Pembrolizumab plus Chemotherapy versus Chemotherapy Only in Non-Small-Cell Lung Cancer: A Meta-Analysis

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Abstract

Immune checkpoint inhibition is a rapidly growing technology in the field of cancer treatment. Drugs blocking the programmed cell death-1 receptor and cytotoxic T-lymphocyte antigen-4 pathways are especially prevalent as effective immune checkpoint targets. Non-small-cell lung cancer (NSCLC) is one type of cancer that immune checkpoint inhibition has been able to effectively treat, but ICI is currently only a second- or third- line treatment for the condition. This meta-analysis evaluates the potential of ICI as a first-line treatment for NSCLC. A literature search of PubMED was performed in search of clinical trials comparing pembrolizumab and chemotherapy, an anti-PD-1 immune checkpoint inhibitor, to a placebo and chemotherapy in patients with NSCLC. Hazard ratios for overall survival and progression-free survival and risk ratios for adverse events were calculated with 95% confidence intervals. The results showed an association between the pembrolizumab combination and a decreased risk of disease progression and death and an association between the pembrolizumab combination and an increased risk of immune-related adverse events. Overall, there is a benefit to the pembrolizumab treatment, but clinicians must also consider the potential for immune-related adverse events.

Introduction

Immune checkpoint inhibition is a rapidly growing technology in the field of cancer treatment. Ever since the introduction of the first immune checkpoint inhibitor immunotherapy, ipilimumab (Yervoy, Bristol-Myers Squibb), in 2010, this revolutionary treatment technology has rapidly increased in clinical relevance and new immune checkpoint inhibitors (ICIs) continue to be developed and tested in clinical trials (Alexander 2016). Certain cancers are able to utilize certain co-inhibitory signaling pathways to block an immune response. ICIs work by interfering with these signaling pathways to reinvigorate the body's natural immune response to dysfunctioning cells (Darvin et al. 2018). The programmed cell death-1 (PD-1) receptor and the cytotoxic T-lymphocyte antigen-4 (CTLA-4) are among the inhibitory pathways that current immune checkpoint inhibitors block (Rajani 2015). Pembrolizumab was the first checkpoint inhibitor blocking the PD-1 pathway to be approved by the FDA, soon following by nivolumab,

both of which continued to gain approvals for a variety of different cancers (Alexander 2016). Today, immune checkpoint inhibitor immunotherapy continues to be on the front lines of cancer treatment research.

ICI is not a completely flawless treatment option. Clinical trials have revealed that many of these treatments cause significant immune-related side effects, including diarrhea, hepatitis, fatigue, fever, pneumonitis, dyspnea, rash, hypophysitis, thyroiditis, hypothyroidism, and adrenal insufficiency among other adverse effects (Dine 2017). These adverse effects need to be considered when clinicians make decisions on when to use ICI therapy.

Non-small-cell lung cancer (NSCLC) has been one of the primary types of cancer ICI has been focused on targeting (Alexander 2016). Currently, ICI is relegated to second- or third- line therapy for NSCLC, behind the common first-line treatment of platinum-based chemotherapy (Gandhi 2018 & Paz-Ares 2018). Given the high potential for ICI in treating cancers such as NSCLC, ICI as a first-line therapy may result in better treatment outcomes (Gandhi 2018 & Paz-Ares 2018).

Materials and Methods

A literature search of the PubMED database was performed to find the articles for this meta-analysis using the search terms “pembrolizumab” and “non-small-cell lung cancer”. The search was limited to clinical trials. The clinical trials chosen were double-blind, phase III trials and evaluated the overall survival and progression-free survival hazard ratios between a pembrolizumab and chemotherapy experimental group and a placebo and chemotherapy control group in non-small-cell lung cancer patients as primary outcomes, as well as adverse events (AEs) of any cause and adverse events of interest, the latter of which was defined as any immune-related adverse event (Gandhi 2018 & Paz-Ares 2018).

Statistical analysis was performed in Cochrane’s RevMan 5 software. Hazard ratios for overall survival and progression-free survival were input using the generic inverse variance data type and evaluated under the inverse variance statistical method and the fixed effect analysis model with 95% confidence intervals (CIs). Risks ratios (RRs) were calculated for AEs, with data inputted using the dichotomous data type and evaluated under the inverse variance statistical method and the fixed effect analysis model with 95% confidence intervals. Statistical significant in both cases was determined by whether or not CIs passed a value of 1.0, with inclusion signifying statistical insignificance.

Results

Overall Survival

Overall, a hazard ratio for death of 0.56 (95% CI, 0.46 to 0.67) was observed. All subgroups evaluated demonstrated the benefit of the pembrolizumab-chemotherapy combination over the placebo combination (See 1.1).

Progression-free Survival

Overall, a hazard ratio for disease progression or death of 0.54 (95% CI, 0.47 to 0.62) was observed. All subgroups evaluated demonstrated the benefit of the pembrolizumab-chemotherapy combination over the placebo combination (See 2.1).

Adverse Events of Any Cause

A risk ratio of 1.01 (95% CI, 0.99 to 1.02 was observed for the incidence of adverse events of any cause and of any grade (See 3.1). For adverse events of any cause of grades 3, 4, and 5, a risk ratio of 1.02 (95% CI, 0.94 to 1.11) was observed (See 3.2). No statistically significant evidence was observed in favor of the pembrolizumab combination or the placebo combination.

