



Adjuvant Therapy With PD1/PDL1 Inhibitors for Human Cancers: A Systematic Review and Meta-Analysis

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Background: Immune checkpoint inhibitors (ICIs) have made a breakthrough in the systemic treatment of patients with advanced tumors. However, little is known about their efficacy and safety in adjuvant settings after the resection of solid tumors.

Methods: We performed a meta-analysis on the efficacy and safety of programmed death 1 (PD1)/PD-1 ligand (PDL1) inhibitors in adjuvant therapy after tumor resection using Review Manager 5.3, based on published clinical studies. The outcomes included recurrence-free survival (RFS), disease-free survival (DFS), overall survival (OS), and adverse events (AEs).

Results: Eight randomized controlled trials (RCTs) were included in the analysis. The use of PD1/PDL1 inhibitors in adjuvant therapy significantly improved RFS (hazard ratio [HR] = 0.72; 95% confidence interval [CI] 0.67–0.78, p < 0.00001). However, there was no statistically significant difference in OS between PD1/PDL1 inhibitors and placebo (HR = 0.86; 95% CI 0.74–1.00, p = 0.05). Gender, age, and PDL1 status were independent predictors of RFS with PD1/PDL1 inhibitors. As for the safety analysis results, PD1/PDL1 inhibitors had a higher incidence of fatigue (risk ratio [RR] = 1.22; 95% CI 1.01–1.49, p = 0.04), nausea (RR = 1.47; 95% CI 1.11–1.94, p = 0.007), and pruritus (RR = 1.96; 95% CI 1.57–2.44, p < 0.00001). In addition, the incidence of any grade adverse events increased in the PD1/PDL1 inhibitor group (RR = 1.03; 95% CI 1.02–1.05, p < 0.0001).

Conclusions: This is the first meta-analysis on the efficacy and safety of PD1/PDL1 inhibitors in adjuvant therapy. The use of PD1/PDL1 inhibitors in adjuvant therapy could significantly reduce the recurrence rate after solid tumor resection. However, the incidence of fatigue, nausea, pruritus, and any grade AEs also increased, which should be monitored with vigilance.

Keywords: human cancers, immune checkpoint inhibitor, PD1, PDL1, adjuvant therapy, meta-analysis

1 INTRODUCTION

As per the theme of ASCO 2021, adjuvant therapy is currently the most popular research direction in oncology. Subgroups of patients with high-risk characteristics of primary tumor and regional lymph node metastasis are at an increased risk of recurrence and a poor prognosis after surgical resection (1, 2). The aim of adjuvant therapy is to eliminate minimal residual disease (MRD) after resection (3, 4). Moreover, it has been found in a variety of solid tumors to improve recurrence-free survival and improve overall survival (5-8). However, in some studies, systemic adjuvant therapy did not provide a significant survival benefit for cancer patients. For example, the STORM trial found that sorafenib in adjuvant therapy for liver cancer patients not only failed to bring survival benefits but also increased the risk of side effects and even death (9). A review by Alessandro et al. revealed that the efficacy of systemic adjuvant therapy for resected biliary tract cancer remains controversial (10). From this perspective, the choice of adjuvant therapy for cancer patients needs to be further explored.

Immune checkpoint inhibitors, such as nivolumab and pembrolizumab, have greatly changed the treatment pattern of several types of advanced and metastatic solid tumors in the past decade, and most importantly, they have achieved significant results (11-13). The results of the ASCO-PACIFIC study in 2021 showed that durvalumab was associated with a higher 5-year recurrence-free survival (RFS) (HR = 0.55; 95% CI 0.45-0.68) and 5-year OS (HR = 0.72; 95% CI, 0.59-0.89) compared to the placebo group in patients after concurrent chemoradiation with unresectable stage III non-small cell lung cancer (NSCLC). All the above evidence indicates that immune checkpoint inhibitors (ICIs) have great potential as an adjuvant therapy strategy for high-risk recurrence tumors. Currently, many large-scale randomized controlled trials (RCTs) (14-18) have focused on the role of ICIs in adjuvant therapy. Some studies have revealed the superiority of ICI as an adjuvant therapy for cancer patients, while others indicated the opposite. Therefore, based on all the clinical study data published thus far, including the latest results of the 2021 ASCO conference, we conducted a systematic review and meta-analysis to provide a higher level of evidence-based medical recommendations on this clinical issue.

2 MATERIALS AND METHODS

2.1 Search Strategy and Study Selection

A systematic literature search was conducted using the following databases: EMBASE, MEDLINE (PubMed), and Web of Science to identify eligible articles published before June 2021. The search terms mainly included adjuvant therapy, PD1 inhibitors, PDL1 inhibitors, immune checkpoints, and cancer. Details of the retrieval strategy are provided in the **Supplementary Material**.

The included studies were selected based on the following criteria (1): study type: randomized controlled trials (RCTs) (2); participants: patients with solid tumors that were histologically confirmed (3); experimental group: PD1/PDL1 inhibitors were

used in adjuvant therapy after surgical resection; control group: placebo or drugs other than PD1/PDL1 inhibitors were used in adjuvant therapy; and (4) outcomes: overall survival (OS), recurrence-free survival (RFS), disease-free survival (DFS), and drug safety. The exclusion criteria were as follows (1): the number of patients <20, non-RCTs (2), insufficient data to estimate, and (3) non-English translation.

2.2 Data Extraction

We extracted the following information from each study: name of first author, year of publication, type of tumor, phase of trials, experimental group and control group, number of patients, hazard ratios (HRs) and confidence intervals (CIs) for outcomes (OS, RFS, and DFS), and the number of patients with adverse events.

2.3 Quality Assessment

Review Manager 5.3 was used to evaluate the quality of the included studies. The evaluation items included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Each item was evaluated and resulted as being either high risk, low risk, or unclear.

2.4 Statistical Analysis

Review Manager 5.3 was used to analyze the data. In this metaanalysis, HRs and their 95% CIs for outcomes (RFS, DFS, and OS) were used to calculate the pooled results. For dichotomous outcomes, the number of events and total patients in the experimental and control groups were extracted and used to calculate the risk ratio (RR). Differences were considered statistically significant at p < 0.05. The I² statistic was used to evaluate the heterogeneity across the included studies. If I² > 50%, it was considered that there was significant heterogeneity across the studies, and the random-effects model was selected. Otherwise, the fixed-effects model was selected. The source of heterogeneity was analyzed using subgroup and sensitivity analyses. Publication bias was assessed using funnel plots.

3 RESULTS

3.1 Study Characteristics

Eligible studies were identified and selected as shown in **Figure 1**. In total, 2,153 articles were initially evaluated, and 1,460 studies were eligible after exclusion of duplicates. The abstracts and titles of these studies were reviewed, and 1,439 studies were excluded. After an abstract review, we identified 29 articles for full manuscript review, and 21 of these articles were excluded for the reasons delineated in **Figure 1**. Finally, eight RCTs involving more than 6,000 patients were included in our study. Of the tumor types, three studies were conducted on melanoma, one study on esophageal cancer or gastroesophageal junction cancer, one study on NSCLC, one study on renal cell carcinoma, and two studies on urothelial carcinoma. The characteristics of each study are summarized in **Table 1**.



3.2 Risk of Bias

All included studies were RCTs; therefore, the overall risk of bias was relatively low. The quality evaluation results of the included studies are shown in **Figures 2A, B**.

3.3 Analysis of Efficacy Outcomes 3.3.1 Recurrence-Free Survival

Overall, eight trials on the RFS of patients receiving ICIs in adjuvant therapy involving 6,347 patients were reviewed. The pooled results revealed that the use of PD1/PDL1 inhibitors in

adjuvant immunotherapy can significantly reduce the risk of recurrence after tumor resection (HR = 0.72; 95% CI 0.67–0.78, p < 0.00001) (**Figure 3A**). The study by Bellmunt et al. was a source of heterogeneity (I² = 31%), in which atezolizumab was the experimental arm. The source of heterogeneity could be that it was the only study in which the experimental group was a PDL1 inhibitor. In the gender subgroup analysis, both men and women could obtain RFS benefits from adjuvant therapy with PD1/PDL1 inhibitors. HR was 0.74 (95% CI 0.67–0.82, p < 0.00001) and 0.72 (95% CI 0.62–0.84, p < 0.0001), respectively

TABLE 1 | Characteristics of the included studies.

Authors Year	Year	Cancer type	RCT	PD1/PDL1	Control group	Case	HR (CI) for PD1/PDL1 inhibitor	
			pnase	Innibitor			RFS	OS
Ascierto et al.	2020	Melanoma	3	Niv 3 mg/kg Q2W	lpi 10 mg/kg Q3W	906	0.71 (95% Cl 0.60–0.86)	0.87 (95% Cl 0.66–1.14)
Bellmunt et al.	2021	Urothelial carcinoma	3	Ate 1,200 mg Q3W	Observation	809	0.89 (95% Cl 0.74–1.08)	0.85 (95% CI 0.66–1.09)
Eggermont et al.	2018	Melanoma	3	Ate 1,200 mg Q3W	Placebo Q3W	1019	0.57 (98.4% Cl 0.43–0.74)	-
Kelly et al.	2021	Esophageal or gastroesophageal junction cancer	3	Niv 240 mg Q2W	Placebo Q2W	794	0.69 (96.4% Cl 0.56–0.86)	-
Zimmer et al.	2020	Melanoma	2	Niv 3 mg/kg Q2W	Placebo Q2W	111	0.56 (97.5% Cl 0.33–0.94)	-
Bajorin et al.	2021	Urothelial carcinoma	3	Niv 240 mg Q2W	Placebo Q2W	709	0.70 (98.31% Cl 0.54–0.89)	-
Wakelee et al.	2021	Non-small cell lung cancer	3	Niv 240 mg Q2W	Best standard care	1005	0.79 (95% Cl 0.64–0.96)	0.99 (95% Cl 0.73–1.33)
Choueiri et al.	2021	Renal cell carcinoma	3	Pem 200 mg Q3W	Placebo Q3W	994	0.68 (95% Cl 0.53–0.87)	0.54 (95% Cl 0.30–0.96)

Ate, atezolizumab; Ipi, ipilimumab; Niv, nivolumab; Pem, pembrolizumab; HR, hazard ratio; PD1, programmed death 1; PDL1, programmed death 1 ligand; RFS, recurrence-free survival; OS, overall survival; Q2W, every 2 weeks; Q3W, every 3 weeks; RCT, randomized controlled trials.

(**Figure 3B**). In the age subgroup analysis, longer RFS could be obtained from the adjuvant treatment of PD1/PDL1 inhibitors for those aged <65 years (HR = 0.71; 95% CI 0.63–0.79, p < 0.00001) or older than 65 years (HR = 0.82; 95% CI 0.71–0.94, p = 0.005) (**Figure 3C**). In the PDL1 status subgroup analysis, the use of PD1/PDL1 inhibitors in adjuvant therapy compared with placebo reduced the risk of disease recurrence in the subgroups with <5% or ≥5% PDL1 status (**Figure 3D**).

3.3.2 Overall Survival

Regarding OS benefits, a total of four trials on the OS of patients receiving ICIs as adjuvant therapy involving 3,714 patients were reviewed. The pooled results showed that there was no statistical difference in OS benefit between the PD1/PDL1 inhibitor arm and the placebo arm in adjuvant therapy (HR = 0.86; 95% CI 0.74–1.00, p = 0.05) (**Figure 4**).

3.4 Analysis of Safety Outcomes

3.4.1 Any Grade Adverse Events

A total of five studies involving 3,603 patients confirmed the safety of PD1/PDL1 inhibitors. The pooled results revealed that the risk of any grade adverse events (AEs) was significantly higher in the adjuvant therapy with PD1/PDL1 inhibitors than in the control group (RR = 1.03; 95% CI 1.02–1.05, p < 0.0001) (**Figure 5**).

