse events. Given the well-known risk of developing serious peripheral neuropathy with classic chemotherapy, this systematic review primarily aimed to compare its relative incidence among different treatment modalities, and therefore, help patients and clinicians in the management of serious peripheral neuropathy by providing evidence on the odds of developing this condition. In fact, according to a previous systematic review and network meta-analysis, which included 23 randomized controlled trials (phase 2 and 3) and 11,687 patients, there is evidence that the risk of develop any-grade peripheral neuropathy is less likely in patients treated with combinations of ICIs than those under chemotherapy. In this systematic review, a total of 220 cases of any-grade peripheral neuropathy were reported among 4390 ICI-treated patients enrolled in 17 cohort studies (incidence of 5%), and 26 cases of serious peripheral neuropathy were observed among 6582 ICI-treated patients enrolled in 21 cohort studies (incidence of 0.4%). The odds ratio of any-grade peripheral neuropathy in patients under anti-PD-L1 and anti-PD-1 was 0.29 (95% CI, 0.18-0.48) and 0.21 (95% CI, 0.14-0.31) respectively compared to those treated with chemotherapy. Regarding the odds of serious peripheral neuropathy, a statistically significant difference was found between patients exposed to anti-PD-1 (OR, 0.16; 95% CI, 0.05-0.54; P=0.003) and chemotherapy. [29]

Furthermore, we also evaluated other nAEs to provide a more comprehensive overview of the relative neurologic safety profile of the different treatment modalities. Due to the low overall incidence of nAEs, these were grouped into categories: nAEs leading to CNS syndromes, nAEs leading to PNS syndromes; and nAEs leading to neurological symptoms.

Finally, we sought to explore factors that could influence the risk of developing serious peripheral neuropathy by conducting network meta-regressions based on overall survival, progression free survival, and the overall risk of bias in each trial. None of these regressions yielded statistically significant correlation coefficients, nor did improved model fit parameters. Therefore, we do not have evidence that overall survival, progression free survival, and the overall risk of bias influence the odds of our primary outcome.

According to a previous non-systematic literature review, without meta-analysis, among the 9208 patients exposed in clinical trials to immune checkpoint inhibitors, the overall incidence of any grade nAEs was 3.8% (range of reported incidence; 0 to 27.3) with anti-CTLA4 antibodies, 6.1% (range of reported incidence; 0 to 26.8) for anti-PD1 antibodies and 12.0% (range of reported incidence; 10.2 to 18.9) with the combination of them. According to the authors, most of these nAEs were grade 1/2 and consisted of non-specific symptoms such as headache (55%), dysgeusia (13%) or dizziness (10%). The incidence of high grade (Gr 3/4) nAEs was below 1% for all types of treatment. The proportion of grade 1/2 and grade 3/4 nAEs due to peripheral neuropathy was 5% and 6% respectively. Nonetheless, the authors recommended that individuals with suspected neuropathies should undergo evaluation for alternative causes as they could be caused by other medications, infectious disease and metabolic, endocrine, or vascular disorders, and that nerve conduction studies can be useful in this regard. [10] In contrast with our study, the authors did not estimate the risk of developing different nAEs according to the ICI type of treatment.

The present systematic review and network meta-analysis included trials of patients with different types of cancer (non-small cell lung cancer, lung cancer, melanoma, gastric cancer, urothelial cancer, renal-cell carcinoma and others), using ICIs in different

treatment modalities (anti-CTLA-4, anti-PD-1, anti-PD-L1 monotherapy or combination). For serious peripheral neuropathy, the worst-ranked treatment modality was anti-CTLA-4 plus conventional, and the best-ranked treatment modality was ICI combination plus conventional. However, none of the pair-wise comparisons yielded statistically significant differences, likely due to the low number of events. The estimated incidence of serious peripheral neuropathy ranges from 0,01% (placebo) to 0,58% (anti-CTLA4 plus conventional). For non-serious peripheral neuropathy, the worst-ranked treatment modality was anti-PD-1/PD-L1 plus conventional. Anti-PD-1/anti-PD-L1 plus conventional therapy have increased odds of non-serious peripheral neuropathy when compared to conventional therapy. The estimated incidence of non-serious peripheral neuropathy ranges from 2,32% (anti-PD-1/PD-L1) to 19,26% (anti-PD-1/PD-L1 plus conventional). These figures highlight the need of monitor the development of peripheral neuropathy among patients exposed to ICI type treatments poising a higher likelihood of developing this condition, which can severely impair patient´s quality of life and trigger a painful disorder.

The results reported in our systematic review should be interpreted taking into account that most of the trials enrolled patients with relapsed or refractory disease who have had previous chemotherapy exposure or had treatment regimens that included concomitant conventional chemotherapy, which could have contributed to the high rates of all-grade peripheral neuropathy. In fact, although patients exposed to ICI monotherapies are at risk of developing peripheral neuropathy, this is risk lower in comparison to patients treated with ICI monotherapy (or combinations) plus conventional therapy.

The underlying mechanism behind peripheral neuropathies induced by ICIs is still unclear. Nevertheless, nerve conduction studies from patients with neuropathy after receiving ICIs have raised the hypothesis that compact myelin is likely to be the major target of ICI-related neuropathy. In addition, sensory nerve conduction studies in all patients showed predominantly axonal changes. These results suggest that ICIs may also cause sensory predominant axonal degeneration and result in painful sensory neuropathy. [12]

Due to the low number of other nAEs, we grouped them into the referred categories: central syndromic (aseptic meningitis, transverse myelitis, posterior reversible leukoencephalopathy and encephalitis); peripheral syndromic (Guillain-Barré myasthenia, and facial nerve palsy); and symptomatic (paranesthesia, headache, dysgeusia, dizziness/vertigo, insomnia, seizures). Conventional therapy was ranked the best treatment modality in all these nAEs categories. The estimated incidence of central syndromic nAEs among patient treated with ICIs combinations was 0,63%, the estimated incidence of peripheral syndromic nAEs patient treated with anti-CTLA-4 plus conventional therapy was 0,58%, and the estimated incidence of symptomatic nAEs was 1,59% among patient treated with anti-CTLA-4 plus conventional therapy.

LIMITATIONS

We chose to combine all available trial evidence independently of the cancer type, as this permitted pooling more data, thereby increasing the power of the analyses. We grouped different clinical situations, from cancer stages to different treatment duration and different populations. This may suggest a violation of the transitivity assumption, although the analysis of rare safety outcomes such neuropathies may justify this more accepting and tumor-agnostic approach. Additionally, the statistical heterogeneity across analyses was low, and we did not find evidence of inconsistency, which further reinforces the option to include as many trials as possible.

Due to the relatively short duration of follow-up in the clinical trials, the true rates of adverse events may have been underestimated. There is evidence that most nAEs develop within the first few weeks to months after treatment initiation, but in case of CIPN it is known that prevalence decreases over time, at least 30% of patients still suffer from CIPN 6 months or more after end of chemotherapy.[30] Longer follow-up times of patients exposed to ICI would be important to better understand the long-term risk of nAEs associated with this treatment option.

FUTURE

Despite the growing experience and familiarity with the use of ICIs, these remain relatively novel agents. Over the coming years, and given a continuing push regarding novel ICI strategies, the growing body of evidence will continue to inform our understanding of the safety of ICIs.