Adverse Events of Interest

A risk ratio of 2.52 (95% CI, 1.87 to 3.39) was observed for adverse events of interest and of any grade (See 4.1). For adverse events of interest of grades 3, 4, and 5, a risk ratio of 2.57 (95% CI, 1.55 to 4.28) was observed (See 4.3). Subgroup evaluation shows statistically significant results in hypothyroidism of any grade (3.44 RR; 95% CI, 1.76 to 6.72), pneumonitis of any grade (2.37 RR; 95% CI, 1.22 to 4.62), hyperthyroidism of any grade (2.39 RR; 95% CI, 1.10 to 5.21), and hepatitis of any grade (7.81 RR; 95% CI, 1.10 to 60.25). The overall results are statistically significant in favor of the placebo combination.

Discussion

This analysis compared the efficacy and adverse effects of a pembrolizumab and chemotherapy combination and a placebo and chemotherapy combination. Overall, the pembrolizumab combination was observed to be more beneficial as a treatment, providing a lower risk of disease progression and death than just chemotherapy, thus suggesting that adding pembrolizumab as a first-line treatment may result in better outcomes. It is important to consider, however, that there

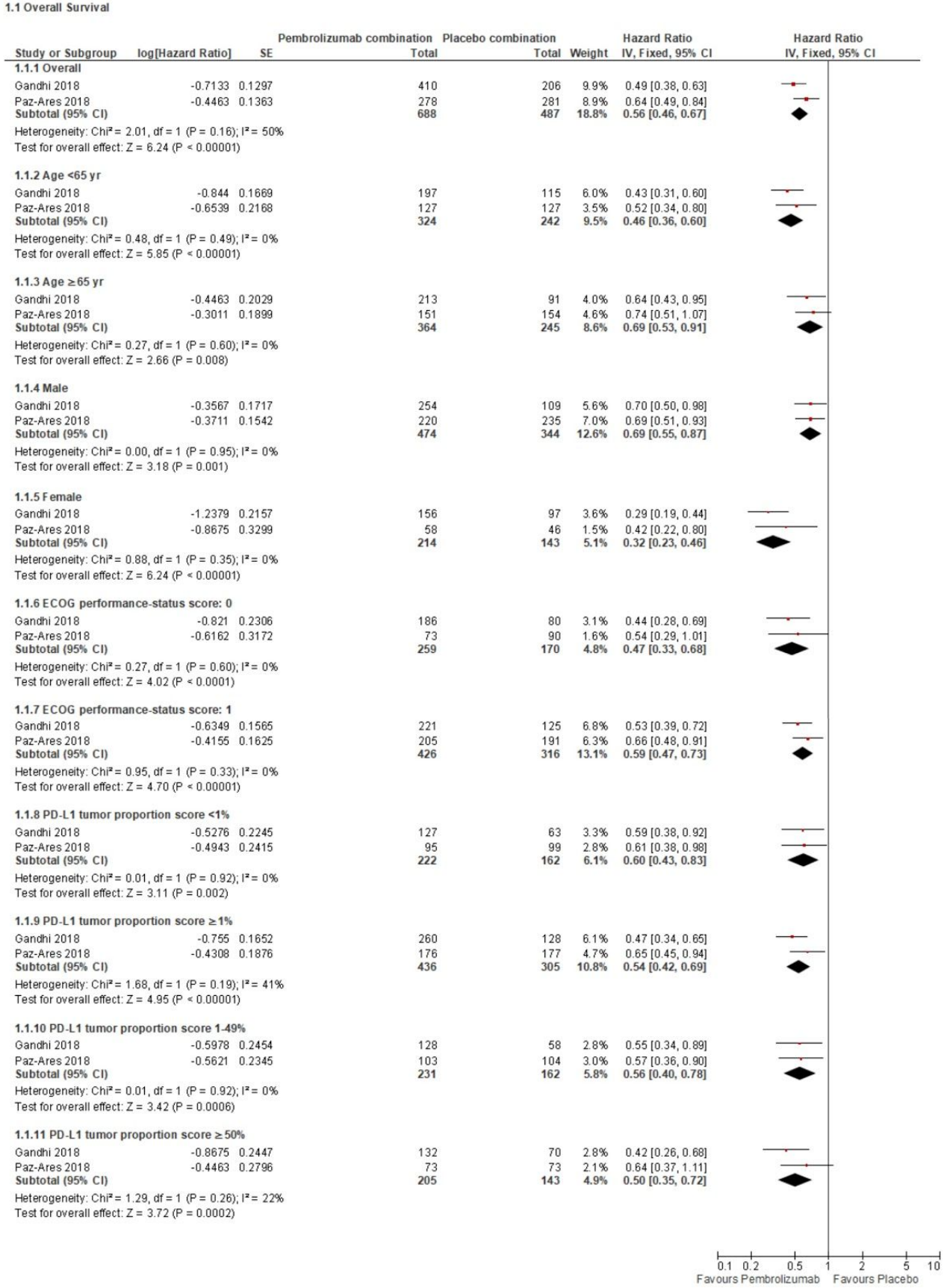
was a statistically significant association between the pembrolizumab combination and the incidence of immune-related adverse effects. This result must be taken in consideration as a potential drawback to the implementation of first-line pembrolizumab treatment. The overall benefit of such treatment, however, is supported by the overall survival and progression-free survival outcomes. This may be incentive enough to enroll patients in first line ICI, despite the potential immune-related adverse events.