3.4.2 Subgroup Analysis of Any Grade Adverse Event

The results of this meta-analysis showed that the incidence of fatigue (RR = 1.22; 95% CI 1.01–1.49, p = 0.04), nausea (RR = 1.47; 95% CI 1.11–1.94, p = 0.007), and pruritus (RR = 1.96; 95% CI 1.57–2.44, p < 0.00001) in patients who received PD1/PDL1 inhibitors in adjuvant therapy was significantly higher than that in the control group. However, there was no significant difference in the incidence of diarrhea (RR = 1.27; 95% CI 0.96–1.68, p = 0.09) (**Figure 6**).

4 PUBLICATION BIAS

Funnel plot analysis neither indicated apparent publication bias affecting the HRs for RFS and OS nor showed apparent publication bias on RRs of any adverse events (**Figure 7**).

5 DISCUSSION

Immune checkpoint inhibitors have been widely used in patients with several types of advanced and metastatic solid tumors and have achieved significant OS benefits (19–21). At present, adjuvant therapy is the theme of the ASCO Conference in 2021 and has become the focus of the current oncology therapy field. Several large clinical studies have focused on the adjuvant therapy of ICIs, but the conclusions have been incongruent (22–24). To the best of our knowledge, this is the first systematic review and meta-analysis on the efficacy and safety of PD1/PDL1 inhibitors in the adjuvant treatment of solid tumors after solid tumor resection.

The pooled results of this meta-analysis showed that PD1/ PDL1 inhibitors were effective as an adjuvant therapy for tumors. This is consistent with the conclusions of previous studies that explored the efficacy of CTLA-4 inhibitors in adjuvant therapy. The phase III EORTC 18071 trial (25, 26) demonstrated that ipilimumab significantly improved 3-year RFS (HR = 0.75; 95% CI 0.64–0.90, p = 0.0013) after complete resection of stage III melanoma compared to placebo. This study led to the approval of ipilimumab for stage III melanoma after resection in 2015 (27) and was the first immune checkpoint inhibitor approved for adjuvant therapy. In the NCT02523313 phase trial, patients with resected stage IV melanoma with no evidence of disease receiving nivolumab plus ipilimumab in adjuvant therapy had significantly longer RFS (HR = 0.23; 97.5% CI 0.12–0.45, p < 0.0001) than those in the placebo group (16).





Our pooled results also revealed that in the subgroup analysis, patients younger than and older than 65 years could benefit from PD1/PDL1 inhibitors. In patients older than 65 years, PD1/PDL1 inhibitors reduced the risk of recurrence by 18%, and a greater benefit was observed in patients younger than 65 years. This is inconsistent with the conclusion of the EORTC-18071 trial, which revealed that there was no significant difference between the ipilimumab and placebo groups in RFS benefits for patients older than 65 years of age (25). In patients with PDL1 status \geq 5%, a 35% reduction in recurrence risk was observed in the PD1/PDL1 inhibitor arm, and comparable results were observed in patients with PDL1 < 5%. This is consistent with the conclusions of two previous clinical trials. In the NCT02362594 trial (28)

confirming the efficacy of pembrolizumab in the adjuvant therapy of stage III melanoma and the phase III NCT02743494 trial (15) exploring the role of nivolumab in adjuvant therapy for esophageal or gastroesophageal junction cancer, RFS benefit was observed in patients receiving pembrolizumab or nivolumab regardless of whether PDL1 expression was >1% or \leq 1%. However, this is inconsistent with the results of the IMvigor010 trial, which revealed that regardless of the expression status of PDL1, atezolizumab did not improve DFS compared with placebo (14). The tumor types involved in our meta-analysis included melanoma, urothelial carcinoma, renal cancer, NSCLC, and esophageal or gastroesophageal junction cancer. There are currently many ongoing clinical trials