The incidences of the neurological AEs studied in this review are comparatively low, though important differences in absolute event rates were identified between treatment modalities. The safety profiles explored in this review may represent important sources of information for clinicians moving forward.

Globally, nAEs pose diagnostic and therapeutic challenges for clinicians. Improving awareness and training clinicians and multidisciplinary teams are essential. By making nAEs easier to predict, their management might be improved. In the future, this knowledge will contribute to providing better treatment to cancer patients.

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APPENDICES

Appendix 1: Search strategy, via Ovid

1. Ipilimumab.ab,kf,ti.
2. Tremelimumab.ab,kf,ti.
3. Pidilizumab.ti,kf,ti.
4. Yervoy.ab,kf,ti.
5. Opdivo.ab,kf,ti.
6. Nivolumab.ab,kf,ti.
7. Pembrolizumab.ab,kf,ti.
8. Keytruda.ab,kf,ti.
9. Tecentriq.ab,kf,ti.
10. Atezolizumab.ab,kf,ti.
11. Durvalumab.ab,kf,ti.
12. Imfinzi.ab,kf,ti.
13. Avelumab.ab,kf,ti.
14. Bavencio.ab,kf,ti.
15. Cemiplimab.ab,kf,ti.
16. Libtayo.ab,kf,ti.
17. Jemperli.ab,kf,ti.
18. Dostarlimab.ab,kf,ti.
19. or/1-18
20. (cancer* or neoplas* or tumor* or tumour* or carcinoma* or metasta* or leukemi* or leukaemi* or lymphoma*or myeloma* or sarcoma* or melanoma*).ab,kf,ti.
21. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
22. exp animals/ not humans.sh.
23. 21 not 22
24. 19 and 20 and 23
25. remove duplicates from 24

1. Ipilimumab.ab,kf,ti.

2. Tremelimumab.ab,kf,ti.

3. Pidilizumab.ti,kf,ti.

4. Yervoy.ab,kf,ti.

5. Opdivo.ab,kf,ti.

6. Nivolumab.ab,kf,ti.

7. Pembrolizumab.ab,kf,ti.

8. Keytruda.ab,kf,ti.

9. Tecentriq.ab,kf,ti.

10. Atezolizumab.ab,kf,ti.

11. Durvalumab.ab,kf,ti.

12. Imfinzi.ab,kf,ti.

13. Avelumab.ab,kf,ti.

14. Bavencio.ab,kf,ti.

15. Cemiplimab.ab,kf,ti.

16. Libtayo.ab,kf,ti.

17. Jemperli.ab,kf,ti.

18. Dostarlimab.ab,kf,ti.

19. or/1-18

20. (cancer* or neoplas* or tumor* or tumour* or carcinoma* or metasta* or leukemi* or leukaemi* or lymphoma*or myeloma* or sarcoma* or melanoma*).ab,kf,ti.

21. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.

22. exp animals/ not humans.sh.

23. 21 not 22

24. 19 and 20 and 23

25. remove duplicates from 24

Appendix 2: List of included trials

Clinical trial	Register number	References
ABC	NCT02374242	Long, G. V., Atkinson, V., Lo, S., Sandhu, S., Guminski, A. D., Brown, M. P., Wilmott, J. S., Edwards, J., Gonzalez, M., Scolyer, R. A., Menzies, A. M., & McArthur, G. A. (2018). Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: A multicentre randomised phase 2 study. The Lancet Oncology, 19(5), 672–681. https://doi.org/10.1016/S1470-2045(18)30139-6
ARTIC-Substudy-A	NCT02352948	Planchard, D., Reinmuth, N., Orlov, S., Fischer, J. R., Sugawara, S., Mandziuk, S., Marquez-Medina, D., Novello, S., Takeda, Y., Soo, R., Park, K., McCleod, M., Geater, S. L., Powell, M., May, R., Scheuring, U., Stockman, P., & Kowalski, D. (2020). ARCTIC: Durvalumab with or without tremelimumab as third-line or later treatment of metastatic non-small-cell lung cancer. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 31(5), 609–618. https://doi.org/10.1016/j.annonc.2020.02.006
ARTIC-Substudy-B	NCT02352948	Planchard, D., Reinmuth, N., Orlov, S., Fischer, J. R., Sugawara, S., Mandziuk, S., Marquez-Medina, D., Novello, S., Takeda, Y., Soo, R., Park, K., McCleod, M., Geater, S. L., Powell, M., May, R., Scheuring, U., Stockman, P., & Kowalski, D. (2020). ARCTIC: Durvalumab with or without tremelimumab as third-line or later treatment of metastatic non-small-cell lung cancer. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 31(5), 609–618. https://doi.org/10.1016/j.annonc.2020.02.006
ATTRACTION-2	NCT02267343	Kang, Y.-K., Boku, N., Satoh, T., Ryu, M.-H., Chao, Y., Kato, K., Chung, H. C., Chen, J.-S., Muro, K., Kang, W. K., Yeh, K.-H., Yoshikawa, T., Oh, S. C., Bai, L.-Y., Tamura, T., Lee, K.-W., Hamamoto, Y., Kim, J. G., Chin, K., … Chen, L.-T. (2017). Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet, 390(10111), 2461–2471. https://doi.org/10.1016/S0140-6736(17)31827-5
CA184-041	NCT00527735	Lynch, T. J., Bondarenko, I., Luft, A., Serwatowski, P., Barlesi, F., Chacko, R., Sebastian, M., Neal, J., Lu, H., Cuillerot, J.-M., & Reck, M. (2012). Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non–Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study. Journal of Clinical Oncology, 30(17), 2046–2054. https://doi.org/10.1200/JCO.2011.38.4032
CA184-043	NCT00861614	Kwon, E. D., Drake, C. G., Scher, H. I., Fizazi, K., Bossi, A., van den Eertwegh, A. J. M., Krainer, M., Houede, N., Santos, R., Mahammedi, H., Ng, S., Maio, M., Franke, F. A., Sundar, S., Agarwal, N., Bergman, A. M., Ciuleanu, T. E., Korbenfeld, E., Sengeløv, L., … Gerritsen, W. R. (2014). Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): A multicentre, randomised, double-blind, phase 3 trial. The Lancet Oncology, 15(7), 700–712. https://doi.org/10.1016/S1470-2045(14)70189-5
CA184-095	NCT01057810	Beer, T. M., Kwon, E. D., Drake, C. G., Fizazi, K., Logothetis, C., Gravis, G., Ganju, V., Polikoff, J., Saad, F., Humanski, P., Piulats, J. M., Gonzalez Mella, P., Ng, S. S., Jaeger, D., Parnis, F. X., Franke, F. A., Puente, J., Carvajal, R., Sengeløv, L., … Gerritsen, W. (2017). Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. Journal of Clinical Oncology, 35(1), 40–47. https://doi.org/10.1200/JCO.2016.69.1584
CA184-104	NCT01285609	Govindan, R., Szczesna, A., Ahn, M.-J., Schneider, C.-P., Gonzalez Mella, P. F., Barlesi, F., Han, B., Ganea, D. E., Von Pawel, J., Vladimirov, V., Fadeeva, N., Lee, K. H., Kurata, T., Zhang, L., Tamura, T., Postmus, P. E., Jassem, J., O'Byrne, K., Kopit, J., … Reck, M. (2017). Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non–Small-Cell Lung Cancer. Journal of Clinical Oncology, 35(30), 3449–3457. https://doi.org/10.1200/JCO.2016.71.7629
CA184-153	NCT02279732	A Randomized, Multicenter, Double-Blind, Multinational, Phase 3 Trial Comparing the Efficacy of Ipilimumab in Addition to Paclitaxel and Carboplatin Versus Placebo in Addition to Paclitaxel and Carboplatin in Subjects With Stage IV/Recurrent Non-Small Cell Lung Cancer (NSCLC) With Squamous Histology (Clinical Trial Registration No. NCT02279732). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT02279732
CA184-162	NCT01585987	Bang, Y.-J., Cho, J. Y., Kim, Y. H., Kim, J. W., Di Bartolomeo, M., Ajani, J. A., Yamaguchi, K., Balogh, A., Sanchez, T., & Moehler, M. (2017). Efficacy of Sequential Ipilimumab Monotherapy versus Best Supportive Care for Unresectable Locally Advanced/Metastatic Gastric or Gastroesophageal Junction Cancer. Clinical Cancer Research, 23(19), 5671–5678. https://doi.org/10.1158/1078-0432.CCR-17-0025
CA184-243	NCT01709162	A Randomized, Open-Label, Multicenter Phase II Study of Ipilimumab Retreatment Versus Chemotherapy for Subjects With Advanced Melanoma Who Progressed After Initially Achieving Disease Control With Ipilimumab Therapy (Clinical Trial Registration No. NCT01709162). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT01709162
CASPIAN	NCT03043872	Paz-Ares, L., Dvorkin, M., Chen, Y., Reinmuth, N., Hotta, K., Trukhin, D., Statsenko, G., Hochmair, M. J., Özgüroğlu, M., Ji, J. H., Voitko, O., Poltoratskiy, A., Ponce, S., Verderame, F., Havel, L., Bondarenko, I., Kazarnowicz, A., Losonczy, G., Conev, N. V., … Williamson, M. (2019). Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): A randomised, controlled, open-label, phase 3 trial. The Lancet, 394(10212), 1929–1939. https://doi.org/10.1016/S0140-6736(19)32222-6