This meta-analysis is a preliminary project that is lacking many aspects of a full, complete analysis, and as such, it has many limitations. A study of this scale would normally be completed by a team and reviewed by other researchers who are well versed in the field. A high degree of statistical knowledge and an advanced understanding of clinical trials would also normally be required of the author of such an analysis. Given the circumstances of this project, many of these requirements were unattainable. This study is thus limited in the number of clinical trials included in the pooling, the suboptimal nature of the statistical analysis, and lack of peer review. Nevertheless, this study is not without its value, as it provides grounds for future research. The established trend of this analysis may prompt further study of ICI and chemotherapy combinations, first-line ICI treatment, and the adverse effects of ICI compared with chemotherapy. More clinical trials testing the same or similar variables would be welcome in performing a new meta-analysis with more data and the quality requirements listed previously.

Conclusion

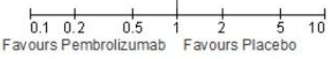
This analysis has found an association between first-line immune checkpoint inhibition therapy combined with chemotherapy and a decreased risk of disease progression and death in patients with non-small-cell lung cancer. This result suggests that utilizing ICI as a first-line treatment for NSCLC may lead to better treatment outcomes. This analysis also found, however, an association between first-line ICI combined with chemotherapy and an increased risk of immune-related adverse events, serving as a cautionary warning to clinicians who may seek to utilize such treatment. Further research and improvements on the methods of this analysis is necessary to come to stronger conclusions about the value of first-line ICI therapy.

Figures


1.1 Overall Survival
Pembrolizumab combination
Placebo combination
Hazard Ratio
Hazard Ratio
Study or Subgroup log[Hazard Ratio] SE Total Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI
1.1.1 Overall
Gandhi 2018 -0.7133 0.1297 410 206 9.9% 0.49 [0.38, 0.63]
Paz-Ares 2018 -0.4463 0.1363 278 281 8.9% 0.64 [0.49, 0.84]
Subtotal (95% CI) 688 487 18.8% 0.56 [0.46, 0.67]
Heterogeneity: Chi² = 2.01, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 6.24 (P < 0.00001)
1.1.2 Age <65 yr
Gandhi 2018 -0.844 0.1669 197 115 6.0% 0.43 [0.31, 0.60]
Paz-Ares 2018 -0.6539 0.2168 127 127 3.5% 0.52 [0.34, 0.80]
Subtotal (95% CI) 324 242 9.5% 0.46 [0.36, 0.60]
Heterogeneity: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 5.85 (P < 0.00001)
1.1.3 Age ≥65 yr
Gandhi 2018 -0.4463 0.2029 213 91 4.0% 0.64 [0.43, 0.95]
Paz-Ares 2018 -0.3011 0.1899 151 154 4.6% 0.74 [0.51, 1.07]
Subtotal (95% CI) 364 245 8.6% 0.69 [0.53, 0.91]
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.66 (P = 0.008)
1.1.4 Male
Gandhi 2018 -0.3567 0.1717 254 109 5.6% 0.70 [0.50, 0.98]
Paz-Ares 2018 -0.3711 0.1542 220 235 7.0% 0.69 [0.51, 0.93]
Subtotal (95% CI) 474 344 12.6% 0.69 [0.55, 0.87]
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 3.18 (P = 0.001)
1.1.5 Female
Gandhi 2018 -1.2379 0.2157 156 97 3.6% 0.29 [0.19, 0.44]
Paz-Ares 2018 -0.8675 0.3299 58 46 1.5% 0.42 [0.22, 0.80]
Subtotal (95% CI) 214 143 5.1% 0.32 [0.23, 0.46]
Heterogeneity: Chi² = 0.88, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 6.24 (P < 0.00001)
1.1.6 ECOG performance-status score: 0
Gandhi 2018 -0.821 0.2306 186 80 3.1% 0.44 [0.28, 0.69]
Paz-Ares 2018 -0.6162 0.3172 73 90 1.6% 0.54 [0.29, 1.01]
Subtotal (95% CI) 259 170 4.8% 0.47 [0.33, 0.68]
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 4.02 (P < 0.0001)
1.1.7 ECOG performance-status score: 1
Gandhi 2018 -0.6349 0.1565 221 125 6.8% 0.53 [0.39, 0.72]
Paz-Ares 2018 -0.4155 0.1625 205 191 6.3% 0.66 [0.48, 0.91]
Subtotal (95% CI) 426 316 13.1% 0.59 [0.47, 0.73]
Heterogeneity: Chi² = 0.95, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 4.70 (P < 0.00001)
1.1.8 PD-L1 tumor proportion score <1%
Gandhi 2018 -0.5276 0.2245 127 63 3.3% 0.59 [0.38, 0.92]
Paz-Ares 2018 -0.4943 0.2415 95 99 2.8% 0.61 [0.38, 0.98]
Subtotal (95% CI) 222 162 6.1% 0.60 [0.43, 0.83]
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.11 (P = 0.002)
1.1.9 PD-L1 tumor proportion score ≥1%
Gandhi 2018 -0.755 0.1652 260 128 6.1% 0.47 [0.34, 0.65]
Paz-Ares 2018 -0.4308 0.1876 176 177 4.7% 0.65 [0.45, 0.94]
Subtotal (95% CI) 436 305 10.8% 0.54 [0.42, 0.69]
Heterogeneity: Chi² = 1.68, df = 1 (P = 0.19); I² = 41%
Test for overall effect: Z = 4.95 (P < 0.00001)
1.1.10 PD-L1 tumor proportion score 1-49%
Gandhi 2018 -0.5978 0.2454 128 58 2.8% 0.55 [0.34, 0.89]
Paz-Ares 2018 -0.5621 0.2345 103 104 3.0% 0.57 [0.36, 0.90]
Subtotal (95% CI) 231 162 5.8% 0.56 [0.40, 0.78]
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.42 (P = 0.0006)
1.1.11 PD-L1 tumor proportion score ≥50%
Gandhi 2018 -0.8675 0.2447 132 70 2.8% 0.42 [0.26, 0.68]
Paz-Ares 2018 -0.4463 0.2796 73 73 2.1% 0.64 [0.37, 1.11]
Subtotal (95% CI) 205 143 4.9% 0.50 [0.35, 0.72]
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 3.72 (P = 0.0002)
0.1 0.2 0.5 1 2 5 10
Favours Pembrolizumab
Favours Placebo