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ref al (2021) - 0.311 0.116 1 46% 0.73 0.50,081 mm of al (2020) - 0.208 0.116 1 1.2% 0.74 0.56,0.81 mm of al (2020) - 0.208 0.121 10.2% 0.74 0.56,0.81 mm of al (2021) - 0.208 0.121 10.2% 0.76 0.56,0.81 T.5% 0.74 (0.67, 0.82) T.5% 0.70 0.52, 0.82 T.5% 0.90 0.57, 1.51 Torremotile al (2021) - 0.208 0.202 13%, 0.90 0.55, 1.52 Torremotile al (2021) - 0.208 0.202 13%, 0.92 (0.38, 1.00) Torremotile al (2021) - 0.214 0.226 0.226 T.5% 0.59 (0.48, 1.14) Torremotile al (2020) - 0.388 0.320 0.13%, 0.27 (0.16, 0.69) Torremotile al (2020) - 0.388 0.370 0.126 0.38% Torremotile al (2020) - 0.388 0.370 0.126 0.48% Torremotile al (2020) - 0.238 0.127 1.138 Torremotile al (2020) - 0.238 0.127 1.14% Torremotile al (2020) - 0.238 0.1028 0.14% 0.27 (0.48, 0.89) Torremotile al (2020) - 0.238 0.1028 0.14% 0.27 (0.48, 0.89) Torremotile al (2020) - 0.238 0.1028 0.14% 0.27 (0.48, 0.89) Torremotile al (2020) - 0.238 0.1028 0.14% 0.27 (0.48, 0.89) Torremotile al (2020) - 0.238 0.1028 0.14% 0.27 (0.16, 0.89) Torremotile al (2020) - 0.238 0.1028 0.14% 0.27 (0.16, 0.89) Torremotile al (2020) - 0.238 0.1028 0.14% 0.27 (0.16, 0.89) Torremotile al (2020) - 0.238 0.1727 1.25% 0.47 (0.48, 0.89) Torremotile al (2020) - 0.238 0.127 1.25% 0.47 (0.48, 0.81) Torremotile al (2020) - 0.238 0.127 1.15% Torremotile al (2020) - 0.311 0.105 0.22% 0.27 (0.56, 0.87) Torremotile al (2020) - 0.321 0.122 7.5% 0.47 (0.38, 0.87) Torremotile al (2020) - 0.321 0.122 7.5% 0.57 (0.57, 0.5	Eggermont et al (2018)	-0.6343	0.1836	5.3%	0.53 [0.37, 0.76]	
$\frac{1000}{100} + \frac{1000}{100} + 10$	Kelly et al (2021)	-0.311	0.1105	14.6%	0.73 [0.59, 0.91]	*
$\begin{array}{c} Harved Part of the end o$	Asciento et al (2020) Zimmer et al (2020)	-0.3001	0.1161	13.2%	0.74 [0.59, 0.93]	
$\begin{aligned} & \text{Here at } (220) & -0.288 \text{ for } (221) & 0.278 \text{ for } (258) \text{ for } ($	Bajorin et al (2020)	-0.3929	0.1235	11.7%	0.68 [0.53, 0.86]	-
$\begin{aligned} & \text{TLS} & \text{LTA} \left[0.57, 0.52 \right] \\ & \text{TLS} & \text{LTA} \left[0.57, 0.52 \right] \\ & \text{To overal effect Z - 5.91 (P = 0.0001) \\ & \text{LTA} \left[0.57, 0.52 \right] \\ & \text{To overal effect Z - 5.91 (P = 0.0001) \\ & \text{LTA} \left[0.57, 0.52 \right] \\ & \text{LTA} \left[0.57, 0.57 \right] \\ & \text{LTA} \left[0.55, 0.57 \right] $	Wakelee et al (2021)	-0.2688	0.132	10.2%	0.76 [0.59, 0.99]	
$\begin{aligned} & \text{progenety}_{C} Ch^{2} = 7.3, \ d^{2} = 6 \ P = 0.29, \ P = 10\% \\ & \text{Promote stal}_{C2010} & -0.000 \ 0.2167 & 3.8\% & 0.39 \ 0.85, 152 \\ & \text{momet stal}_{C2010} & -0.382 \ 0.148 & 3.8\% & 0.39 \ 0.85, 152 \\ & \text{momet stal}_{C2010} & -0.382 \ 0.148 & 3.8\% & 0.39 \ 0.85, 152 \\ & \text{momet stal}_{C2010} & -0.382 \ 0.148 & 3.8\% & 0.37 \ 0.16, 0.77 \\ & \text{min stal}_{C2010} & -0.382 \ 0.148 & 3.8\% & 0.37 \ 0.16, 0.77 \\ & \text{min stal}_{C2010} & -0.283 \ 0.148 & 3.8\% & 0.37 \ 0.16, 0.77 \\ & \text{min stal}_{C2010} & -0.283 \ 0.148 & 3.8\% & 0.37 \ 0.16, 0.77 \\ & \text{min stal}_{C2010} & -0.283 \ 0.148 & 3.8\% & 0.37 \ 0.16, 0.77 \\ & \text{min stal}_{C2010} & -0.283 \ 0.148 & 3.8\% & 0.37 \ 0.16, 0.77 \\ & \text{min stal}_{C2010} & -0.283 \ 0.178 & 5.8\% & 0.27 \ 0.065, 0.0105, 7, 1.13 \\ & \text{min stal}_{C2010} & -0.283 \ 0.178 & 5.8\% & 0.27 \ 0.05, 0.0105, 7, 1.13 \\ & \text{momet stal}_{C2010} & -0.283 \ 0.178 & 5.8\% & 0.27 \ 0.16, 0.015 \\ & \text{momet stal}_{C2010} & -0.283 \ 0.178 & 5.8\% & 0.37 \ 0.16, 0.015 \\ & \text{momet stal}_{C2010} & -0.14 \ d^{2} = 10^{-0.07} \ 100.0\% & 0.74 \ (0.58, 0.09) \\ & \text{momet stal}_{C2010} & -0.238 \ 0.1257 \ 1.27 \ 0.58 \ 0.57 \ 0.16, 0.38 \\ & \text{momet stal}_{C2010} & -0.238 \ 0.1257 \ 1.27 \ 0.58 \ 0.77 \ 0.57$	Subtotal (95% CI)			71.5%	0.74 [0.67, 0.82]	•
100 0006 0.217 3.96 0.90 0.55, 150 100 -0.5240 0.278 2.96 0.92, 0.55, 150 101 -0.5240 0.278 2.96 0.92, 0.55, 150 102 -0.5240 0.278 2.96 0.92, 0.55, 150 103 -0.5240 0.278 2.96 0.92, 0.55, 150 104 -0.200 -0.9861 0.370, 0.27, 133 0.37, 0.18, 0.77 104 -0.21, 0.14, 0.45, 0.200, 0.57, 113 0.25, 0.25, 0.25, 0.35, 0.25, 0.35, 114 105 -0.22, 0.174, 6.59, 0.000, 0.57, 113 0.26, 0.27, 133 106 ropenety, Ch ²⁺ e 1.419, dr = 1.07 = 0.35, P = 1%, 0.000, 0.74 (0.86, 0.80) 107 For overall effect 2 = 7.23 (P = 0.0000) 100, 0.5 0.74 (0.85, 0.95) 1199, -655 yeards Normal effect 2 = 7.23 (P = 0.0000) 100 0.10, 0.1 100 1199, -655 yeards Normal effect 2 = 7.23 (P = 0.0000) 100, 0.75, 0.37 (0.47, 0.45, 0.59) 100 0.48, 0.28, 0.59 1199, -655 yeards Normal effect 2 = 2.77 (P = 0.00001) 100, 0.75, 0.48, 0.51, 0.50 100 100 100 1199, -555 yeards Normal effect 2 = 2.73, 0 = 70, 0.0000<	Heterogeneity: Chi2 = 7.31,	df = 6 (P = 0.29); I ² = 1	8%			
$ \frac{27 \text{ emails}}{1000} + \frac{1}{1000} + 1$	lest for overall effect: Z = 5.	.91 (P < 0.00001)				
$\frac{1}{100} = \frac{1}{100} \frac{1}{100} + \frac{1}{100} $.7.2 Female					
errors tai (2015) $-0.4766 0.2422 115 0.02 [2037, 100] error et al (201) -0.2342 0.278 2.55 0.058 [0.35, 100] error et al (2020) -0.382 0.143 8.15 0.07 0.052, 0.39 error et al (2021) -0.221 0.2154 0.38 0.75 [0.49, 1.14] total (95% C) 2.22 0.1746 5.97 0.0000 (0.10) 100.0% 0.74 [0.60, 0.80] 100.0% 0.74 [0.60, 0.80] 100.0% 0.74 [0.60, 0.80] 100.0% 0.74 [0.60, 0.80] 100.0% 0.74 [0.60, 0.80] 101 0.1 1 101 0 10 0 0 0 0 0 0 0 0 0 0 0$	Bellmunt et al (2021)	-0.006	0.2167	3.8%	0.99 [0.65 1.52]	+
ref at (2021) $-0.249 0.278 2.258 0.59 (0.35, 1.00)$ mer et al (2020) $-0.3881 0.2708 1.38 0.37 (0.16, 0.77)$ inter 41 (2021) $-0.228 0.2148 5.98 0.05 (0.57, 1.3)$ all (2021) $-0.22 0.2154 3.88 0.75 (0.48, 1.14)$ regenetic (Ch ⁺⁺ 6.74, df = 6 (P = 0.36); P = 11% bit or overall effect 2 = 1.3 (P = 0.000) 100.0% 0.74 (0.68, 0.80) progenetic Ch ⁺⁺ = 1.41, gf = 13 (P = 0.36); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.14, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.14, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.430; P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.430; P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46, df = 1 (P = 0.71); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 0.46); P = 0% Hazard Ratio Nor Subarous differences: Ch ⁺ = 2.45, df = 1 (P = 0.12); P = 59, 2% Hazard Ratio Hazard Ratio Nor Subarous differences: Ch ⁺ = 2.45, df = 1 (P = 0.12); P = 59, 2% Hazard Ratio Hazard Ratio H	Eggermont et al (2018)	-0.4708	0.2402	3.1%	0.62 [0.39, 1.00]	
effe et al (2020) -0.382 0.1483 8.1% 0.70 (b.52, 0.93) init et al (2020) -0.2812 0.2154 3.8% 0.75 (b.45, 1.14) effect al (2021) -0.221 0.1746 5.0% 0.80 (b.57, 1.13) total (69% C) 2.22 0.1746 5.0% 0.80 (b.57, 1.13) (109% C) 2.25 1.27 (b.62, 0.84] infor overall effect 2.2 4.18 ($P = 0.36$), $P = 118$, for overall effect 2.2 4.18 ($P = 0.36$), $P = 118$, for overall effect 2.2 4.18 ($P = 0.36$), $P = 118$, for overall effect 2.2 4.18 ($P = 0.36$), $P = 100.0\%$, 0.74 (b.68, 0.80) infor overall effect 2.2 4.18 ($P = 0.36$), $P = 100.0\%$, 0.74 (b.68, 0.80) infor overall effect 2.2 1.29 ($P = 0.0001$) thor subarroup ion/Hazard Ratio the of Subgroup ion/Hazard Ratio SE Weight V. (Fixed, 95% C) V. (Fix	<elly (2021)<="" al="" et="" td=""><td>-0.5249</td><td>0.2678</td><td>2.5%</td><td>0.59 [0.35, 1.00]</td><td></td></elly>	-0.5249	0.2678	2.5%	0.59 [0.35, 1.00]	
mer et al (2020) -0.3881 0.3708 1.3% 0.37 0.15, 0.77 int et al (2021) -0.32 0.174 5.5% 0.80 (0.57, 1.13) see et al (2021) -0.22 0.174 5.5% 0.80 (0.57, 1.13) arcogenetic, Ch ^m = 5.74, df = 6 (P = 0.35), P = 11% torgenetic, Ch ^m = 5.74, df = 6 (P = 0.35), P = 11% torgenetic, Ch ^m = 5.74, df = 6 (P = 0.35), P = 15% torgenetic, Ch ^m = 1.419, df = 12 (P = 0.36), P = 0%, torgenetic, Ch ^m = 1.419, df = 12 (P = 0.36), P = 0%, torgenetic, Ch ^m = 1.419, df = 12 (P = 0.36), P = 0%, torgenetic, Ch ^m = 0.14, df = 1 (P = 0.71), P = 0%. Hazard Ratio tor subaroup differences: Ch ^m = 0.14, df = 1 (P = 0.71), P = 0%. Hazard Ratio tor subaroup differences: Ch ^m = 0.14, df = 1 (P = 0.71), P = 0%. Hazard Ratio tor subaroup differences: Ch ^m = 0.14, df = 1 (P = 0.71), P = 0%. Hazard Ratio tor subaroup differences: Ch ^m = 0.14, df = 1 (P = 0.71), P = 0%. Hazard Ratio tor subaroup differences: Ch ^m = 0.14, df = 1 (P = 0.71), P = 0%. Hazard Ratio tor subaroup differences: Ch ^m = 0.14, df = 1 (P = 0.71), P = 0%. Hazard Ratio tor subaroup differences: Ch ^m = 0.14, df = 1 (P = 0.71), P = 0%. Hazard Ratio tor subaroup differences: Ch ^m = 0.14, df = 1 (P = 0.12), P = 0.50, 0.75 (0.54, 1.08) torgenetic, Ch ^m = 0.14, df = 1 (P = 0.29), P = 0% At the subaroup differences: Ch ^m = 2.45, df = 1 (P = 0.12), P = 59.2%. Hazard Ratio tor subaroup differences: Ch ^m = 2.45, df = 1 (P = 0.12), P = 59.2%. Hazard Ratio tor subaroup differences: Ch ^m = 2.45, df = 1 (P = 0.12), P = 59.2%. Hazard Ratio tor subaroup differences: Ch ^m = 2.45, df = 1 (P = 0.29), P = 15%, torgenetic, Ch ^m = 1.411, df = 12 (P = 0.29), P = 15%, torgenetic, Ch ^m = 1.411, df = 12 (P = 0.29), P = 15%, torgenetic, Ch ^m = 2.45, df = 1 (P = 0.29), P = 0.8%. Hazard Ratio tor orsubaroup differences: Ch ^m = 2.45, df = 1 (P = 0.29), P = 0.8%. Hazard Ratio tor orsubaroup differences: Ch ^m = 2.45, df = 1 (P = 0.20), P = 0.8%. Hazard Ratio torgenetic, Ch ^m = 1.14, df = 3 (P = 0.27), P = 0.8%. Hazard Ratio Hazard Ratio Hazard	Ascierto et al (2020)	-0.3632	0.1483	8.1%	0.70 [0.52, 0.93]	