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NCT02775903	NCT02775903	A Randomized, Multicenter, Open-label, Phase 2 Study Evaluating the Efficacy and Safety of Azacitidine Subcutaneous in Combination With Durvalumab (MEDI4736) in Previously Untreated Subjects With Higher-Risk Myelodysplastic Syndromes (MDS) or in Elderly (>= 65 Years) Acute Myeloid Leukemia (AML) Subjects Not Eligible for Hematopoietic Stem Cell Transplantation (HSCT) (Clinical Trial Registration No. NCT02775903). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT02775903
OAK	NCT02008227	Rittmeyer, A., Barlesi, F., Waterkamp, D., Park, K., Ciardiello, F., von Pawel, J., Gadgeel, S. M., Hida, T., Kowalski, D. M., Dols, M. C., Cortinovis, D. L., Leach, J., Polikoff, J., Barrios, C., Kabbinavar, F., Frontera, O. A., De Marinis, F., Turna, H., Lee, J.-S., … Gandara, D. R. (2017). Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. The Lancet, 389(10066), 255–265. https://doi.org/10.1016/S0140-6736(16)32517-X
PACIFIC	NCT02125461	Antonia, S. J., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., Yokoi, T., Chiappori, A., Lee, K. H., de Wit, M., Cho, B. C., Bourhaba, M., Quantin, X., Tokito, T., Mekhail, T., Planchard, D., Kim, Y.-C., Karapetis, C. S., Hiret, S., … Özgüroğlu, M. (2017). Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. New England Journal of Medicine, 377(20), 1919–1929. https://doi.org/10.1056/NEJMoa1709937
POPLAR	NCT01903993	Fehrenbacher, L., Spira, A., Ballinger, M., Kowanetz, M., Vansteenkiste, J., Mazieres, J., Park, K., Smith, D., Artal-Cortes, A., Lewanski, C., Braiteh, F., Waterkamp, D., He, P., Zou, W., Chen, D. S., Yi, J., Sandler, A., & Rittmeyer, A. (2016). Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. The Lancet, 387(10030), 1837–1846. https://doi.org/10.1016/S0140-6736(16)00587-0
PROLUNG	NCT02574598	Arrieta, O., Barrón, F., Ramírez-Tirado, L. A., Zatarain-Barrón, Z. L., Cardona, A. F., Díaz-García, D., Yamamoto Ramos, M., Mota-Vega, B., Carmona, A., Peralta Álvarez, M. P., Bautista, Y., Aldaco, F., Gerson, R., Rolfo, C., & Rosell, R. (2020). Efficacy and Safety of Pembrolizumab Plus Docetaxel vs Docetaxel Alone in Patients With Previously Treated Advanced Non–Small Cell Lung Cancer: The PROLUNG Phase 2 Randomized Clinical Trial. JAMA Oncology, 6(6), 856. https://doi.org/10.1001/jamaoncol.2020.0409

Appendix 3: Characteristics of included trials

Table 13. Clinical and methodological characteristics of included trials.

Trial Title	Date of publication	Masking	Mean age	Age standard deviation	N Female	N Total	Site of primary tumor	Stage
ABC	2018	Open-label	-	-	12	60	Melanoma Brain Metastasis	Stage IV
ARTIC-Substudy-A	2019	Open-label	-	-	197	595	Non-Small Cell Lung Cancer	Locally advanced; Metastatic
ARTIC-Substudy-B	2019	Open-label	-	-	197	595	Non-Small Cell Lung Cancer	Locally advanced; Metastatic
ATTRACTION-2	2019	Double-blind	-	-	145	493	Gastric or Gastroesophageal Junction	unresectable advanced or recurrent
CA184-041	2012	Double-blind	-	-	85	334	Non-Small Cell Lung Cancer	Stage IIIb or IV
CA184-043	2016	Double-blind	67.6	7.56	0	799	Prostate	Metastatic
CA184-095	2016	Double-blind	69	0	0	602	Prostate	Metastatic
CA184-104	2016	Double-blind	63.7	8.47	114	749	Non-Small Cell Lung Cancer	Stage IV; Recurrent
CA184-153	2019	Double-blind	60.3	7.61	24	204	Squamous Non-Small Cell Lung Cancer	Stage IV; Recurrent