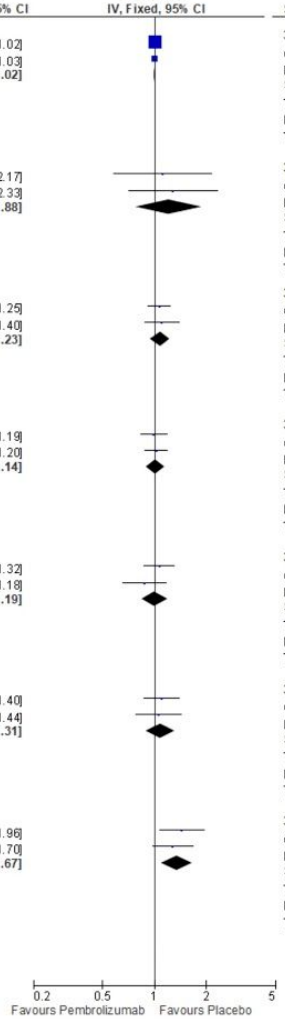
2.1 Progression-free Survival

Study or Subgroup	log[Hazard Ratio]	SE	Pembrolizumab combination Total	Placebo combination Total	Weight	Hazard Ratio IV, Fixed, 95% CI
2.1.1 Overall						
Gandhi 2018	-0.6539	0.097	410	206	10.8%	0.52 [0.43, 0.63]
Paz-Ares 2018	-0.5798	0.1116	278	281	8.1%	0.56 [0.45, 0.70]
Subtotal (95% CI)			**688**	**487**	**18.9%**	**0.54 [0.47, 0.62]**
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 8.50 (P < 0.00001)						
2.1.2 Age <65 yr						
Gandhi 2018	-0.844	0.1507	197	115	4.5%	0.43 [0.32, 0.58]
Paz-Ares 2018	-0.6931	0.1536	127	127	4.3%	0.50 [0.37, 0.68]
Subtotal (95% CI)			**324**	**242**	**8.7%**	**0.46 [0.38, 0.57]**
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 7.16 (P < 0.00001)						
2.1.3 Age ≥65 yr						
Gandhi 2018	-0.2877	0.1582	213	91	4.0%	0.75 [0.55, 1.02]
Paz-Ares 2018	-0.462	0.1495	151	154	4.5%	0.63 [0.47, 0.84]
Subtotal (95% CI)			**364**	**245**	**8.6%**	**0.68 [0.55, 0.85]**
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 3.50 (P = 0.0005)						
2.1.4 Male						
Gandhi 2018	-0.4155	0.1417	254	109	5.0%	0.66 [0.50, 0.87]
Paz-Ares 2018	-0.5447	0.1183	220	235	7.2%	0.58 [0.46, 0.73]
Subtotal (95% CI)			**474**	**344**	**12.3%**	**0.61 [0.51, 0.73]**
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 5.41 (P < 0.00001)						
2.1.5 Female						
Gandhi 2018	-0.9163	0.1641	156	97	3.8%	0.40 [0.29, 0.55]
Paz-Ares 2018	-0.7133	0.2503	58	46	1.6%	0.49 [0.30, 0.80]
Subtotal (95% CI)			**214**	**143**	**5.4%**	**0.43 [0.32, 0.56]**
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 6.23 (P < 0.00001)						
2.1.6 ECOG performance-status score: 0						
Gandhi 2018	-0.7133	0.1717	186	80	3.4%	0.49 [0.35, 0.69]
Paz-Ares 2018	-0.7985	0.2242	73	90	2.0%	0.45 [0.29, 0.70]
Subtotal (95% CI)			**259**	**170**	**5.4%**	**0.47 [0.36, 0.62]**
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 5.46 (P < 0.00001)						
2.1.7 ECOG performance-status score: 1						
Gandhi 2018	-0.5798	0.1348	221	125	5.6%	0.56 [0.43, 0.73]
Paz-Ares 2018	-0.4943	0.1223	205	191	6.8%	0.61 [0.48, 0.78]
Subtotal (95% CI)			**426**	**316**	**12.3%**	**0.59 [0.49, 0.70]**
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 5.88 (P < 0.00001)						
2.1.8 PD-L1 tumor proportion score <1%						
Gandhi 2018	-0.2877	0.1771	127	63	3.2%	0.75 [0.53, 1.06]
Paz-Ares 2018	-0.3857	0.1885	95	99	2.8%	0.68 [0.47, 0.98]
Subtotal (95% CI)			**222**	**162**	**6.1%**	**0.72 [0.56, 0.92]**
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 2.58 (P = 0.010)						
2.1.9 PD-L1 tumor proportion score ≥1%						
Gandhi 2018	-0.821	0.1315	260	128	5.9%	0.44 [0.34, 0.57]
Paz-Ares 2018	-0.7133	0.1297	176	177	6.0%	0.49 [0.38, 0.63]
Subtotal (95% CI)			**436**	**305**	**11.9%**	**0.46 [0.39, 0.56]**
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 8.30 (P < 0.00001)						
2.1.10 PD-L1 tumor proportion score 1-49%						
Gandhi 2018	-0.5978	0.2023	128	58	2.5%	0.55 [0.37, 0.82]
Paz-Ares 2018	-0.5798	0.1846	103	104	3.0%	0.56 [0.39, 0.80]
Subtotal (95% CI)			**231**	**162**	**5.4%**	**0.56 [0.43, 0.73]**
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 4.31 (P < 0.0001)						
2.1.11 PD-L1 tumor proportion score ≥50%						
Gandhi 2018	-1.0217	0.186	132	70	2.9%	0.36 [0.25, 0.52]
Paz-Ares 2018	-0.9943	0.2209	73	73	2.1%	0.37 [0.24, 0.57]
Subtotal (95% CI)			**205**	**143**	**5.0%**	**0.36 [0.28, 0.48]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 7.10 (P < 0.00001)						