$\frac{1}{1000} = \frac{1}{1000} \frac{1}{10$	Immer et al (2020)	-0.9881	0.3708	1.3%	0.37 [0.18, 0.77]	
$ \begin{array}{c} \mbox{trans} (55:61) & \mbox{trans} ($	Nakelee et al (2021)	-0.2912	0.1746	5.6%	0.80 [0.57 1 13]	
roopenelty: Ch ² = 5.4, df = 6 (P = 0.35), P = 11% for overall effect Z = 4.18 (P < 0.0001) 100.0%, 0.74 (0.68, 0.80] 101 0.1 0.1 10 000 105 ct) 105	Subtotal (95% CI)	-0.22	2.1740	28.5%	0.72 [0.62, 0.84]	•
$ \begin{array}{c} \text{intro overall effect } \mathcal{L}^{2} = 4.18 \ (\text{P}^{2} < 0.0001) \\ \text{if (95 CI)} \\ if $	leterogeneity: Chi ² = 6.74,	df = 6 (P = 0.35); I ² = 1	1%			
I(955 C) = 10, 0.05, 0.74 (0.68, 0.80) = 0.0001 = 0.0001 = 0.74 (0.68, 0.80) = 0.01 = 0.14, df = 1 (P = 0.71), P = 0.5 = 0.71 = 0.71, P = 0.5 = 0.71 = 0.71, P = 0.5 = 0.71 = 0.71, P = 0.5 = 0.71 =	est for overall effect: Z = 4.	.18 (P < 0.0001)				
roopeneity: Ch ² = 14 19, df = 13 ($P = 0.36$); $P = 9\%$ for oreal effect 2 = 27.32 ($P = 0.0001$) For subaroup differences: Ch ² = 0.14, df = 1 ($P = 0.71$), $P = 0\%$. Hazard Ratio Hazard Ra	otal (95% CI)			100.0%	0.74 [0.68, 0.80]	•
Construction of the second o	leterogeneity: Chi ² = 14.19	9, df = 13 (P = 0.36); l ²	= 8%			0.01 0.1 1 10 100
Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio Note that the intervention of the interventinterventine interventintervention of the intervention of the int	est for overall effect: Z = 7.	.23 (P < 0.00001)				PD1/PDL1 inhibitor better Placebo better
$ a_{10}^{\text{table}}, x_{10}^{\text{table}} = 0.1905 0.155 8.2\% 0.83 [0.61, 1.12] \\ = montet al (2021) -0.4238 0.175 6.7\% 0.57 [0.41, 0.80] \\ = ret al (2021) -0.4238 0.172 12.1\% 0.65 [0.51, 0.84] \\ = ret al (2021) -0.2328 0.1736 1.0\% 0.78 [0.61, 1.03] \\ = ret al (2021) -0.2224 0.1336 1.0\% 0.78 [0.61, 1.03] \\ = ret al (2021) -0.2279 0.1721 6.6\% 0.78 [0.61, 1.03] \\ = ret al (2021) -0.229 0.1721 6.6\% 0.78 [0.61, 1.03] \\ = ret al (2021) -0.279 0.1721 6.6\% 0.78 [0.61, 1.03] \\ = ret al (2021) -0.279 0.1721 6.6\% 0.78 [0.61, 1.03] \\ = ret al (2021) -0.279 0.1721 6.6\% 0.78 [0.63, 1.66] \\ = ret al (2021) -0.2837 0.1696 6.8\% 0.71 [0.61, 0.03] \\ = ret al (2021) -0.2837 0.1696 6.8\% 0.71 [0.51, 1.00] \\ = ret al (2020) -0.3480 0.491 1.2\% 0.78 [0.55, 1.74] \\ = ret al (2020) -0.3480 0.491 1.2\% 0.78 [0.55, 1.74] \\ = ret al (2020) -0.2439 0.1696 6.8\% 0.76 [0.54, 1.05] \\ = ret al (2021) -0.2837 0.1696 6.8\% 0.76 [0.54, 1.05] \\ = ret al (2021) -0.2837 0.1696 6.8\% 0.76 [0.54, 1.05] \\ = ret al (2020) -0.3480 0.491 1.2\% 0.78 [0.55, 1.74] \\ = ret al (2020) -0.3480 0.491 1.2\% 0.78 [0.55, 1.74] \\ = ret al (2020) -0.2439 0.1696 6.8\% 0.76 [0.54, 1.05] \\ = ret al (2021) -0.2837 0.1696 6.8\% 0.76 [0.54, 1.05] \\ = ret al (2020) -0.311 0.1105 62.6\% 0.73 [0.59, 0.91] \\ = ret al (2020) -0.5921 0.3122 7.8\% 0.55 [0.30, 1.02] \\ = ret al (2020) -0.5921 0.3122 7.8\% 0.55 [0.30, 1.02] \\ = ret al (2020) -0.5921 0.3122 7.8\% 0.55 [0.30, 1.02] \\ = ret al (2020) -0.5921 0.3122 7.8\% 0.55 [0.30, 1.02] \\ = ret al (2020) -0.5921 0.3122 7.8\% 0.55 [0.30, 1.02] \\ = ret al (2020) -0.5921 0.3122 7.8\% 0.55 [0.30, 1.02] \\ = ret al (2020) -0.5921 0.3122 7.8\% 0.55 [0.37, 1.03] \\ = ret al (2020) -0.568 0.3242 6.5\% 0.57 [0.28, 1.11] \\ = ret al (2020) -0.568 0.3424 6.5\% 0.57 [0.28, 0.87] \\ = ret al (2020) -0.5686 0.3424 6.5\% 0.5$						
$\frac{1}{100} \text{ mer statuch} = \frac{1}{100} + $	tudy or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% Cl	Hazard Ratio IV, Fixed, 95% Cl
ref at (2021) - 0.233 0.1273 12.1% 0.65 (0.51, 0.84) mer et at (2020) - 0.330 0.1072 12.6 (% 0.72 [0.56, 0.83] mer et at (2021) - 0.2324 0.1336 11.0% 0.72 [0.61, 1.03] et at (2021) - 0.2324 0.1336 11.0% 0.72 [0.61, 1.03] int et at (2021) - 0.279 0.172 1 6.6% 0.75 [0.54, 1.06] tror overall effect Z = 6.27 (P < 0.0001) 2 age, 2-65 years munut et at (2021) - 0.0095 0.1251 12.5% 1.01 [0.79, 1.29] erront et at (2021) - 0.2340 0.1723 6.6% 0.80 [0.57, 1.12] erront et at (2021) - 0.2340 0.1723 6.6% 0.80 [0.57, 1.12] erront et at (2020) - 0.367 0.1718 6.6% 0.71 [0.51, 100] error et at (2020) - 0.3467 0.1718 6.6% 0.71 [0.51, 100] error et at (2020) - 0.3467 0.1718 6.6% 0.71 [0.51, 100] error et at (2020) - 0.2480 0.0491 1.2% 0.78 (0.54, 1.05] total (95% CI) - 0.2837 0.1696 6.6% 0.75 [0.54, 1.05] total (95% CI) - 0.2837 0.1696 6.6% 0.75 [0.54, 1.05] it (95% CI) - 0.0091 1.2% 0.74 (0.68, 0.81] 0.01 0.1 10 - 10 PD1/PDL1 inhibitor better Placebo better Placebo better Placebo better Placebo better 100 PD1/PDL1 inhibitor better Placebo better Placebo better P	Study or Subgroup 1.8.1 age, <65 years	log[Hazard Ratio]	SE	Weight	Hazard Ratio	Hazard Ratio IV. Fixed, 95% CI
ethe et al (2020) -0.3360 0.1092 16.4% 0.72 (0.58, 0.89] ethe et al (2021) -0.729 0.772 2.5% 0.48 (0.28, 0.83] ethe et al (2021) -0.279 0.1721 6.5% 0.76 (0.54, 1.03] int et al (2021) -0.279 0.1721 6.5% 0.76 (0.54, 1.03] int et al (2021) -0.279 0.1721 6.5% 0.76 (0.54, 1.05] int et al (2021) -0.279 0.1721 6.5% 0.76 (0.54, 1.05] ethe et al (2021) 0.0095 0.1251 12.5% 1.01 (0.79, 1.29] ethe et al (2021) -0.283 0.1261 12.5% 0.55 (0.32, 0.3] ethe et al (2020) -0.367 0.1718 6.5% 0.71 (0.54, 1.05] ethe et al (2020) -0.249 0.4091 12.% 0.78 (0.55, 1.10] ethe et al (2021) -0.283 7.0.196 6.8% 0.71 (0.54, 1.05] ethe et al (2021) -0.283 7.0.196 6.8% 0.76 (0.54, 1.05] ethe et al (2021) -0.283 7.0.196 6.8% 0.76 (0.54, 1.05] into overall effect Z = 2.78 (P = 0.005) at (95% CI) 100.0% 0.74 (0.68, 0.81] into overall effect Z = 6.80 (P = 0.0001) FO I/PDL1 simbibitor better Placebo better thor overall effect Z = 6.80 (P = 0.0001) FO I/PDL1 inhibitor better Placebo better thor overall effect Z = 6.80 (P = 0.0001) FO I/PDL1 inhibitor better Placebo better thor overall effect Z = 6.80 (P = 0.0001) PD I/PDL1 inhibitor better Placebo better thor overall effect Z = 0.80 (P = 0.0001) PD I/PDL1 inhibitor better Placebo better thor overall effect Z = 2.39 (P = 0.0001) PD I/PDL1 inhibitor better Placebo better PD I/PDL1 status, $\geq 5\%$ thor overall effect Z = 3.29 (P = 0.001) 2 PDL1 status, $\geq 5\%$ thor overall effect Z = 3.29 (P = 0.001) 2 PDL1 status, $\geq 5\%$ thor overall effect Z = 3.29 (P = 0.001) 2 PDL1 status, $\geq 5\%$ thor overall effect Z = 3.29 (P = 0.007) 2 PDL1 status, $\geq 5\%$ thor overall effect Z = 3.27 (P = 0.007) at (95% CI) 1 00.0% 0.69 [0.58, 0.82] 0 0 1 0 1 0 1 0 1 0 0 1 0 0 0 0 0 0 0 0	Study or Subgroup I.8.1 age, <65 years Bellmunt et al (2021) Eccermont et al (2018)	log[Hazard Ratio] -0.1905 -0.5574	0.155 0.1705	Weight 8.2% 6.7%	Hazard Ratio IV, Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80]	Hazard Ratio IV. Fixed, 95% Cl
mer et al (2020) $-0.729 \ 0.2772 \ 2.6\% \ 0.48 \ 0.28 \ 0.38 \ 0.57 \ 0.54 \ 0.03 \ 0.79 \ 0.61, 1.03 \ 0.79 \ 0.61, 1.03 \ 0.79 \ 0.61, 1.03 \ 0.79 \ 0.61, 1.03 \ 0.79 \ 0.61, 1.03 \ 0.79 \ 0.61, 1.03 \ 0.79 \ 0.61, 1.03 \ 0.79 \ 0.61, 1.03 \ 0.79 \ 0.61, 1.04 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.65\% \ 0.77 \ 0.5\% \$	Study or Subgroup I.8.1 age, <65 years Sellmunt et al (2021) Eggermont et al (2018) (elly et al (2021)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238	0.155 0.1705 0.1273	Weight 8.2% 6.7% 12.1%	Hazard Ratio IV, Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84]	Hazard Ratio
elle et al (2021) $-0.279 cdots 0.72 cdots 0.76 cdots 1.03 total (95% C) -0.279 cdots 0.77 cdots 0.65, 0.67 cdots 0.679 cdots$	tudy or Subgroup .8.1 age, <65 years tellmunt et al (2021) :ggermont et al (2018) (elly et al (2021) scierto et al (2020)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306	0.155 0.1705 0.1273 0.1092	Weight 8.2% 6.7% 12.1% 16.4%	Hazard Ratio IV, Fixed, 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.65 (0.51, 0.84) 0.72 (0.58, 0.89)	Hazard Ratio
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	tudy or Subgroup 8.1 age, <65 years elimunt et al (2021) ggermont et al (2018) eliy et al (2021) scierto et al (2020) immer et al (2020)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296	SE 0.155 0.1705 0.1273 0.1092 0.2772	Weight 8.2% 6.7% 12.1% 16.4% 2.6%	Hazard Ratio IV, Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.89] 0.48 [0.28, 0.83]	Hazard Ratio
$ \begin{array}{c} \mbox{rogenehy} ChP = 5.73, df = 6 (P = 0.45); P = 0\% \\ \mbox{tfor overall effect $Z = 6.27 (P < 0.0001) \\ \label{eq:action} \end{tabular} \end{tabular} \\ \label{eq:action} \end{tabular} \\ \label{eq:action} \end{tabular} \\ \label{eq:action} \end{tabular} \end{tabular} \end{tabular} \\ \label{eq:action} \end{tabular} \end{tabular} \\ \label{eq:action} \end{tabular} \end{tabular} \end{tabular} \end{tabular} \\ \label{eq:action} \end{tabular} tabu$	Study or Subgroup 1.8.1 age, <65 years 3elimunt et al (2021) 5ggermont et al (2018) (2020) Seciento et al (2020) Vakelee et al (2021) Vakelee et al (2021) 3elorin et al (2021)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.2324	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 11.0% 6.6%	Hazard Ratio IV, Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.89] 0.48 [0.28, 0.83] 0.79 [0.61, 1.03] 0.76 [0.64, 1.06]	Hazard Ratio