CA184-162	2015	Open-label	-	-	37	114	Gastric or Gastroesophageal Junction	Locally advanced; Metastatic
CA184-243	2015	Open-label	62.7	10.2	7	23	Melanoma	Stage III or IV
CASPIAN	2021	Open-label	62.6	8.35	229	805	Small Cell Lung Cancer	Stage III or IV
CheckMate 017	2016	Open-label	63.3	8.36	64	272	Squamous Non-Small Cell Lung Cancer	Stage IIIb or IV
CheckMate 025	2016	Open-label	61.3	10.66	202	821	Renal Cell Carcinoma	Advanced; Metastatic
CheckMate 026	2017	Open-label	63.1	9.94	209	541	Non-Small Cell Lung Cancer	Stage IV; Recurrent
CheckMate 037	2017	Open-label	59.2	13.59	144	405	Melanoma	Advanced
CheckMate 057	2016	Open-label	61.6	9.53	263	582	Non-Small Cell Lung Cancer	Advanced
CheckMate 066	2016	Double-blind	62.7	12.83	172	418	Melanoma	Stage III or IV
CheckMate 067	2017	Double-blind	59.6	13.69	335	945	Melanoma	Stage III or IV
CheckMate 069	2016	Double-blind	63.7	10.74	47	142	Melanoma	Stage III or IV
CheckMate 078	2019	Open-label	59.1	8.77	107	504	Non-Small Cell Lung Cancer	Advanced; Metastatic
CheckMate 141	2017	Open-label	59.1	10.43	61	361	Head and Neck	Stage III or IV
CheckMate 143	2018	Open-label	-	-	9	20	Glioblastoma	Stage IV; Recurrent
CheckMate 143 Cohort 2	2020	Open-label	-	-	134	369	Glioblastoma	Stage IV; Recurrent
CheckMate 214	2018	Open-label	60.9	9.93	288	1096	Renal Cell Carcinoma	Metastatic; Advanced
CheckMate 238	2021	Double-blind	54	13.42	379	906	Melanoma	Stage IIIb–c or IV
CheckMate 331	2020	Open-label	61.6	8.8	218	569	Small Cell Lung Cancer	Relapsed

CheckMate 451	2019	Double-blind	63.9	8.5	302	834	Small Cell Lung Cancer	Extensive
CheckMate 743	2021	Open-label	68.2	9.1	138	605	Mesothelioma	Unresectable
CheckMate 9LA	2020	Open-label	-	9.4	215	719	Non-Small Cell Lung Cancer	Metastatic
CONDOR	2018	Open-label	-	-	47	267	Head and Neck	Recurrent; Metastatic
DANUBE	2021	Open-label	66.5	9.6	253	1032	Urothelial	Unresectable locally advanced; Metastatic
EAGLE	2019	Open-label	59.4	9.86	118	736	Head and Neck	Recurrent; Metastatic
EORTC 18071	2014	Double-blind	51.1	12.86	362	951	Melanoma	Stage III
GeparNuevo	2019	Double-blind	-	-	174	174	Triple Negative Breast Cancer	Nonmetastatic invasive
I-SPY	2020	Open-label	-	-	270	270	Breast	Early-Stage (II or III)
IMblaze370	2019	Open-label	57.8	11.1	145	363	Colorectal	Unresectable locally advanced; Metastatic
IMmotion150	2017	Open-label	60.3	10.6	75	305	Renal Cell Carcinoma	Metastatic
IMMUNED	2020	Double-blind	-	-	72	167	Melanoma	Stage IV; Resected
IMpassion031	2021	Double-blind	50.2	12.4	333	333	Triple Negative Breast Cancer	Primary invasive
IMpassion130	2021	Double-blind	54.9	12.2	899	902	Triple Negative Breast Cancer	Unresectable locally advanced; Metastatic
IMpower110	2021	Open-label	63.4	8.8	176	572	Non-Small Cell Lung Cancer	Stage IV
IMpower130	2019	Open-label	64	9.3	308	723	Non-Small Cell Lung Cancer	Stage IV
IMpower132	2020	Open-label	62.6	9.4	194	578	Non-Small Cell Lung Cancer	Metastatic
IMpower133	2019	Double-blind	63.7	8.9	142	403	Small Cell Lung Cancer	Extensive

IMpower150	2020	Open-label	62.8	9.3	482	1202	Non-Small Cell Lung Cancer	Stage IV
IMspire150	2020	Double-blind	53.6	14.1	215	514	Melanoma	Stage IV; Unresectable IIIc
IMspire170	2020	Open-label	63.6	13	176	446	Melanoma	Locally advanced; Unresectable; Metastatic
IMvigor130	2020	Double-blind	-	-	297	1213	Urothelial	Metastatic
IMvigor211	2018	Open-label	66	9.4	213	931	Urothelial	Advanced; Metastatic
JAVELIN Bladder 100	2020	Open-label	67.44	9.4	159	700	Urothelial	Unresectable locally advanced; Metastatic
JAVELIN Gastric 100	2021	Open-label	60.7	11.36	168	499	Gastric or Gastroesophageal Junction	Unresectable locally advanced; Metastatic
JAVELIN Gastric 300	2018	Open-label	59.5	12.31	104	371	Gastric or Gastroesophageal Junction	Locally advanced; Metastatic
JAVELIN Lung 200	2018	Open-label	62.7	9.81	250	792	Non-Small Cell Lung Cancer	Stage IIIb or IV
JAVELIN Ovarian 100	2019	Open-label	57.86	11.05	998	998	Ovarian Cancer	Stage III or IV
JAVELIN Ovarian 200	2019	Open-label	60.3	10.32	566	566	Ovarian Cancer	Refractory
KATE2	2019	Double-blind	53.9	10.3	200	202	HER2-Positive Breast Cancer	Locally advanced; Metastatic
KEYNOTE-006	2016	Open-label	60.3	14.1	337	834	Melanoma	Advanced
KEYNOTE-010	2017	Open-label	62	9.7	399	1034	Non-Small Cell Lung Cancer	Advanced
KEYNOTE-021	2017	Open-label	61.8	9.5	147	267	Non-Small Cell Lung Cancer	Stage IIIb or IV
KEYNOTE-024	2017	Open-label	64.2	9.8	118	305	Non-Small Cell Lung Cancer	Stage IV
KEYNOTE-040	2018	Open-label	60.2	9.2	83	495	Head and Neck	Recurrent; Metastatic

KEYNOTE-042	2019	Open-label	62.8	9.7	372	1274	Non-Small Cell Lung Cancer	Locally advanced; Metastatic
KEYNOTE-045	2017	Open-label	65.5	9.7	140	542	Urothelial	Metastatic; Locally advanced; Unresectable
KEYNOTE-048	2020	Open-label	61	9.7	147	882	Head and Neck	Recurrent; Metastatic
KEYNOTE-054	2019	Double-blind	53.8	13.9	391	1019	Melanoma	Stage III
KEYNOTE-061	2018	Open-label	60.2	11.9	182	592	Gastric or Gastroesophageal Junction	Metastatic; Locally advanced; Unresectable
KEYNOTE-062	2020	Double-blind	60.5	12	209	763	Gastric or Gastroesophageal Junction	Advanced
KEYNOTE-119	2020	Open-label	52	11.3	620	622	Triple Negative Breast Cancer	Metastatic
KEYNOTE-144	2019	Open-label	62.1	9.69	37	73	Pancreas	Metastatic
KEYNOTE-177	2020	Open-label	-	-	154	307	Colorectal	Stage IV
KEYNOTE-181	2019	Open-label	62.3	9.5	84	628	Esophageal or Esophagogastric Junction	Metastatic; Locally advanced; Unresectable
KEYNOTE-183	2019	Open-label	65.9	9.6	94	251	Multiple Myeloma	Relapsed; Refractory
KEYNOTE-185	2019	Open-label	74.3	6	166	310	Multiple Myeloma	Stage I, II or III
KEYNOTE-189	2018	Double-blind	63.1	9.3	253	616	Non-Small Cell Lung Cancer	Metastatic
KEYNOTE-240	2020	Double-blind	65.2	10.8	75	413	Hepatocellular Carcinoma	Stage C; Stage B
KEYNOTE-355	2020	Double-blind	-	-	847	847	Breast (triple negative)	locally recurrent inoperable or metastatic
KEYNOTE-407	2019	Double-blind	64.9	8.7	104	559	Squamous Non-small Cell Lung Cancer	Metastatic
KEYNOTE-590	2021	Double-blind	62.4	9.5	124	749	Esophageal	Locally advanced; Metastatic