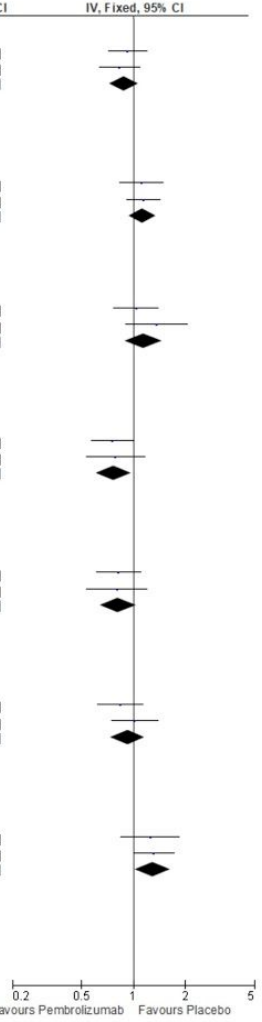


3.1 Adverse Events of Any Cause and of Any Grade

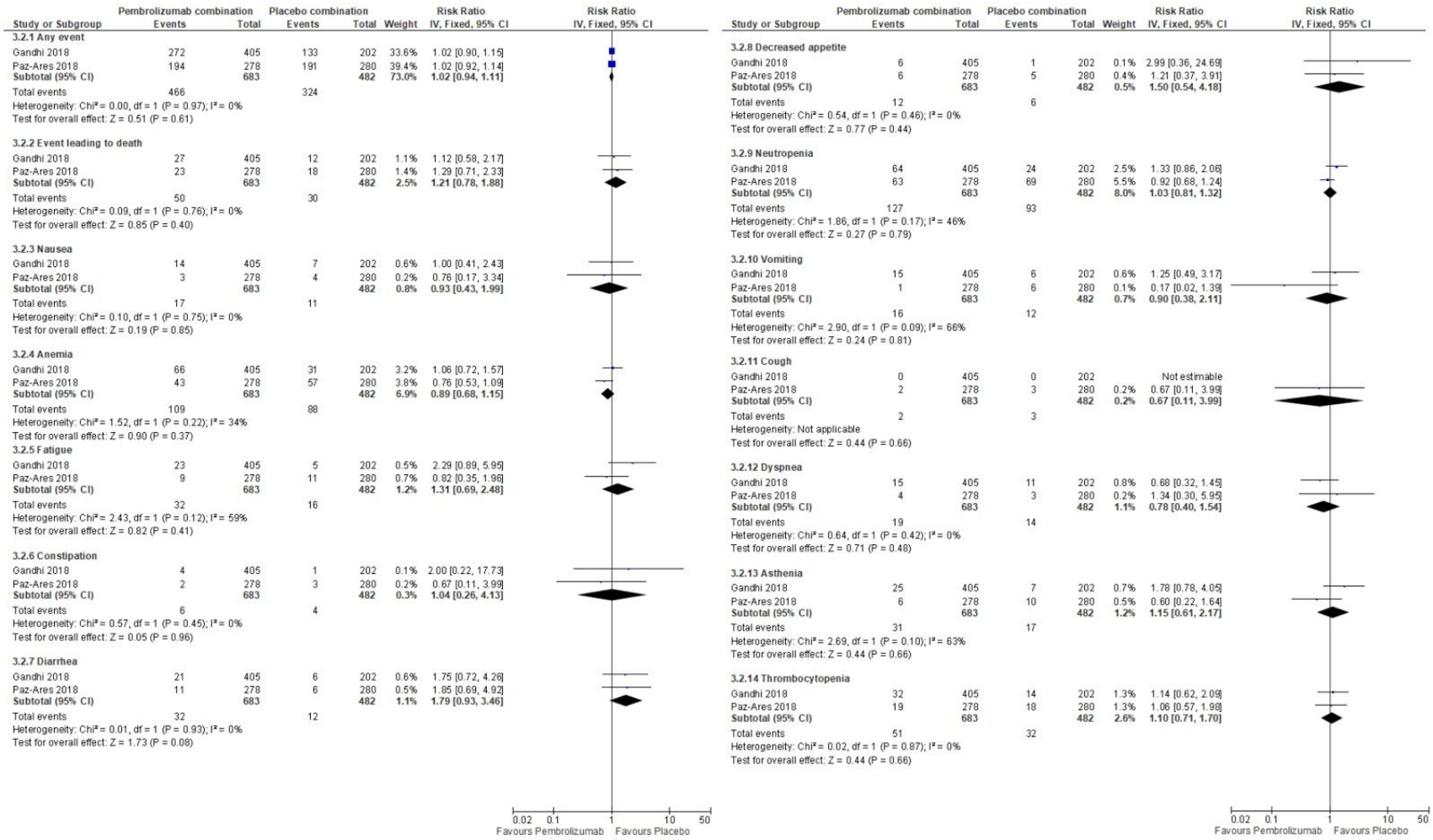
Study or Subgroup	Pembrolizumab combination Events	Total	Placebo combination Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.1.1 Any Event						
Gandhi 2018	404	405	200	202	68.3%	1.01 [0.99, 1.02]
Paz-Ares 2018	273	278	274	280	26.3%	1.00 [0.98, 1.03]
Subtotal (95% CI)		683		482	94.6%	**1.01 [0.99, 1.02]**
Total events	677		474			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
3.1.2 Event leading to death						
Gandhi 2018	27	405	12	202	0.0%	1.12 [0.58, 2.17]
Paz-Ares 2018	23	278	18	280	0.0%	1.29 [0.71, 2.33]
Subtotal (95% CI)		683		482	0.1%	**1.21 [0.78, 1.88]**
Total events	50		30			
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.40)						
3.1.3 Nausea						
Gandhi 2018	225	405	105	202	0.6%	1.07 [0.91, 1.25]
Paz-Ares 2018	99	278	90	280	0.3%	1.11 [0.88, 1.40]
Subtotal (95% CI)		683		482	0.8%	**1.08 [0.95, 1.23]**
Total events	324		195			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
3.1.4 Anemia						
Gandhi 2018	187	405	94	202	0.4%	0.99 [0.83, 1.19]
Paz-Ares 2018	148	278	145	280	0.6%	1.03 [0.88, 1.20]
Subtotal (95% CI)		683		482	1.0%	**1.01 [0.90, 1.14]**
Total events	335		239			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
3.1.5 Fatigue						
Gandhi 2018	165	405	77	202	0.3%	1.07 [0.87, 1.32]
Paz-Ares 2018	63	278	72	280	0.2%	0.88 [0.66, 1.18]
Subtotal (95% CI)		683		482	0.5%	**1.00 [0.84, 1.19]**
Total events	228		149			
Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 0.01 (P = 0.99)						
3.1.6 Constipation						
Gandhi 2018	141	405	64	202	0.2%	1.10 [0.86, 1.40]
Paz-Ares 2018	64	278	61	280	0.2%	1.06 [0.78, 1.44]
Subtotal (95% CI)		683		482	0.4%	**1.08 [0.89, 1.31]**
Total events	205		125			
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
3.1.7 Diarrhea						
Gandhi 2018	125	405	43	202	0.2%	1.45 [1.07, 1.96]
Paz-Ares 2018	83	278	65	280	0.2%	1.29 [0.97, 1.70]
Subtotal (95% CI)		683		482	0.3%	**1.36 [1.11, 1.67]**
Total events	208		108			
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.93 (P = 0.003)						