2 age, ≥65 years wrunt et al (2021) 0.0095 0.1251 12.5% 1.01 [0.79, 1.29] errmont et al (2021) 0.0224 0.1723 6.8% 0.05 [0.32, 0.31 err et al (2020) 0.03267 0.1718 0.68% 0.71 [0.51, 1.00] err et al (2020) 0.0243 0.1718 0.68% 0.71 [0.51, 1.00] err et al (2021) 0.2437 0.1718 0.68% 0.71 [0.51, 1.05] add (95% CI) 0.2437 0.1718 0.68% 0.75 [0.54, 1.05] tor overall effect Z = 2.78 (P = 0.005) it (95% CI) 100.0% 0.74 [0.68, 0.81] orgeneity. ChP = 14.11, df = 12 (P = 0.29), P = 15% tor overall effect Z = 6.68 (P = 0.30001) Hogeneity. ChP = 14.11, df = 12 (P = 0.29), P = 15% tor overall effect Z = 6.68 (P = 0.00001) Hazard Ratio Hazard Ratio Haza	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) ggermont et al (2020) (scierto et al (2020) Timmer et al (2020) Vakelee et al (2021) Jajorin et al (2021) Subtotal (95% CI)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279	SE 0.155 0.1273 0.1092 0.2772 0.1336 0.1721	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 11.0% 6.6% 63.6%	Hazard Ratio IV, Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.89] 0.48 [0.28, 0.83] 0.79 [0.61, 1.03] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79]	Hazard Ratio
$ \begin{array}{c} \text{carge}, \neq \text{obs} \text{years} \\ \text{remont et al} (201) & 0.0095 & 0.1251 & 12.5\% & 1.01 [0.79, 1.29] \\ \text{ermont et al} (2021) & -0.0095 & 0.1251 & 12.5\% & 1.01 [0.79, 1.29] \\ \text{ermont et al} (2021) & -0.2244 & 0.1718 & 6.6\% & 0.081 [0.57, 1.12] \\ \text{et o et al} (2020) & -0.3267 & 0.1718 & 6.6\% & 0.071 [0.51, 1.00] \\ \text{ere et al} (2020) & -0.2480 & 0.0491 & 1.2\% & 0.78 [0.55, 1.74] \\ \text{et eve et al} (2021) & -0.2837 & 0.1696 & 6.8\% & 0.75 [0.54, 1.05] \\ \text{ot al} (95\% CI) & 0.0091 & 1.2\% & 0.76 [0.54, 1.05] \\ \text{into overall effect } Z = 2.78 (P = 0.005) \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.58, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.68, 0.81] \\ \text{it} (95\% CI) & 100.0\% & 0.74 [0.58, 0.71] \\ \text{it} (95\% CI) & 100.0\% & 0.75 [0.30, 1.02] \\ \text{regeneiby} Ch^2 = 0.72, df = 1 (P = 0.40); F = 0\% \\ \text{it} (95\% CI) & 100.0\% & 0.67 [0.47, 0.96] \\ \text{regeneiby} Ch^2 = 0.72, df = 1 (P = 0.40); F = 0\% \\ \text{it} (2020) & -0.3979 & 0.1822 & 23.0\% & 0.67 [0.47, 0.96] \\ \text{regeneiby} Ch^2 = 0.14 \text{ status}, ₹5\% \\ \text{it} (10 \text{ overall effect Z = 2.71 (P = 0.007) \\ \text{at} (95\% CI) & 0.100.0\% & 0.69 [0.58, 0.82] \\ \text{regeneiby} Ch^2 = 1.14, df = 3 (P = 0.77); F = 0\% \\ \text{it} (95\% CI) & 0.100.0\% & 0.69 [0.58, 0.82] \\ \text{regeneiby} Ch^2 = 1.14, df = 3 (P = 0.77); F = 0\% \\ \text{regeneiby} Ch^2 = 0.017 \\ \text{regeneiby} Ch^2 = 0.017 \\ \text{regeneiby} Ch^2 = 0.017 \\ regenei$	Study or Subgroup 1.8.1 age, <65 years Sellmunt et al (2021) ggermont et al (2018) (elly et al (2020) tixciento et al (2020) Wakelee et al (2021) silorito et al (2021) subtotal (95-6) tiototal (95-6) reaft on weard legistre - 5 - 7 - 3.	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.2324 -0.279 (df = 6 (P = 0.45)) P = 0 27 (P ≤ 0.0001)	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 11.0% 6.6% 63.6%	Hazard Ratio IV, Fixed, 95% C1 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.89] 0.48 [0.28, 0.83] 0.79 [0.61, 1.03] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79]	Hazard Ratio
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	itudy or Subaroup .8.1 age, 465 years belimunt et al (2021) gegrennot et al (2018) (elly et al (2020) timmer et al (2020) timmer et al (2020) timotet al (2021) takete et al (2021) taketot al (5%; Cl) Heterogeneik; Chi ² = 5.73, es tor overail effect Z= 6.	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 df = 6 (P = 0.45); IP = 0 .27 (P < 0.00001)	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 11.0% 6.6% 63.6%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.89] 0.79 [0.61, 1.03] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.53, 0.79]	Hazard Ratio
$\frac{1}{100} = \frac{1}{100} = \frac{1}$	itudy or Subgroup .8.1 age, <65 years belimunt et al (2021) iggermont et al (2018) isgermont et al (2020) immer et al (2020) immer et al (2020) immer et al (2020) isgoint et al (2021) ubtotal (95% CI) letterogeneity. Chi ² = 5.73, est for overall effect Z = 6. .8.2 age, ≥65 years Union et al (2021)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.2324 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 .27 (P < 0.00001)	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 9%	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 11.0% 6.6% 63.6%	Hazard Ratio IV. Fixed, 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.65 (0.51, 0.84) 0.72 (0.58, 0.89) 0.48 (0.28, 0.83) 0.79 (0.61, 1.03) 0.76 (0.54, 1.06) 0.71 (0.63, 0.79) 1.01 (0.70, 1.02)	Hazard Ratio
eto et al (2020) -0.3367 0.1716 6.6% 0.71 (0.51, 1.00) mer et al (2020) -0.248 0.4091 1.2% 0.78 (0.35, 1.74) etel et al (2021) -0.2637 0.196 6.8% 0.75 (0.54, 1.05) total (95% CI) 36.4% 0.82 (0.74, 0.94) if or overall effect $Z = 2.78 (P = 0.31); P = 15\%$ for overall effect $Z = 2.78 (P = 0.29); P = 15\%$ for overall effect $Z = 5.68 (P < 0.00001)$ for overall effect $Z = 2.78 (P = 0.001)$ 2 PDL1 status, $\leq 5\%$ left o et al (2020) -0.5921 0.3122 7.8% 0.55 (0.30, 1.02] roto: overall effect $Z = 3.29 (P = 0.001)$ 2 PDL1 status, $\geq 5\%$ left o et al (2020) -0.5668 0.3424 6.5% 0.57 (0.47, 0.96] error et al (2020) -0.5668 0.3424 0.54% 0.57 (0.47, 0.96] error et al (2020) -0.5668 0.3424 0.54% 0.57 (0.47, 0.96] error et al (2020) -0.5668 0.3424 0.54% 0.57 (0.47, 0.96] error et al (2020) -0.5668 0.3424 0.55 (0.47, 0.96] error et al (2020) -0.5668 0.3424 0.56 (0.47, 0.96] error et al (2020) -0.5668 0.3424 0.56 (0.47, 0.96] error et al (2020) -0.5668 0.3424 0.56 (0.547, 0.59] error et al (2020) -0.5668 0.3424 0.56 (0.547, 0	Study of Subgroup 1.8.1 age, <65 years Selimunt et al (2021) isggemont et al (2020) issciento et al (2020) immer et al (2020) Vakelee et al (2021) subtotal (95% CI) Heterogeneity. Chi [#] = 5.73, "est for verail effect Z = 6. 1.8.2 age, ≥65 years Selimunt et al (2021)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 , df = 6 (P = 0.45); P = 0 .27 (P < 0.00001) 0.0095 0.0095	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 0%	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 11.0% 6.6% 63.6%	Hazard Ratio IV. Fixed, 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.65 (0.51, 0.84) 0.72 (0.58, 0.89) 0.48 (0.28, 0.83) 0.79 (0.61, 1.03) 0.76 (0.54, 1.06) 0.77 (0.63, 0.79)	Hazard Ratio
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) gegerron et al (2018) (clip et al (2021) Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2021) Subtotal (95% CI) Heterogeneity- Chi ^m = 5.73, fest for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Sigermont et al (2021)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 .27 (P < 0.00001) 0.0095 -0.6006 -0.2244	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 0% 0.1251 0.2722 0.1723	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.6% 63.6% 12.5% 6.6%	Hazard Ratio <u>IV. Fixed, 95% CI</u> 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.65 (0.51, 0.84) 0.72 (0.58, 0.83) 0.79 (0.61, 1.03) 0.76 (0.54, 1.06) 0.71 (0.63, 0.79) 1.01 (0.79, 1.29) 0.55 (0.32, 0.93)	Hazard Ratio
elee et al (2021) -0.2837 0.166 6.8% 0.75 [0.54, 1.05] 36.4% 0.82 [0.71, 0.94] tropsenetly, ChP = 5.94, df = 5 (P = 0.31); P = 16% tror overall effect Z = 2.78 (P = 0.005) 10 0.0% 0.74 [0.68, 0.81] 0.01 0.1 10 100 PD 1/PDL1 inhibitor better Placebo better Placebo better Hazard Ratio Hazard Ratio Holl (95% CI) H = 114, df = 3 (P = 0.77); F = 0% H = 100, 0, 0.59 [0.58, 0.82] H = 10, 0, 1 1 0, 1 10 100 H = 10, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Eggermont et al (2020) Kelly et al (2020) Cimmer et al (2020) Wakelee et al (2020) Subtotal (95% CI) Jeatorgoneity- Chi ² = 5.73, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Secient o et al (2021) Kelly et al (2021) Kelly et al (2021)	log[Hazard Ratio] -0.1905 -0.5574 -0.3206 -0.7296 -0.2324 -0.2324 -0.279 df = 6 (P = 0.45); IP = 0 .27 (P < 0.00001)	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 0% 0.1251 0.2722 0.1723 0.1723 0.1718	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.6% 63.6% 12.5% 2.6% 6.6%	Hazard Ratio IV. Fixed. 95% CI 0.83 [0.61, 1, 12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.89] 0.79 [0.64, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.52, 0.93] 0.80 [0.57, 1, 120] 0.80 [0.57, 1, 120] 0.81 [0.57, 1, 120] 0.85 [0.57, 120] 0.85 [0.57, 120] 0.85 [0.57, 120] 0.85 [0.57, 120] 0.85 [0	Hazard Ratio
tora trover sub rouge heity. Ch ² = 5.94, df = 5 (P = 0.31); P = 16%, there over all effect Z = 2.78 (P = 0.005) 100.0% 0.74 [0.68, 0.81] 100.0% 0.74 [0.68, 0.81] 100.0% 0.74 [0.68, 0.81] 100.1 0.1 10 PD 1/PDL1 inhibitor better Placebo better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better 100 PD 1/PDL1 inhibitor better 100 PD 1/PDL1 inhibitor better 100 PD 1/PDL1 inhibitor better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better Placebo better Placebo better 100 PD 1/PDL1 inhibitor better Placebo better 100 PD 1/PDL1 inhibitor better Placebo	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Eggermont et al (2020) Masciento et al (2020) Zimmer et al (2020) Wakelee et al (2021) Subtotal (95% C) Heterogeneity: Chi [#] = 5.73, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Kelly et al (2021) Asciento et al (2020) Xestito et al (2020)	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 .27 (P < 0.00001) 0.0095 -0.606 -0.2244 -0.3367 -0.248	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 0% 0.1251 0.2722 0.1723 0.1728 0.1718 0.1718 0.1718	Weight 8.2% 6.7% 12.1% 2.6% 6.6% 63.6% 2.6% 6.6% 6.6% 6.6% 1.2%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.72 [0.58, 0.83] 0.79 [0.54, 1.03] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 1.00] 0.78 [0.55, 1.74]	Hazard Ratio