KEYNOTE-598	2021	Double-blind	64.1	9.1	174	568	Non-Small Cell Lung Cancer	Metastatic
KEYNOTE-604	2020	Double-blind	64.7	8.3	159	453	Small Cell Lung Cancer	Stage IV
MDX010-20	2011	Double-blind	56.2	-	275	676	Melanoma	Unresectable; Stage III or IV
MYSTIC	2019	Open-label	63.7	9.74	346	1118	Non-Small Cell Lung Cancer	Stage IV
NCT00324155	2014	Double-blind	57	13.61	201	502	Melanoma	Metastatic
NCT01450761	2016	Double-blind	61.9	8.78	311	954	Small Cell Lung Cancer	Extensive
NCT01471197	2014	Open-label	62.3	7.54	3	8	Non-Small Cell Lung Cancer	Recurrent; Metastatic
NCT01843374	2017	Double-blind	65.6	9.1	137	571	Mesothelioma	Unresectable
NCT02243371	2019	Open-label	63.4	8.6	32	93	Pancreas	Metastatic
NCT02340975	2020	Open-label	59.4	12.9	30	113	Gastric or Gastroesophageal Junction	Recurrent; Metastatic
NCT02498600	2020	Open-label	NR	NR	100	100	Ovarian Cancer	Recurrent; Persistent
NCT02558894	2018	Open-label	61.5	9.49	31	65	Pancreas	Metastatic
NCT02775903	2020	Open-label	74.6	6.7	84	213	Acute Myeloid Leukemia or Acute Myelodysplastic Syndromes	-
OAK	2017	Open-label	62.8	9.5	467	1225	Non-Small Cell Lung Cancer	Stage IIIb/IV; Recurrent
PACIFIC	2019	Double-blind	62.9	8.99	213	713	Non-Small Cell Lung Cancer	Stage III; Unresectable
POPLAR	2017	Open-label	61.6	9.3	118	287	Non-Small Cell Lung Cancer	Metastatic; Advanced
PROLUNG	2020	Open-label	60.01	12.5	46	78	Non-Small Cell Lung Cancer	Locally advanced

Table 14. Characterization of drug interventions.

Trial Title	Arm 1	Arm 1 n	Arm 2	Arm 2 n	Arm 3	Arm 3 n	Arm 4	Arm 4 n
ABC	nivolumab + ipilimumab 1 mg/kg + 3 mg/kg Q3W 4 cycles then nivolumab 3 mg/kg Q2W	35	nivolumab 3 mg/kg Q2W	25	-	-	-	-
ARTIC-Substudy-A	durvalumab 10 mg/kg Q2W	62	chemotherapy	64	-	-	-	-
ARTIC-Substudy-B	durvalumab + tremelimumab 20 mg/kg + 1 mg/kg Q4W 4 cycles then durvalumab 10 mg/kg Q2W	174	chemotherapy	118	durvalumab 10 mg/kg Q2W	117	tremelimumab 10 mg/kg Q4W for 24 weeks then Q12W	60
ATTRACTION-2	nivolumab 3 mg/kg Q2W	330	placebo	163	-	-	-	-
CA184-041	ipilimumab + chemotherapy 10 mg/kg Q3W 4 cycles then Q12W	113	ipilimumab + chemother-apy (phased) 10 mg/kg Q3W 4 cycles then Q12W	109	placebo + chemotherapy	109	-	-
CA184-043	ipilimumab + radiation therapy 10 mg/kg Q3W 4 cycles then Q12W	393	placebo + radiation therapy	396	-	-	-	-
CA184-095	ipilimumab 10 mg/kg Q3W 4 cycles then Q12W	400	placebo	202	-	-	-	-
CA184-104	ipilimumab + chemotherapy 10 mg/kg Q3W 4 cycles then Q12W	479	placebo + chemotherapy	477	-	-	-	-
CA184-153	ipilimumab + chemotherapy 10 mg/kg Q3W during induction then Q12W	148	placebo + chemotherapy	147	-	-	-	-

CA184-162	chemotherapy (lead-in) + ipili-mumab 10 mg/kg Q3W 4 cycles then Q12W	57	chemotherapy (lead-in) + chemotherapy	45	-	-	-	-
CA184-243	ipilimumab 3 mg/kg Q3W 4 cycles	18	chemotherapy	5	-	-	-	-
CASPIAN	durvalumab + chemotherapy 1500 mg Q3W 4 cycles	268	chemotherapy	269	-	-	-	-
CheckMate 017	nivolumab 3 mg/kg Q2W	135	chemotherapy	137	-	-	-	-
CheckMate 025	nivolumab 3 mg/kg Q2W	410	chemotherapy	411	-	-	-	-
CheckMate 026	nivolumab 3 mg/kg Q2W	271	chemotherapy	270	-	-	-	-
CheckMate 037	nivolumab 3 mg/kg Q2W	272	chemotherapy	133	-	-	-	-
CheckMate 057	chemotherapy NA	290	nivolumab 3 mg/kg Q2W	292	-	-	-	-
CheckMate 066	nivolumab 3 mg/kg Q2W	210	chemotherapy	208	-	-	-	-
CheckMate 067	nivolumab + placebo 3 mg/kg Q2W	316	nivolumab + ipilimumab 1 mg/kg + 3 mg/kg Q3W 4 cycles then nivolumab 3 mg/kg Q2W	314	ipilimumab + placebo 3 mg/kg Q3W 4 cycles	315	-	-
CheckMate 069	nivolumab + ipilimumab 1 mg/kg + 3 mg/kg Q3W 4 cycles then nivolumab 3 mg/kg Q2W	95	placebo + ipilimumab 3 mg/kg Q3W 4 cycles	47	-	-	-	-
CheckMate 078	nivolumab 3 mg/kg Q2W	338	chemotherapy	166	-	-	-	-
CheckMate 141	nivolumab 3 mg/kg Q2W	240	chemotherapy	121	-	-	-	-
CheckMate 143	nivolumab 3 mg/kg Q2W	10	nivolumab + ipilimumab 1 mg/kg + 3 mg/kg Q3W 4 cycles then nivolumab 3 mg/kg Q2W	10	-	-	-	-

CheckMate 143 Cohort 2	nivolumab 3 mg/kg Q2W	184	bevacizumab	185	-	-	-	-
CheckMate 214	nivolumab + ipilimumab 3 mg/kg + 1 mg/kg Q3W 4 cycles then nivolumab 3 mg/kg Q2W	550	sunitinib	546	-	-	-	-
CheckMate 238	nivolumab 3 mg/kg Q2W	453	ipilimumab 10 mg/kg Q3W 4 cycles then Q12W	453	-	-	-	-
CheckMate 331	nivolumab 240mg Q2W	284	chemotherapy	285	-	-	-	-
CheckMate 451	placebo NA	275	nivolumab 240 mg Q2W	280	nivolumab + ipilimumab 1 mg/kg + 3 mg/kg Q3W 4 cycles then nivolumab 240 mg Q2W	279	-	-
CheckMate 743	nivolumab + ipilimumab 3 mg/kg Q2W + 1 mg/kg Q6W	303	chemotherapy	302	-	-	-	-
CheckMate 9LA	nivolumab + ipilimumab + chemo-therapy 360 mg Q3W + 1 mg/kg Q6W	358	chemotherapy	349	-	-	-	-
CONDOR	durvalumab 10 mg/kg Q2W 12 months	67	tremelimumab 10 mg/kg Q4W 7 cycles then Q12W	67	durvalumab + tremelimumab 20 mg/kg + 1 mg/kg Q4W 4 cycles then durvalumab 10 mg/kg Q2W	133	-	-
DANUBE	durvalumab 1.5 g Q4W	346	durvalumab + tremelimumab 1.5 g + 75 mg Q4W 4 cycles then dur-valumab 1.5 g Q4W	342	chemotherapy	344	-	-