Study or Subgroup	Pembrolizumab combination Events	Total	Placebo combination Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.1.8 Decreased appetite						
Gandhi 2018	114	405	61	202	0.2%	0.93 [0.72, 1.21]
Paz-Ares 2018	68	278	82	280	0.2%	0.84 [0.63, 1.10]
Subtotal (95% CI)		683		482	0.4%	**0.88 [0.73, 1.07]**
Total events	182		143			
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
3.1.9 Neutropenia						
Gandhi 2018	110	405	49	202	0.2%	1.12 [0.84, 1.50]
Paz-Ares 2018	105	278	92	280	0.3%	1.15 [0.92, 1.44]
Subtotal (95% CI)		683		482	0.5%	**1.14 [0.95, 1.36]**
Total events	215		141			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.15)						
3.1.10 Vomiting						
Gandhi 2018	98	405	47	202	0.2%	1.04 [0.77, 1.41]
Paz-Ares 2018	45	278	33	280	0.1%	1.37 [0.90, 2.08]
Subtotal (95% CI)		683		482	0.2%	**1.15 [0.90, 1.46]**
Total events	143		80			
Heterogeneity: Chi² = 1.11, df = 1 (P = 0.29); I² = 10%						
Test for overall effect: Z = 1.08 (P = 0.28)						
3.1.11 Cough						
Gandhi 2018	87	405	57	202	0.2%	0.76 [0.57, 1.02]
Paz-Ares 2018	37	278	47	280	0.1%	0.79 [0.53, 1.18]
Subtotal (95% CI)		683		482	0.3%	**0.77 [0.61, 0.97]**
Total events	124		104			
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 2.17 (P = 0.03)						
3.1.12 Dyspnea						
Gandhi 2018	86	405	52	202	0.2%	0.82 [0.61, 1.11]
Paz-Ares 2018	36	278	45	280	0.1%	0.81 [0.54, 1.21]
Subtotal (95% CI)		683		482	0.3%	**0.82 [0.64, 1.04]**
Total events	122		97			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.63 (P = 0.10)						
3.1.13 Asthenia						
Gandhi 2018	83	405	49	202	0.2%	0.84 [0.62, 1.15]
Paz-Ares 2018	60	278	59	280	0.1%	1.02 [0.74, 1.41]
Subtotal (95% CI)		683		482	0.3%	**0.93 [0.74, 1.16]**
Total events	143		108			
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
3.1.14 Thrombocytopenia						
Gandhi 2018	73	405	29	202	0.1%	1.26 [0.85, 1.86]
Paz-Ares 2018	85	278	65	280	0.2%	1.32 [1.00, 1.74]
Subtotal (95% CI)		683		482	0.3%	**1.30 [1.03, 1.63]**
Total events	158		94			
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 2.24 (P = 0.02)						