$\begin{aligned} \text{Hazard Ratio} & \text{Hazard Ratio} \\ \text{Hzard Ratio} & \text{Hzard Ratio} \\ \text{Hzard Ratio} & \text{Hzard Ratio} \\ \text{PD1/PDL1 linhibitor better} & \text{Placebo better} \\ \text{Hzard Ratio} & \text{Hzard Ratio} \\ \text{PD1/PDL1 linhibitor better} & \text{Placebo better} \\ \text{Hzard Ratio} & \text{Hzard Ratio} \\ \text{Hzard Ratio} & \text{Hzard Ratio} \\ \text{Hzard Ratio} & \text{Hzard Ratio} \\ \text{PD1/PDL1 linhibitor better} & \text{Placebo better} \\ \text{Hzard Ratio} & \text{Hzard Ratio} \\ \text{Hzard Ratio}$	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Secient et al (2021) Secient et al (2020) Zimmer et al (2020) Wakelee et al (2021) Subtotal (95% Cl) Heterogeneity Ch ² = 5.73, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Secient et al (2020) Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2020)	logfHazard Ratiol -0.1905 -0.5574 -0.4238 -0.3304 -0.2796 -0.279 .0.271 .027 .057 .0.0095 -0.606 .0.2244 -0.3367 -0.2437	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 0% 0.1251 0.2722 0.1723 0.1718 0.4091 0.1696	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.6% 6.6% 6.6% 6.6% 6.6% 6.6% 6.8%	Hazard Ratio <u>IV. Fixed. 95% CI</u> 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.56, 0.83) 0.79 (0.64, 1.08) 0.76 (0.54, 1.06) 0.76 (0.54, 1.06) 0.76 (0.54, 1.06) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.71 (0.51, 1.10) 0.78 (0.54, 1.05) 0.75 (0.54, 1.05)	Hazard Ratio
$ \begin{array}{c} 100.0\% & 0.74 \ [0.68, 0.81] \\ \hline 0.01 & 0.1 & 10 \\ \hline 0.01 & 0.1 & 0.1 \\ \hline 0.01 & 0.1 &$	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Segement et al (2020) Gelly et al (2020) Makelee et al (2020) Makelee et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 5.73, Test for overall effect $Z = 6$. 1.8.2 age, ≥65 years Bellmunt et al (2021) Suchet al (2021) Subtotal (2021) Subtotal (2021) Subtotal (95% CI) Heterogeneity. Chi ² = 5.42 Makelee et al (2021) Subtotal (95% CI) Heterogeneity. Chi ² = 5.42 Subtotal (95% CI)	log[Hazard Ratio] -0.1905 -0.5574 -0.3206 -0.7296 -0.2324 -0.2324 -0.279 .0.279 .0.279 .0.279 .0.279 .0.279 .0.279 .0.279 .0.279 .0.307 .0.0095 -0.2044 .0.3807 .0.2837 df = 5 (P = 0.19)	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 0% 0.1251 0.2722 0.1723 0.1718 0.4091 0.1696	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.6% 6.6% 6.6% 6.6% 6.6% 6.6% 1.2% 6.8% 36.4%	Hazard Ratio IV. Fixed. 95% CI 0.83 [0.61, 1.12] 0.57 (0.41, 0.80) 0.65 [0.51, 0.84] 0.72 (0.58, 0.83) 0.79 [0.64, 1.03] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.77 [0.54, 1.05] 0.75 [0.54, 1.05] 0.82 [0.71, 0.94]	Hazard Ratio
$ \begin{array}{c} 1(95\% C) & 100.0\% & 0.74 \ [0.68, 0.81] \\ \hline 0.01 & 0.1 & 10 \\ \hline 0.01 & 0.1 & 0.1 \\ \hline 0.01 & 0.1 & 10 \\ \hline 0.01 & 0.1 & 0.1 \\ \hline 0$	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Eggermont et al (2020) Keily et al (2020) Makelee et al (2020) Makelee et al (2020) Makelee et al (2021) Subtotal (95% Cl) Heterogeneity: Chi ⁺ = 5.73, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Subtotal (95% Cl) Makelee et al (2021) Makelee et al (2021) Makelee et al (2020) Makelee et al (2020) Makelee et al (2020) Makelee et al (2021) Makelee e	Iog[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 27 (P < 0.00001) 0.0095 -0.606 -0.2244 -0.367 -0.248 -0.258	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 0% 0.1251 0.2722 0.1723 0.1723 0.1778 0.4091 0.1696 6%	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.6% 11.0% 6.6% 6.6% 6.6% 1.2% 6.6% 36.4%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.83] 0.78 [0.64, 1.06] 0.74 [0.54, 1.06] 0.71 [0.54, 1.06] 0.71 [0.54, 1.06] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.54, 1.05] 0.78 [0.55, 1.74] 0.75 [0.54, 1.05] 0.82 [0.71, 0.94]	Hazard Ratio
trogenently: Chi ⁺ = 1.4.1, df = 12 (P = 0.29); F = 15% fror overall effect Z = 6.6 (P < 0.0001) thor subarroup differences: Chi ⁺ = 2.45. df = 1 (P = 0.12); P = 59.2% Hazard Ratio Hazard Rat	Study or Subgroup 1.8.1 age, <65 years Selimunt et al (2021) (gerronn et al (2021) (elly et al (2021) Siciento et al (2020) Simmer et al (2020) Subtotal (2021) Sajorin et al (2021) Sajorin et al (2021) Signimet et al (2021) Signiment et al (2021) Signermont et al (2021) Signer et al (2020) Simmer et al (2020) Signer et al (2020) S	logIHazard Ratiol -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 .0.2324 .0.273 .0.27 (P < 0.00001) 0.0095 -0.606 -0.2244 -0.3267 -0.248 -0.248 -0.249 -0.259 -0.050 -0.05	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1721 1% 0.1251 0.2722 0.1723 0.1718 0.4091 0.1696 6%	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.6% 63.6% 12.5% 6.6% 6.6% 3.6% 3.6.4%	Hazard Ratio <u>IV. Fixed. 95% CI</u> 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.56, 0.83) 0.79 (0.64, 1.06) 0.76 (0.54, 1.06) 0.76 (0.54, 1.06) 0.76 (0.54, 1.06) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.71 (0.51, 1.00) 0.78 (0.54, 1.05) 0.75 (0.54, 1.05) 0.75 (0.54, 1.05) 0.82 (0.71, 0.94]	Hazard Ratio
PD I/PDL1 inhibitor better PI I/PDL1 inhibitor better <td>itudy or Subgroup .8.1 age, <65 years Jellmunt et al (2021) gegernont et al (2018) (ally et al (2020) Simmer et al (2020) Simmer et al (2020) Simmer et al (2021) Subtotal (95% CI) Jellmunt et al (2021) Sigermont et al (2021) Sigermon</td> <td>log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 df = 6 (P = 0.45); IP = 0 .27 (P < 0.00001) 0.0095 -0.606 -0.2244 -0.3367 -0.2434 -0.367 -0.2437 df = 5 (P = 0.31); IP = 1 .78 (P = 0.005)</td> <td>SE 0.155 0.1705 0.1705 0.1727 0.1702 0.2772 0.0336 0.1721 0.336 0.1721 0.1326 0.1723 0.1718 0.4091 0.1696 6%</td> <td>Weight 8.2% 6.7% 12.1% 16.4% 6.6% 6.3.6% 6.3.6% 8.6% 6.6% 6.8% 36.4%</td> <td>Hazard Ratio IV. Fixed. 95% CI 0.83 [0.61, 1, 12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.89] 0.79 [0.64, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 1.20] 0.75 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81]</td> <td>Hazard Ratio</td>	itudy or Subgroup .8.1 age, <65 years Jellmunt et al (2021) gegernont et al (2018) (ally et al (2020) Simmer et al (2020) Simmer et al (2020) Simmer et al (2021) Subtotal (95% CI) Jellmunt et al (2021) Sigermont et al (2021) Sigermon	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 df = 6 (P = 0.45); IP = 0 .27 (P < 0.00001) 0.0095 -0.606 -0.2244 -0.3367 -0.2434 -0.367 -0.2437 df = 5 (P = 0.31); IP = 1 .78 (P = 0.005)	SE 0.155 0.1705 0.1705 0.1727 0.1702 0.2772 0.0336 0.1721 0.336 0.1721 0.1326 0.1723 0.1718 0.4091 0.1696 6%	Weight 8.2% 6.7% 12.1% 16.4% 6.6% 6.3.6% 6.3.6% 8.6% 6.6% 6.8% 36.4%	Hazard Ratio IV. Fixed. 95% CI 0.83 [0.61, 1, 12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.89] 0.79 [0.64, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 1.20] 0.75 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81]	Hazard Ratio
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Hazard Ratio Hazard Ratio Hazard Ratio Hazard Ratio dv or Subproup log[Hazard Ratio] SE Weight IV. Fixed, 95% CI IV. Fixed, 95% CI IPDL1 status, <5%	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Eggermont et al (2021) Asciento et al (2020) Zimmer et al (2020) Zimmer et al (2021) Subtotal (95% CI) Heterogeneity Chi [™] = 5.73, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Subtotal (2021) Asciento et al (2021) Subtotal (95% CI) Heterogeneity: Chi [™] = 5.94, Test for overall effect Z = 2. Total (95% CI) Heterogeneity: Chi [™] = 1.4.11 Test for overall effect Z = 4.	log/Hazard Ratiol -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 .27 (P < 0.00001) 0.0095 -0.606 -0.2244 -0.3367 -0.244 -0.3367 -0.2437 df = 5 (P = 0.31); P = 1 .78 (P = 0.005) 1, df = 12 (P = 0.29); P :	SE 0.155 0.1705 0.1273 0.1092 0.1272 0.1336 0.1721 1% 0.1251 0.2722 0.1723 0.1723 0.1723 0.1721 0.5 0.1251 0.2722 0.1366 0.1725 0.1251 0.2722 0.1366 0.1255 0.	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 63.6% 11.0% 63.6% 12.5% 63.6% 12.5% 63.6% 12.5% 63.6% 12.5% 6.6% 3.6.4%	Hazard Ratio IV. Fixed. 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.56, 0.83) 0.79 (0.54, 1.06) 0.74 (0.63, 0.79) 1.01 (0.79, 1.29) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.77 (0.54, 1.06) 0.78 (0.54, 1.06) 0.77 (0.54, 1.06) 0.78 (0.54, 1.05) 0.82 (0.71, 0.94] 0.74 (0.68, 0.81]	Hazard Ratio IV. Fixed, 95% Cl