EAGLE	durvalumab + tremelimumab 20 mg/kg + 1 mg/kg Q4W 4 cycles then durvalumab 10 mg/kg Q2W	247	durvalumab 10 mg/kg Q2W	240	chemotherapy	249	-	-
EORTC 18071	ipilimumab 10 mg/kg Q3W 4 cycles then Q12W	475	placebo	476	-	-	-	-
GeparNuevo	durvalumab + chemotherapy 1500 mg Q4W	88	placebo + chemotherapy	86	-	-	-	-
I-SPY	pembrolizumab + chemotherapy 200 mg Q3W	69	chemotherapy	201	-	-	-	-
IMblaze370	atezolizumab 1200 mg Q3W	183	atezolizumab + cobimetinib 1200 mg Q3W	90	regorafenib	90	-	-
IMmotion150	atezolizumab + bevacizumab 1200 mg Q3W	101	atezolizumab 1200 mg Q3W	103	sunitinib	101	-	-
IMMUNED	nivolumab + ipilimumab 1 mg/kg + 3 mg/kg Q3W 4 cycles then nivolumab 3 mg/kg Q2W	56	nivolumab + placebo 3 mg/kg Q2W	59	placebo	52	-	-
IMpassion031	atezolizumab + chemotherapy 840 mg Q2W then 1200 mg Q3W 11 cycles	165	placebo + chemotherapy	168	-	-	-	-
IMpassion130	atezolizumab + chemotherapy 840 mg Q2W	451	placebo + chemotherapy	451	-	-	-	-
IMpower110	chemotherapy NA	287	atezolizumab 1200 mg Q3W	285	-	-	-	-
IMpower130	atezolizumab + chemotherapy 1200 mg Q3W	483	chemotherapy	240	-	-	-	-

IMpower132	chemotherapy NA	286	atezolizumab + chemother-apy 1200 mg Q3W	292	-	-	-	-
IMpower133	atezolizumab + chemotherapy 1200 mg Q3W	201	placebo + chemotherapy	202	-	-	-	-
IMpower150	atezolizumab + chemotherapy 1200 mg Q3W	400	chemotherapy	400	-	-	-	-
IMspire150	atezolizumab + vemurafenib + cobimetinib 840 mg Q2W	256	placebo + vemurafenib + cobimetinib	255	-	-	-	-
IMspire170	pembrolizumab 200 mg Q3W	224	atezolizumab + cobimetinib 840 mg Q2W	222	-	-	-	-
IMvigor130	atezolizumab + chemotherapy 1200 mg Q3W	451	atezolizumab 1200 mg Q3W	362	placebo + chemotherapy	400	-	-
IMvigor211	atezolizumab 1200 mg Q3W	467	chemotherapy	464	-	-	-	-
JAVELIN Bladder 100	avelumab 10 mg/kg Q2W	350	no intervention	350	-	-	-	-
JAVELIN Gastric 100	avelumab 10 mg/kg Q2W	249	chemotherapy	250	-	-	-	-
JAVELIN Gastric 300	avelumab 10 mg/kg Q2W	186	chemotherapy	185	-	-	-	-
JAVELIN Lung 200	avelumab 10 mg/kg Q2W	396	chemotherapy	265	-	-	-	-
JAVELIN Ovarian 100	avelumab + chemotherapy (phased) 10 mg/kg Q2W 24 months	332	avelumab + chemotherapy 10 mg/kg Q3W 24 months	331	chemotherapy	335	-	-
JAVELIN Ovarian 200	avelumab 10 mg/kg Q2W	188	avelumab + chemotherapy 10 mg/kg Q2W	188	chemotherapy	190	-	-
KATE2	atezolizumab + trastuzumab emtansine 1200 mg Q3W	133	placebo + trastuzumab em-tansine	69	-	-	-	-

KEYNOTE-006	ipilimumab 3 mg/kg Q3W 4 cycles	278	pembrolizumab 10 mg/kg Q2W 24 months	279	pembrolizumab 10 mg/kg Q3W 24 months	277	-	-
KEYNOTE-010	pembrolizumab 2 mg/kg Q3W 24 months	345	pembrolizumab 10 mg/kg Q3W 24 months	343	chemotherapy	343	-	-
KEYNOTE-021	pembrolizumab + chemotherapy 200 mg Q3W	60	chemotherapy	63	-	-	-	-
KEYNOTE-024	pembrolizumab 200 mg Q3W	154	chemotherapy	151	-	-	-	-
KEYNOTE-040	pembrolizumab 200 mg Q3W 35 cycles	247	chemotherapy	248	-	-	-	-
KEYNOTE-042	pembrolizumab 200 mg Q3W	637	chemotherapy	637	-	-	-	-
KEYNOTE-045	pembrolizumab 200 mg Q3W 35 cycles	270	chemotherapy	272	-	-	-	-
KEYNOTE-048	pembrolizumab 200 mg Q3W	301	pembrolizumab + chemo-therapy 200 mg Q3W	281	chemotherapy + cetuximab	300	-	-
KEYNOTE-054	pembrolizumab 200 mg Q3W	514	placebo	505	-	-	-	-
KEYNOTE-061	pembrolizumab 200 mg Q3W 35 cycles	296	chemotherapy	296	-	-	-	-
KEYNOTE-062	pembrolizumab 200 mg Q3W	256	pembrolizumab + chemo-therapy 200 mg Q3W	257	placebo + chemotherapy	250	-	-
KEYNOTE-119	pembrolizumab 200 mg Q3W	212	chemotherapy	310	-	-	-	-
KEYNOTE-144	acalabrutinib NA	37	pembrolizumab + acalabru-tinib 200 mg Q3W	40	-	-	-	-
KEYNOTE-177	pembrolizumab 200 mg Q3W	153	chemotherapy	154	-	-	-	-
KEYNOTE-181	pembrolizumab 200 mg Q3W	314	chemotherapy	314	-	-	-	-