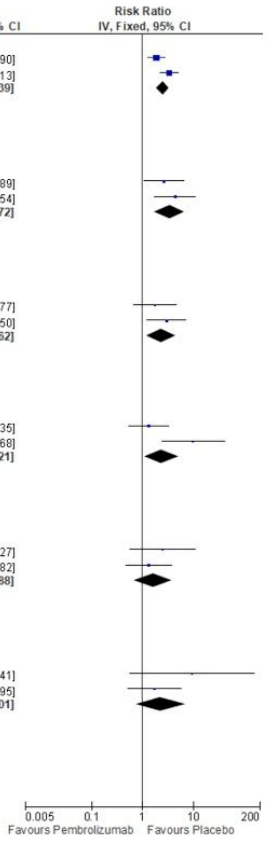


3.2 Adverse Events of Any Cause and of Grade 3, 4, or 5

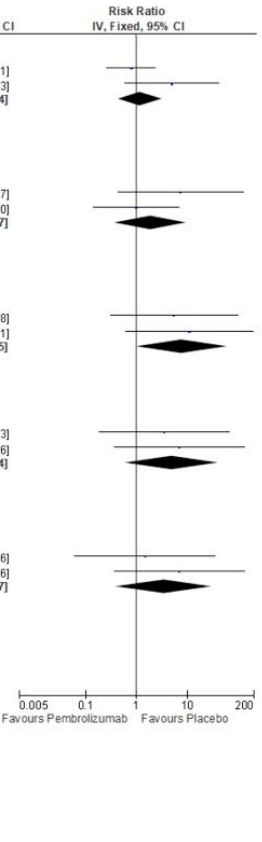


4.1 Adverse Events of Interest and of Any Grade

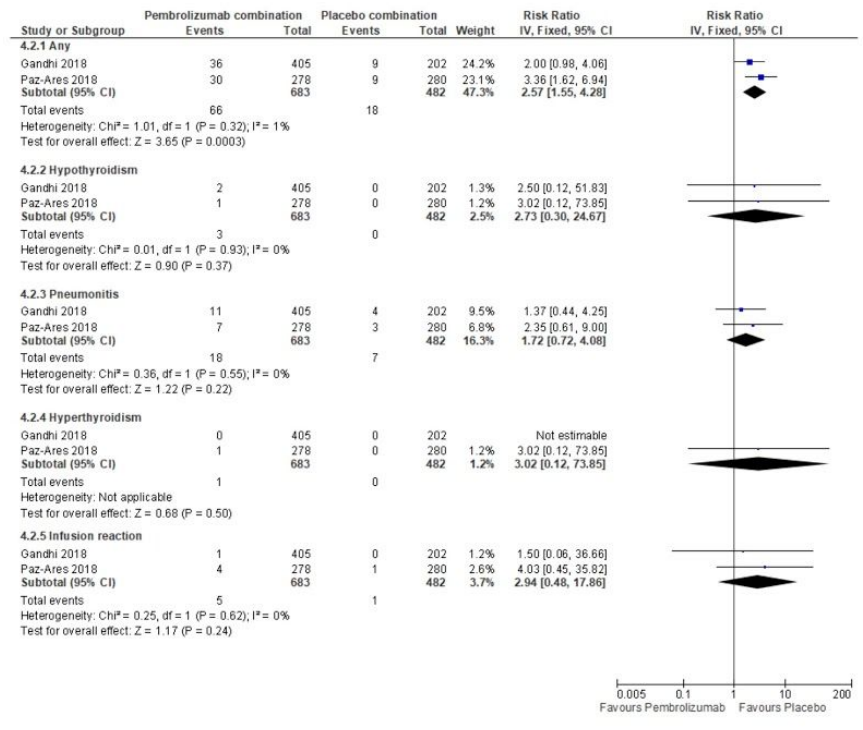
Study or Subgroup	Pembrolizumab combination Events	Total	Placebo combination Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.1.1 Any						
Gandhi 2018	92	405	24	202	26.6%	1.91 [1.26, 2.90]
Paz-Ares 2018	80	278	24	280	25.5%	3.36 [2.20, 5.13]
Subtotal (95% CI)		683		482	52.1%	**2.52 [1.87, 3.39]**
Total events	172		48			
Heterogeneity: Chi² = 3.44, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 6.09 (P < 0.00001)						
4.1.2 Hypothyroidism						
Gandhi 2018	27	405	5	202	5.2%	2.69 [1.05, 6.89]
Paz-Ares 2018	22	278	5	280	5.0%	4.43 [1.70, 11.54]
Subtotal (95% CI)		683		482	10.3%	**3.44 [1.76, 6.72]**
Total events	49		10			
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 3.61 (P = 0.0003)						
4.1.3 Pneumonitis						
Gandhi 2018	18	405	5	202	4.8%	1.80 [0.68, 4.77]
Paz-Ares 2018	18	278	6	280	5.6%	3.02 [1.22, 7.50]
Subtotal (95% CI)		683		482	10.4%	**2.37 [1.22, 4.62]**
Total events	36		11			
Heterogeneity: Chi² = 0.58, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.55 (P = 0.01)						
4.1.4 Hyperthyroidism						
Gandhi 2018	16	405	6	202	5.4%	1.33 [0.53, 3.35]
Paz-Ares 2018	20	278	2	280	2.2%	10.07 [2.38, 42.68]
Subtotal (95% CI)		683		482	7.6%	**2.39 [1.10, 5.21]**
Total events	36		8			
Heterogeneity: Chi² = 5.36, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 2.20 (P = 0.03)						
4.1.5 Infusion reaction						
Gandhi 2018	10	405	2	202	2.0%	2.49 [0.55, 11.27]
Paz-Ares 2018	8	278	6	280	4.2%	1.34 [0.47, 3.82]
Subtotal (95% CI)		683		482	6.2%	**1.64 [0.70, 3.88]**
Total events	18		8			
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
4.1.6 Colitis						
Gandhi 2018	9	405	0	202	0.6%	9.50 [0.56, 162.41]
Paz-Ares 2018	7	278	4	280	3.1%	1.76 [0.52, 5.95]
Subtotal (95% CI)		683		482	3.7%	**2.29 [0.75, 7.01]**
Total events	16		4			
Heterogeneity: Chi² = 1.14, df = 1 (P = 0.29); I² = 12%						
Test for overall effect: Z = 1.45 (P = 0.15)						