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Segermont et al (2020) Kelly et al (2020) Kimmer et al (2020) Makelee et al (2020) Subtotal (95% CI) Bellmunt et al (2021) Subtotal (95% CI) Akkelee et al (2021) Subtotal (2021) Kelly et al (2021) Kelly et al (2021) Subtotal (2021) Subtotal (2021) Subtotal (95% CI) Test for overail effect Z = 6. Total (95% CI) Heterogeneity: Chi [#] = 14.11 Fest for subaroup different	log[Hazard Ratio] -0.1905 -0.5574 -0.3206 -0.7296 -0.2324 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 .0.0095 -0.606 -0.2244 -0.20001) 0.0095 -0.606 -0.2244 -0.3367 -0.2483 -0.2837 df = 5 (P = 0.31); P = 1 .78 (P = 0.030) 1, df = 12 (P = 0.29); P] 188 (P < 0.0001)	SE 0.155 0.1705 0.1773 0.1092 0.2772 0.1336 0.1721 0% 0.1251 0.2722 0.1723 0.1723 0.1723 0.1718 0.4091 0.1696 6% = 15% (P = 0.1	Weight 8.2% 6.7% 12.1% 2.6% 11.0.4% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 1.2% 6.8% 6.8% 1.2% 1.2% 6.8%	Hazard Ratio IV. Fixed. 95% CI 0.83 [0.61, 1.12] 0.57 (0.41, 0.80) 0.65 [0.51, 0.84] 0.72 (0.58, 0.83) 0.79 [0.64, 1.03] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 1.20] 0.78 [0.54, 1.05] 0.82 [0.71, 0.94] 0.75 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2%	Hazard Ratio IV, Fixed, 95% Cl
Instant R400 Instant R400 Instant R400 ty or Subgroup log[Hazard Ratio] SE Weight U, Kixed, 95% CI (V, Kixed, 95% CI t PDL1 status, <5%	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Eggermont et al (2020) Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2020) Subtotal (95% CI) Heterogeneity. Chi [™] = 5.3, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Saciento et al (2020) Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2021) Subtotal (95% CI) Heterogeneity. Chi [™] = 5.94, Test for overall effect Z = 6. Fest for subaroub difference	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 df = 6 (P = 0.45); IP = 0 .27 (P < 0.00001)	SE 0.155 0.1705 0.1773 0.1092 0.2772 0.1336 0.1721 0.2722 0.1723 0.1723 0.1723 0.1718 0.4091 0.1696 6% = 15% (P = 0.1	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 11.0% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 6.8% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.0.0% 1.2%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.83] 0.79 [0.64, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.80 [0.57, 1.12] 0.71 [0.51, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2%	Hazard Ratio IV. Fixed, 95% Cl
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Eggermont et al (2020) Xeily et al (2020) Zimmer et al (2020) Zimmer et al (2021) Bajorin et al (2021) Bajorin et al (2021) Subtotal (95% CI) Heterogeneity. Chi [™] = 5.73, Test for overall effect Z = 6 1.8.2 age, ≫65 years Bellmunt et al (2021) Segermont et al (2021) Segermont et al (2021) Subtotal (95% CI) Makelee et al (2021) Makelee et al (2021) Makelee et al (2021) Makelee et al (2021) Heterogeneity. Chi [™] = 5.94, Test for overall effect Z = 2. Total (95% CI) Heterogeneity. Chi [™] = 14.11 Test for subaroup difference	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3306 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 .27 (P < 0.00001) 0.0095 -0.606 -0.2244 -0.3867 -0.2848 -0.2848 -0.2847 -0.2887 df = 5 (P = 0.31); P = 1 .78 (P = 0.005) 1, df = 12 (P = 0.29); P = 1 .68 (P < 0.00001) res: ChiP = 2.45. df = 1	SE 0.155 0.1705 0.1273 0.1092 0.1721 0.1336 0.1721 0.1251 0.1723 0.1723 0.1718 6% = 15% (P = 0.1.1	Weight 8.2% 6.7% 16.4% 2.6% 63.6% 12.5% 2.6% 6.6% 1.2% 6.6% 1.2% 6.6% 1.2% 10.0% 2.1% 2.6% 1.2% 2.6% 1.2% 1.4% 1.1% 1.2%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.83] 0.79 [0.54, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.71 [0.55, 1.74] 0.75 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2%	Hazard Ratio N. Fixed, 95% Cl
leto et al (2020) -0.311 0.1105 62.6% 0.73 [0.59, 0.91] mer et al (2020) -0.5921 0.3122 7.8% 0.55 [0.30, 1.02] rorogenelly: Chi ² = 0.72, df = 1 (P = 0.40); F = 0% tfor overall effect Z = 3.29 (P = 0.001) POL1 status, $\ge 5\%$ leto et al (2020) -0.5688 0.3424 6.5% 0.57 [0.29, 1.11] 29.5% 0.65 [0.47, 0.99] erogenelly: Chi ² = 0.19, df = 1 (P = 0.66); F = 0% tfor overall effect Z = 2.71 (P = 0.067); F = 0% tfor overall effect Z = 2.71 (P = 0.077); F = 0% 100.0% 0.69 [0.58, 0.82] 100.0% 0.69 [0.58, 0.82]	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Secient of al (2021) Secient of al (2020) Zimmer et al (2020) Wakelee et al (2021) Subtotal (95% CI) Heterogeneity Chi [®] = 5.73, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Secient of al (2021) Secient of al (2021) Subtotal (2021) Subtotal (95% CI) Heterogeneity Chi [®] = 5.94, Test for overall effect Z = 2. Total (95% CI) Heterogeneity Chi [®] = 5.44, Test for overall effect Z = 2. Total (95% CI) Heterogeneity Chi [®] = 5.44, Test for overall effect Z = 2. Total (95% CI) Heterogeneity Chi [®] = 14.11 Test for subaroup difference Study or Subarona Definition (2000) Study or Subarona Definit	log/Hazard Ratiol -0.1905 -0.5574 -0.4238 -0.3284 -0.2796 -0.279 -0.279 .027 .0574 .02739 .02739 .0274 .0366 .02244 .03837 .02837 .02837 .02837 .178 (P = 0.005) 1, df = 12 (P = 0.29); P = 1 .68 (P < 0.00001)	SE 0.155 0.1705 0.1273 0.1092 0.2772 0.1336 0.1251 0.1723 0.1723 0.1723 0.1723 0.1724 0.1251 0.1696 6% = 15% (P = 0.1	Weight 8.2% 6.7% 16.4% 2.6% 6.6% 6.6% 12.5% 2.6% 6.6% 12.5% 3.6.4% 100.0% 100.0% Height	Hazard Ratio IV. Fixed. 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.58, 0.83) 0.79 (0.64, 1.06) 0.71 (0.63, 0.79) 1.01 (0.79, 1.29) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.77 (0.51, 1.20) 0.77 (0.51, 1.20) 0.78 (0.54, 1.06) 0.82 (0.71, 0.94) 0.74 (0.68, 0.81) 2% azard Ratio Fixed. 95% CI	Hazard Ratio
mer et al (2020) -0.5921 0.3122 7.8% 0.55 [0.30, 1.02] total (95% C1) 70.5% 0.71 [0.58, 0.87] rogeneity. Ch ² = 0.72, df = 1 (P = 0.40); $P = 0\%$ tfor overall effect Z = 3.29 (P = 0.001) 2 PDL1 status, ≥5% left o et al (2020) -0.3979 0.1822 23.0% 0.67 [0.47, 0.96] mer et al (2020) -0.5668 0.3242 6.5% 0.67 [0.29, 1.11] total (95% C1) 29.5% 0.65 [0.47, 0.89] rogeneity. Ch ² = 0.19, df = 1 (P = 0.66); $P = 0\%$ tfor overall effect Z = 2.71 (P = 0.007) al (95% C) 100.0% 0.69 [0.58, 0.82] rogeneity. Ch ² = 1.14, df = 3 (P = 0.77); $P = 0\%$	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Gegermont et al (2020) Gegermont et al (2020) Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 5.73, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2021) Subtotal (2021) Zimmer et al (2021) Zimmer et al (2020) Zimmer et al (2021) Zimmer et al (2021) Subtotal (95% CI) Heterogeneity. Chi ² = 14.11 Test for overall effect Z = 6. Test for suboroup differenc Study or Subgroup loo	log[Hazard Ratio] -0.1905 -0.5574 -0.3306 -0.7296 -0.2324 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 .0.0095 -0.606 -0.2244 -0.2091 .0.0095 -0.606 -0.2481 -0.387 .0.387 .0.2837 .df = 5 (P = 0.31); P = 1 .78 (P = 0.030) 1, df = 12 (P = 0.29); P1 .88 (P < 0.0001)	SE 0.155 0.1705 0.1273 0.01092 0.2772 0.1326 0.1326 0.1721 0.1326 0.1721 0.136 0.136 0.1376 0.136 0.1721 0.136 0.136 0.1372 0.1372 0.1376 0.1376 0.1376 0.1376 0.1721 0.136 0.136 0.17210 0.17210 0.	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.6% 6.6% 6.6% 6.6% 6.8% 12.5% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.2% 1.1% 1.2% 1.1% 1.1% 1.2% 1.2% 1.1% 1.1% 1.2% 1.2% 1.1% 1.2% 1	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 (0.41, 0.80) 0.65 [0.51, 0.84] 0.72 (0.58, 0.83) 0.79 [0.64, 1.03] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 1.24] 0.74 [0.68, 0.81] 2% azard Ratio Fixed, 95% CI	Hazard Ratio N, Fixed, 95% Cl ++++++++++++++++++++++++++++++++++++
totat (9% C1) 70.5% 0.71 [0.58, 0.87] errogeneity: Chi ² = 0.72, df = 1 (P = 0.40); P = 0% tior overall effect Z = 3.29 (P = 0.001) 2 PDL1 status, \geq 5% left of at (2020) -0.3979 0.1822 23.0% 0.67 [0.47, 0.96] mer et al (2020) -0.5668 0.3424 6.5% 0.57 [0.29, 1.11] errogeneity: Chi ² = 0.19, df = 1 (P = 0.66); P = 0% tior overall effect Z = 2.71 (P = 0.07) al (95% C1) 100.0% 0.69 [0.58, 0.82] 0.01 0.1 1 1 0 100	Study or Subgroup 1.8.1 age, <65 years	log/Hazard Ratiol -0.1905 -0.5574 -0.4338 -0.306 -0.2324 -0.279 .df = 6 (P = 0.45); P = 0 .27 (P < 0.00001)	SE 0.155 0.1703 0.1723 0.1723 0.1723 0.1723 0.1724 0.1725 0.1726 0.1721 % 0.1251 0.1723 0.1724 0.1724 0.1726 0.1728 0.1704 0.1696 6% = 15% (P = 0.1 SE W 105 6	Weight 8.2% 6.7% 12.1% 16.4% 2.1% 11.0% 6.6% 6.6% 6.6% 6.6% 6.6% 6.6% 7.25% 100.0% 100.0% Height IV Height IV	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.83] 0.79 [0.64, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.71 [0.51, 0.32] 0.73 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 [0.59, 0.91]	Hazard Ratio IV. Fixed, 95% CI Hazard Ratio PD1/PDL1 inhibitor better Hazard Ratio IV. Fixed, 95% CI
progenenty: Chi ⁺ = 0.72, (f = 1 (f = 0.40), (F = 0%) tfor overall effect Z = 3.29 (F = 0.001) 2 PDL1 status, ≥5% ierto et al (2020) -0.5668 0.3979 0.1822 23.0% 0.67 [0.47, 0.96] mer et al (2020) -0.5668 0.3424 6.5% 0.55 [0.47, 0.89] progenently: Chi ⁺ = 0.19, df = 1 (P = 0.66); F = 0% tfor overall effect Z = 2.71 (P = 0.007) al (95% Cl) 10.5% 0.51 100.0% 0.69 [0.58, 0.82]	Study or Subgroup 18.1 age, <65 years	IogIHazard Ratiol -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 df = 6 (P = 0.45); P = 0 .27 (P < 0.00001) 0.0095 -0.606 -0.2244 -0.3367 -0.244 -0.3367 -0.243 (df = 5 (P = 0.31); P = 1 .78 (P = 0.005) 1, df = 12 (P = 0.29); P. .88 (P < 0.00001) tes: Chi ^P = 2.45, df = 1 -0.311 0.11 -0.5921 0.3	SE 0.155 0.1703 0.1273 0.1326 0.1721 1% 0.1251 0.1722 0.1723 0.1718 0.1718 0.1718 0.1718 0.1718 0.1724 0.1725 0.1721 0.1723 0.1718 0.1794 0.1795 6	Weight 8.2% 6.7% 12.1% 16.4% 2.1% 11.0% 6.6% 6.6% 6.6% 6.6% 6.8% 1.2% 100.0% H eight IV 2.2% 0	Hazard Ratio IV. Fixed. 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.58, 0.83) 0.79 (0.64, 1.06) 0.76 (0.54, 1.06) 0.76 (0.54, 1.06) 0.76 (0.54, 1.06) 0.77 (0.51, 0.23, 0.79) 1.01 (0.79, 1.29) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.77 (0.54, 1.05) 0.82 (0.71, 0.94) 0.74 (0.68, 0.81) 2% azard Ratio Fixed. 95% CI 73 (0.59, 0.91) 55 (0.32, 0.29)	Hazard Ratio IV, Fixed, 95% CI