KEYNOTE-183	pembrolizumab + pomalidomide + dexametasone 200 mg Q3W	122	placebo + pomalidomide + dexametasone	123	-	-	-	-
KEYNOTE-185	pembrolizumab + lenalidomide + dexamethasone 200 mg Q3W 18 cycles	156	lenalidomide + dexame-thasone	154	-	-	-	-
KEYNOTE-189	pembrolizumab + chemotherapy 200 mg Q3W	405	placebo + chemotherapy	202	-	-	-	-
KEYNOTE-240	pembrolizumab 200 mg Q3W	278	placebo	135	-	-	-	-
KEYNOTE-355	pembrolizumab + chemotherapy 200 mg Q3W	566	placebo + chemotherapy	281	-	-	-	-
KEYNOTE-407	pembrolizumab + chemotherapy 200 mg Q3W 35 cycles	278	placebo + chemotherapy	280	-	-	-	-
KEYNOTE-590	pembrolizumab + chemotherapy 200 mg Q3W	373	placebo + chemotherapy	376	-	-	-	-
KEYNOTE-598	pembrolizumab + ipilimumab 200 mg Q3W + 1 mg/kg Q6W	284	pembrolizumab + placebo 200 mg Q3W	284	-	-	-	-
KEYNOTE-604	pembrolizumab + chemotherapy 200 mg Q3W	228	placebo + chemotherapy	225	-	-	-	-
MDX010-20	ipilimumab + gp100 Melanoma Peptide Vaccine 3 mg/kg Q3W	403	gp100 Melanoma Peptide Vaccine	136	-	-	-	-
MYSTIC	durvalumab 20 mg/kg Q4W	374	durvalumab + tremelimumab 20 mg/kg + 1 mg/kg Q4W 4 cycles then durvalumab 20 mg/kg Q4W	372	chemotherapy	372	-	-

NCT00324155	ipilimumab + chemotherapy 10 mg/kg Q3W 4 cycles then Q12W	250	placebo + chemotherapy	252	-	-	-	-
NCT01450761	ipilimumab + chemotherapy 10 mg/kg Q3W 4 cycles then Q12W	478	placebo + chemotherapy	476	-	-	-	-
NCT01471197	ipilimumab 10 mg/kg Q3W 4 cycles then Q12W	6	chemotherapy	2	-	-	-	-
NCT01843374	placebo NA	189	tremelimumab 10 mg/kg	382	-	-	-	-
NCT02243371	nivolumab + chemotherapy + GVAX Pancreas Vaccine + CRS-207 3 mg/kg Q3W	51	chemotherapy + GVAX Pancreas Vaccine + CRS-207	42	-	-	-	-
NCT02340975	durvalumab + tremelimumab 20 mg/kg + 1 mg/kg Q4W 4 cycles then durvalumab 10 mg/kg Q2W	27	durvalumab 10 mg/kg Q2W	24	tremelimumab 10mg/kg Q4W	12	-	-
NCT02498600	nivolumab 3 mg/kg Q2W	49	nivolumab + ipilimumab 3 mg/kg + 1 mg/kg Q3W 4 cycles then nivolumab 3 mg/kg Q2W	51	-	-	-	-
NCT02558894	durvalumab + tremelimumab 1.5 g + 1 mg/kg Q4W 4 cycles then durvalumab 1.5 g Q4W	33	durvalumab 1.5 g Q4W	32	-	-	-	-
NCT02775903	durvalumab + chemotherapy 1500 mg Q3W	42	chemotherapy	42	durvalumab + chemotherapy 1500 mg Q3W	64	chemotherapy	65
OAK	atezolizumab 1200 mg Q3W	612	chemotherapy	613	-	-	-	-
PACIFIC	durvalumab 10 mg/kg Q2W 12 months	476	placebo	237	-	-	-	-

POPLAR	chemotherapy NA	144	atezolizumab 1200 mg Q3W	143	-	-	-	-
PROLUNG	pembrolizumab + chemotherapy 200 mg Q3W	40	chemotherapy	38	-	-	-	-

Appendix 4: Characteristics of excluded trials

Population

- A Randomized, Double-Blind, Placebo-Controlled Study of a Single Dose of Pembrolizumab in HIV-Infected Patients (Clinical Trial Registration No. NCT03367754). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT03367754
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Intervention

- A Pilot Study to Test the Feasibility and Immunologic Impact of Sipuleucel-T (Provenge) Administered With or Without Anti-PD-1 mAb (CT-011) and Low Dose Cyclophosphamide in Men With Advanced Castrate-Resistant Prostate Cancer (Clinical Trial Registration No. NCT01420965). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT01420965
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Comparator

- A Phase IIa, Open-Label, Multi-Center, Multi-Cohort, Immune-Modulated Study of Selected Small Molecules (Gefitinib, AZD9291, or Selumetinib + Docetaxel) or a 1st Immune-Mediated Therapy (IMT; Tremelimumab) With a Sequential Switch to a 2nd IMT (MEDI4736) in Patients With Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (Stage IIIB-IV) (Clinical Trial Registration No. NCT02179671). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT02179671
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Study Design

- A Multi-arm Phase I Safety Study of Nivolumab in Combination With Gemcitabine/Cisplatin, Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in Subjects With Stage IIIB/IV Non-small Cell Lung Cancer (NSCLC) (Clinical Trial Registration No. NCT01454102). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT01454102
- A Phase IIa, Open-Label, Multi-Center, Multi-Cohort, Immune-Modulated Study of Selected Small Molecules (Gefitinib, AZD9291, or Selumetinib + Docetaxel) or a 1st Immune-Mediated Therapy (IMT; Tremelimumab) With a Sequential Switch to a 2nd IMT (MEDI4736) in Patients With Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (Stage IIIB-IV) (Clinical Trial Registration No. NCT02179671). Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT02179671
- A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects With Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus That Have Progressed After First-Line Standard Therapy (KEYNOTE-181) (Clinical Trial Registration No. NCT03933449). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT03933449
- A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) Versus Platinum Based Chemotherapy in Treatment Naïve Subjects With PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042) (Clinical Trial Registration No. NCT03850444). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT03850444
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No results

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No adverse events of interest

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Intervention

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Comparator

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Study Design

- A Multi-arm Phase I Safety Study of Nivolumab in Combination With Gemcitabine/Cisplatin, Pemetrexed/Cisplatin, Carboplatin/Paclitaxel, Bevacizumab Maintenance, Erlotinib, Ipilimumab or as Monotherapy in Subjects With Stage IIIB/IV Non-small Cell Lung Cancer (NSCLC) (Clinical Trial Registration No. NCT01454102). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT01454102

- A Phase IIa, Open-Label, Multi-Center, Multi-Cohort, Immune-Modulated Study of Selected Small Molecules (Gefitinib, AZD9291, or Selumetinib + Docetaxel) or a 1st Immune-Mediated Therapy (IMT; Tremelimumab) With a Sequential Switch to a 2nd IMT (MEDI4736) in Patients With Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (Stage IIIB-IV) (Clinical Trial Registration No. NCT02179671). Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT02179671
- A Phase III Randomized Open-Label Study of Single Agent Pembrolizumab vs Physicians' Choice of Single Agent Docetaxel, Paclitaxel, or Irinotecan in Subjects With Advanced/Metastatic Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus That Have Progressed After First-Line Standard Therapy (KEYNOTE-181) (Clinical Trial Registration No. NCT03933449). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT03933449
- A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) Versus Platinum Based Chemotherapy in Treatment Naïve Subjects With PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042) (Clinical Trial Registration No. NCT03850444). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT03850444
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No results

- A Multicentre Phase II Randomised Trial of Durvalumab (MEDI4736) Versus Physician's Choice Chemotherapy in Recurrent Ovarian Clear Cell Adenocarcinomas (MOCCA) (Clinical Trial Registration No. NCT03405454). clinicaltrials.gov. Retrieved 13 December 2021, from https://clinicaltrials.gov/ct2/show/NCT03405454
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No adverse events of interest

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Appendix 5: Risk of bias assessment

Table 15. Trial-based risk of bias assessment.