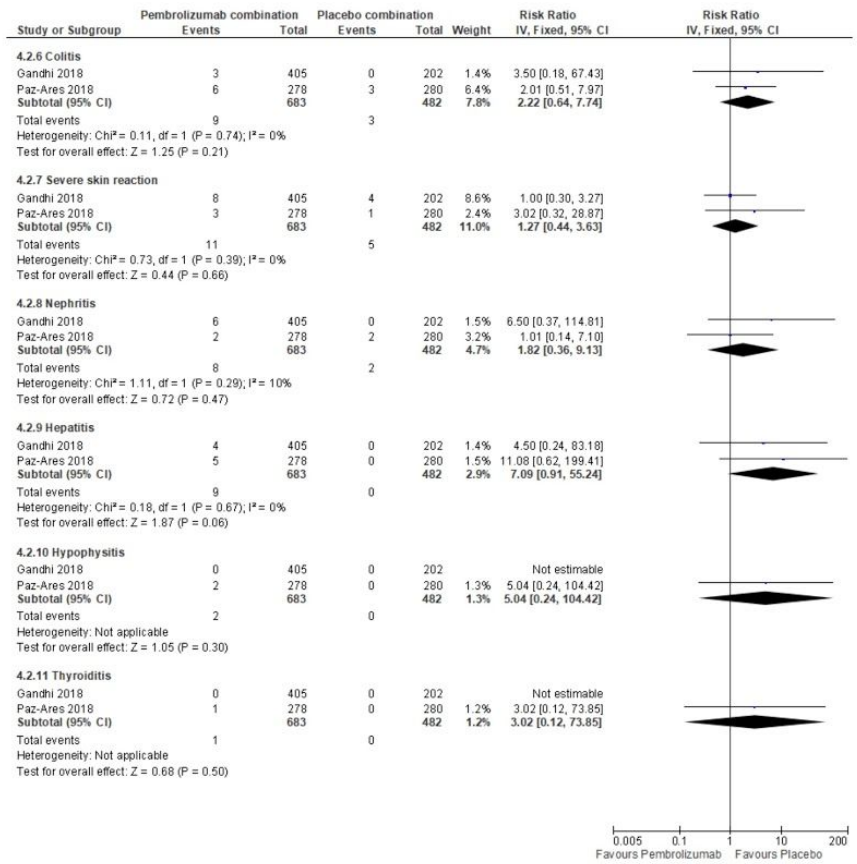


Study or Subgroup	Pembrolizumab combination Events	Total	Placebo combination Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
4.1.7 Severe skin reaction						
Gandhi 2018	8	405	5	202	3.8%	0.80 [0.26, 2.41]
Paz-Ares 2018	5	278	1	280	1.0%	5.04 [0.59, 42.83]
Subtotal (95% CI)		683		482	4.8%	**1.18 [0.44, 3.14]**
Total events	13		6			
Heterogeneity: Chi² = 2.25, df = 1 (P = 0.13); I² = 55%						
Test for overall effect: Z = 0.32 (P = 0.75)						
4.1.8 Nephritis						
Gandhi 2018	7	405	0	202	0.6%	7.50 [0.43, 130.67]
Paz-Ares 2018	2	278	2	280	1.2%	1.01 [0.14, 7.10]
Subtotal (95% CI)		683		482	1.8%	**1.91 [0.38, 9.57]**
Total events	9		2			
Heterogeneity: Chi² = 1.29, df = 1 (P = 0.26); I² = 23%						
Test for overall effect: Z = 0.79 (P = 0.43)						
4.1.9 Hepatitis						
Gandhi 2018	5	405	0	202	0.6%	5.50 [0.31, 98.98]
Paz-Ares 2018	5	278	0	280	0.6%	11.08 [0.62, 199.41]
Subtotal (95% CI)		683		482	1.1%	**7.81 [1.01, 60.25]**
Total events	10		0			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.97 (P = 0.05)						
4.1.10 Hypophysitis						
Gandhi 2018	3	405	0	202	0.5%	3.50 [0.18, 67.43]
Paz-Ares 2018	3	278	0	280	0.5%	7.05 [0.37, 135.86]
Subtotal (95% CI)		683		482	1.1%	**4.97 [0.61, 40.24]**
Total events	6		0			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.50 (P = 0.13)						
4.1.11 Thyroiditis						
Gandhi 2018	1	405	0	202	0.5%	1.50 [0.06, 36.66]
Paz-Ares 2018	3	278	0	280	0.5%	7.05 [0.37, 135.86]
Subtotal (95% CI)		683		482	1.0%	**3.45 [0.39, 30.27]**
Total events	4		0			
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						



4.2 Adverse Events of Interest and of Grade 3, 4, or 5





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