Trial	Random sequence generation	Allocation conceal-ment	Perfor-mance bias	Detection bias	Attrition bias	Selective reporting bias	Over-all risk of bias
ABC	Low	Low	High	High	Unclear	High	High
ARTIC-Substudy-A	Low	Low	High	Low	High	High	High
ARTIC-Substudy-B	Low	Low	High	Low	High	Low	High
ATTRACTION-2	Low	Low	Low	Low	Unclear	Low	Low
CA184-041	Low	Unclear	Low	Low	Low	Low	High
CA184-043	Low	Low	Low	Low	High	Low	Low
CA184-095	Low	Unclear	High	Unclear	Low	Low	High
CA184-104	Low	Unclear	Low	Low	Low	Low	High
CA184-153	Unclear	Unclear	Low	Unclear	Unclear	Low	High
CA184-162	Low	Unclear	High	Unclear	Low	Low	High
CA184-243	Unclear	Unclear	High	High	Unclear	High	Low
CASPIAN	Low	Low	High	Unclear	Unclear	Low	High
Checkmate 017	Low	Low	High	Unclear	Unclear	Low	High
Checkmate 025	Low	Unclear	High	Unclear	Low	Low	High
Checkmate 026	Low	Unclear	High	Unclear	Low	Low	High
Checkmate 037	Low	Low	High	Low	Low	High	Low
Checkmate 057	Low	Low	High	Unclear	Low	Low	Low
Checkmate 066	Low	Unclear	Low	Low	Low	Low	High
Checkmate 067	Low	Low	Low	Low	Low	Low	High
Checkmate 069	Low	Low	Low	Low	Low	Low	High
Checkmate 078	Low	Low	High	Unclear	Unclear	Low	High
Checkmate 141	Low	Unclear	High	Unclear	High	Low	High
Checkmate 143	Low	Unclear	High	Low	Low	High	Low
Checkmate 143 Cohort 2	Low	Low	High	High	Unclear	High	High
Checkmate 214	Low	Unclear	High	Low	High	High	High
Checkmate 238	Low	Low	Low	Low	Low	High	High
Checkmate 331	Low	Low	High	Low	High	Low	High
Checkmate 451	Low	Low	Low	Low	Unclear	Low	High
Checkmate 743	Low	Low	High	Unclear	High	Low	High
Checkmate 9LA	Low	Low	High	Low	High	High	High
CONDOR	Low	Low	High	Unclear	Low	Low	High
DANUBE	Low	Low	High	Low	Low	High	High

EAGLE	Low	Low	High	Unclear	Low	Low	High
EORTC 18071	Low	Low	Low	Low	High	Low	High
Geparnuevo	Low	Unclear	Low	Low	High	High	Low
I-SPY	Low	High	High	Unclear	Unclear	High	High
Imblaze370	Low	Low	High	Low	Low	High	High
Imblaze370	Low	Low	High	Low	Low	High	High
Immotion150	Low	Unclear	High	Unclear	Low	High	High
IMMUNED	Low	Low	Low	Low	Unclear	High	High
Impassion031	Low	Low	Low	Low	Low	Low	Low
Impassion130	Low	Low	Low	Low	Low	Low	Low
Impower110	Low	Low	High	Unclear	Unclear	Low	High
Impower130	Low	Low	High	Unclear	Low	Low	High
Impower132	Low	Low	High	Unclear	Low	Low	High
Impower133	Low	Unclear	Low	Low	Unclear	Low	High
Impower150	Low	Unclear	High	Unclear	Unclear	Low	High
Imspire150	Low	Low	Low	Low	Low	High	High
Imspire170	Low	Low	High	Unclear	High	High	Low
Imvigor130	Low	Low	Low	Low	High	High	High
Imvigor211	Low	High	High	Unclear	High	Low	High
JAVELIN Bladder 100	Low	Unclear	High	Low	Unclear	High	High
JAVELIN Gastric 100	Low	High	High	Unclear	Low	Low	High
JAVELIN Lung 200	Low	Unclear	High	Unclear	Low	Low	High
JAVELIN Ovarian 100	Low	Low	High	Unclear	Unclear	Low	High
KATE2	Low	Low	High	Unclear	High	Low	Low
KEYNOTE-006	Low	Low	High	Unclear	High	Low	High
KEYNOTE-010	Low	Low	High	Unclear	Low	Low	High
KEYNOTE-021	Low	Low	High	Low	Low	High	High
KEYNOTE-024	Low	Unclear	High	Low	Unclear	Low	High
KEYNOTE-040	Low	Low	High	Unclear	Low	Low	High
KEYNOTE-042	Low	Low	High	Unclear	Low	Low	High
KEYNOTE-045	Low	Unclear	High	Unclear	Low	Low	High
KEYNOTE-048	Low	Low	High	Unclear	Low	High	High
KEYNOTE-054	Low	Unclear	Low	Low	Low	Low	High
KEYNOTE-061	Low	Low	High	Unclear	Low	Low	High
KEYNOTE-062	Low	Low	High	Low	Low	Low	High
KEYNOTE-119	Unclear	Unclear	High	High	Unclear	Unclear	High
KEYNOTE-144	Low	Low	High	High	Low	Unclear	High
KEYNOTE-177	Low	High	High	Low	Low	High	High
KEYNOTE-181	Low	Low	High	Unclear	Unclear	Low	High
KEYNOTE-183	Low	Low	High	Low	Low	Unclear	High
KEYNOTE-185	Low	High	High	Low	Low	High	High

KEYNOTE-189	Low	Low	Low	Low	High	Low	Low
KEYNOTE-240	Low	Low	High	Low	Unclear	Low	High
KEYNOTE-355	Low	Low	Low	Low	Unclear	Low	Low
KEYNOTE-407	Low	Low	Low	Low	High	Low	Low
KEYNOTE-590	Low	Low	Low	Unclear	Low	Low	Low
KEYNOTE-598	Low	Low	Low	Low	Low	High	High
KEYNOTE-604	Low	Low	Low	Low	Unclear	High	High
MDX010-20	Unclear	Unclear	Low	Low	High	Low	High
MYSTIC	Low	Low	High	Low	Low	Low	High
NCT00324155	Low	Low	Low	Low	Low	Low	Low
NCT01450761	Low	Low	Low	Low	Low	Low	Low
NCT01471197	Low	High	High	Low	Low	Low	High
NCT01843374	Low	Low	Low	Low	High	Low	High
NCT02243371	Low	Unclear	High	High	Unclear	Unclear	High
NCT02340975	Unclear	Unclear	High	Unclear	Low	Low	High
NCT02498600	Low	Low	High	Unclear	High	Low	High
NCT02558894	Low	Low	High	High	Unclear	Unclear	High
NCT02775903	Unclear	Low	High	High	Unclear	Unclear	High
OAK	Low	High	High	Unclear	Low	Low	High
PACIFIC	Low	Low	Low	Unclear	Low	High	High
PACIFIC	Low	Low	Low	Unclear	Low	High	High
POPLAR	Low	Low	High	Unclear	Low	Low	High
PROLUNG	Low	Unclear	High	Unclear	Unclear	Low	High