2 PDL 1 status, ≥5% ierto et al (2020) -0.5698 0.3424 6.5% 0.67 [0.47, 0.96] ■ mer et al (2020) -0.5698 0.3424 6.5% 0.57 [0.29, 1.11] total (9% Ct) 29.5% 0.65 [0.47, 0.89] ■ orgeneity: Chi ^P = 0.19, df = 1 (P = 0.66); P = 0% tor overall effect: Z = 2.71 (P = 0.007) al (95% Ct) 100.0% 0.69 [0.58, 0.82] ■ optimized and the state of th	Study or Subgroup 1.8.1 age, <65 years	log[Hazard Ratio] -0.1905 -0.5574 -0.3206 -0.7296 -0.2324 -0.2324 -0.279 .0279 .0306 -0.7296 .02344 .0.2344 .0.279 .0507 .0508 .0.2044 .0.367 .0.244 .0.367 .0.2484 .0.367 .0.2837 df=5 (P = 0.31); F = 1 .78 (P = 0.0001) ces: ChiP = 2.45. df = 1 sell P < 0.00001)	SE 0.155 0.1703 0.1273 0.1272 0.1336 0.1721 0.1721 0.1723 0.1721 0.1721 0.1723 0.1721 0.1251 0.1723 0.1724 0.1725 0.1726 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1721 0.1723 0.1721 0.1725 0.1721 0.1721 0.1723 0.1251 0.1251 0.1251 0.1251 0.1251 0.1251 0.1251 0.1251<	Weight 8,2% 6,7% 12,1% 16,4% 2,1% 11,0% 6,6% 6,6% 6,6% 6,6% 6,6% 1,25% 12,5% 6,6% 6,6% 6,6% 6,6% 6,6% 1,25% 100,0% 2,0% 100,0% 2,0% 0,0% 12,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0% 0,0%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 (0.41, 0.80) 0.65 [0.51, 0.84] 0.72 (0.58, 0.89] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.77 [0.63, 0.79] 1.01 [0.79, 1.29] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 0.03] 0.78 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 [0.59, 0.91] 55 [0.30, 1.02]	Hazard Ratio IV, Fixed, 95% CI
2 PDL1 status, ≥5% lefto et al (2020) -0.3979 0.1822 23.0% 0.67 [0.47, 0.96] mer et al (2020) -0.5668 0.324 6.5% 0.57 [0.29, 1.11] total (95% CI) 29.5% 0.65 [0.47, 0.89] orogeneiby. Ch ² = 0.19, df = 1 (P = 0.66); P = 0% tfor overall effect Z = 2.71 (P = 0.007) al (95% CI) 100.0% 0.69 [0.58, 0.82] 0.01 0.1 1 10 100	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) gegerront et al (2020) Call yet al (2020) Zimmer et al (2020) Zimmer et al (2021) Subtotal (95% CI) Heterogeneity. Chi ^a = 5.73, fest for overall effect Z = 6 1.8.2 age, ≫65 years Bellmunt et al (2021) Sociento et al (2021) Sociento et al (2021) Sociento et al (2020) Zimmer et al (2020) Heterogeneity. Chi ^a = 5.94, fest for overall effect Z = 2. Fotal (95% CI) Heterogeneity. Chi ^a = 5.94, fest for subgroup loo Study or Subgroup loo 1.9.1 PDL1 status, <5% Subtotal (95% CI) Heterogeneity. Chi ^a = 2. Study or Subgroup loo 1.9.1 PDL1 status, <5% Subtotal (95% CI) Heterogeneity. Chi ^a = 0. 2. Study or Subgroup loo 2. Zimmer et al (2020) Zimmer et al (2020) Zimmer et al (2020)	log/Hazard Ratiol -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.7296 -0.279 -0.271 0.3006 -0.2324 -0.279 -0.279 -0.231 -0.270 0.0095 -0.606 -0.2244 -0.3837 -0.248 -0.249 -0.361 -0.311 -0.311 -0.5921 -0.311 -0.249 -0.25921	SE 0.155 0.1703 0.1271 0.1201 0.1271 0.1261 0.1271 0.1261 0.1272 0.1261 0.1271 0.1261 0.1261 0.1272 0.1261 0.1271 0.1896 6% = 15% (P = 0.1 SE W 105 6 122 7 0.0%	Weight 8.2%, 6.3%, 12.1%, 16.4%, 2.6%, 63.6%, 11.0%, 6.3%, 12.5%, 2.6%, 6.3%, 12.5%, 2.6%, 6.8%, 3.6.4%, 100.0%, H eight IV 2.6%, 0.7,8%, 0.0,5%,	Hazard Ratio IV. Fixed. 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.56, 0.83) 0.79 (0.54, 1.06) 0.71 (0.63, 0.79) 1.01 (0.79, 1.29) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.71 (0.51, 1.00) 0.78 (0.54, 1.05) 0.82 (0.71, 0.94] 0.74 (0.68, 0.81) 2% azard Ratio Fixed. 95% CI 73 (0.59, 0.91) 55 (0.30, 1.02) 71 (0.58, 0.87]	Hazard Ratio N. Fixed, 95% Cl Hazard Ratio PD1/PDL1 Inhibitor better Hazard Ratio N. Fixed, 95% Cl Hazard Ratio
lerto et al (2020) -0.3979 0.1822 23.0% 0.67 [0.47, 0.96] mer et al (2020) -0.5668 0.3424 6.5% 0.57 [0.29, 1.11] progenelly: Chi ² = 0.19, df = 1 (P = 0.66); P = 0% tfor overall effect Z = 2.71 (P = 0.007) al (95% Cl) 100.0% 0.69 [0.58, 0.82] 0.01 0.1 1 1 10 100	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Eggermont et al (2021) Kelly et al (2021) Xascient et al (2021) Subtotal (2021) Subtotal (95% CI) Heterogeneity Chi ⁺ = 5.73, Test for overall effect Z = 6. 1.8.2 age, ≥65 years Bellmunt et al (2021) Subtotal (2021) Ascient et al (2021) Subtotal (95% CI) Heterogeneity: Chi ⁺ = 5.47, Test for subarroup Ins.1 PDL 1 status, <5% Ascient et al (2020) Subtotal (95% CI) Heterogeneity: Chi ⁺ = 0.72 Test for overall effect Z = 6. Test for subarroup Ins.1 PDL 1 status, <5% Ascient et al (2020) Subtotal (95% CI) Heterogeneity: Chi ⁺ = 0.72 Test for overall effect Z = 7 Test for ov	Indiffazard Ratio -0.1905 -0.5574 -0.4238 -0.3306 -0.7296 -0.2324 -0.279 -0.279 -0.279 -0.279 -0.2324 -0.244 -0.367 -0.244 -0.3267 -0.243 -0.2837 df = 5 (P = 0.31); P = 1 .78 (P = 0.005) 1, df = 12 (P = 0.29); P: .88 (P < 0.0001) Indifference (P = 0.29); P: .89 (P = 0.001) Indifference (P = 0.40); P = 1 3.29 (P = 0.001)	SE 0.155 0.1703 0.1271 0.1272 0.1272 0.1271 1% 0.1251 0.1723 0.1723 0.1724 0.1723 0.1724 0.1725 0.1251 0.1261 0.1723 0.1723 0.1724 0.1723 0.1723 0.1724 0.1251 0.1261 0.1272 0.1723 0.1261 0.1261 0.1261 0.1261 0.1261 0.1261 0.1261 0.1261 0.1261 0.1261 0.1272 0.1401 0.1596 0.1596 0.1597 0.1597 0.1597 0.1597 0.1597 0.1597 0.1597	Weight 8.2% 6.7% 12.1% 16.4% 2.21% 11.0% 6.3.6% 6.3.6% 12.5% 1.2% 6.6% 3.6.4% 100.0% 2.1° = 59 H W 2.8% 0,0,5% 0,0,5%	Hazard Ratio IV. Fixed. 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.56, 0.82) 0.79 (0.63, 0.79) 1.01 (0.78, 1.29) 0.56 (0.32, 0.93) 0.80 (0.57, 1.12) 0.56 (0.32, 0.93) 0.80 (0.57, 1.12) 0.71 (0.51, 0.35, 1.74) 0.74 (0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 (0.59, 0.91] 74 (0.58, 0.87]	Hazard Ratio IV, Fixed, 95% CI
mer et al (2020) -0.5688 0.3424 6.5% 0.57 [0.29, 1.11] total (9% Ct) 29.5% 0.65 [0.47, 0.89] progeneity: Chi ² = 0.19, df = 1 (P = 0.66); P = 0% tor overall effect Z = 2.71 (P = 0.007) al (95% Ct) 100.0% 0.69 [0.58, 0.82] progeneity: Chi ² = 1.14, df = 3 (P = 0.77); P = 0%	Study or Subgroup 1.8.1 age, <65 years	$\begin{array}{c} \mbox{log[Hazard Ratio]} \\ -0.1905 \\ -0.5574 \\ -0.4238 \\ -0.3006 \\ -0.7296 \\ -0.2324 \\ -0.279 \\ -0.2324 \\ -0.279 \\ -0.2616 \\ -0.244 \\ -0.2837 \\ -0.606 \\ -0.244 \\ -0.367 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.2837 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.248 \\ -0.281 \\ -0.248 \\ -0.281 \\ -0.311 \\ -0.5921 \\ 0.3 \\ 2. df = 1 (P = 0.40); P = 1 \\ -0.291 \\ -$	SE 0.155 0.1703 0.1271 0.1272 0.130 0.1272 0.131 0.1271 0.1251 0.1272 0.1261 0.1721 0.1272 0.1336 0.1271 0.101718 0.4091 0.1696 6% = = 15% (P = 0.1.1) SE W 105 102 7 .0% 7	Weight 8,2% 6,7% 12,1% 16,4% 2,6% 63,6% 63,6% 12,5% 63,6% 64,4% 100,0% 12,5% 9,6% 0,5% 0,5%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 (0.41, 0.80) 0.65 [0.51, 0.84] 0.72 (0.58, 0.83) 0.79 [0.64, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 0.35, 1.74] 0.74 [0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 [0.59, 0.91] 55 [0.30, 1.02] 74 [0.58, 0.87]	Hazard Ratio N. Fixed, 95% Cl 0.01 0.1 10 PD1/PDL1 inhibitor better Placebo better Hazard Ratio N. Fixed, 95% Cl
total (95% Cl) 29.5% 0.65 [0.47, 0.89] progeneiby: Chi [™] = 0.19, df = 1 (P = 0.66); I [™] = 0% tfor overall effect Z = 2.71 (P = 0.007) i (95% Cl) 100.0% 0.69 [0.58, 0.82] progeneiby: Chi [™] = 1.14, df = 3 (P = 0.77); I [™] = 0%	Study or Subgroup 1.8.1 ape, <65 years	$\begin{array}{c} \text{logIHazard Ratiol} \\ & -0.1905 \\ & -0.5574 \\ & -0.4238 \\ & -0.3306 \\ & -0.7296 \\ & -0.2796 \\ & -0.2796 \\ & -0.2796 \\ & -0.2324 \\ & -0.2244 \\ & -0.2244 \\ & -0.2244 \\ & -0.2244 \\ & -0.2244 \\ & -0.2244 \\ & -0.2247 \\ & -0.248 $	SE 0.1555 0.1273 0.01705 0.01273 0.01273 0.01273 0.01271 0.01271 0.01221 0.1723 0.1723 0.1723 0.1723 0.1712 0.101718 0.101716 6% = 15% (P = 0.1 SE W 105 6 122 7 0.0% 822 2	Weight 8.2% 5.7 12.1% 16.4% 12.1% 16.4% 11.0% 6.3.6% 6.3.6% 6.3% 12.5% 6.8% 6.8% 3.6.4% 100.0% H eight IV 2.6% 0.5% 2.6% 0.5% 0.	Hazard Ratio IV. Fixed, 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.56, 0.83) 0.78 (0.54, 1.06) 0.74 (0.63, 0.79) 1.01 (0.79, 1.29) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.77 (0.51, 1.00) 0.78 (0.54, 1.06) 0.74 (0.68, 0.81) 2% azard Ratio Fixed, 95% CI 73 (0.59, 0.91) 55 (0.30, 1.02) 71 (0.58, 0.87] 67 (0.47, 0.96)	Hazard Ratio N. Fixed, 95% Cl
erogeneity: Chi ^P = 0.19, df = 1 (P = 0.66); P = 0% for overall effect Z = 2.71 (P = 0.007) al (95% Cl) 100.0% 0.69 [0.58, 0.82] erogeneity: Chi ^P = 1.14, df = 3 (P = 0.77); P = 0%	Study or Subgroup 1.8.1 age, <65 years	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3244 -0.2796 -0.7296 -0.2797 .0576 .02324 .02796 .02324 .02324 .02397 .016 .0279 .0370 .01796 .00095 .00095 .00095 .00095 .00095 .0244 .02367 .02483 .02444 .0367 .02484 .02397 .05688 .02497 .011 .05921 .0321 .0311 .0329 .03329 .03321 .011 .0329 .03379 .03979 .03979 .03979	SE 0.155 0.0723 0.1273 0.02772 0.13251 0.1251 0.1252 0.1272 0.1272 0.1272 0.1272 0.1251 0.1272 0.1272 0.1272 0.1261 0.1272 0.1066 6% = 15% (P = 0.1 SE W 105 6 122 7 0% 822 2 822 2 824 24	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.6% 6.6% 6.6% 12.5% 12.5% 11.0% 6.3.6% 12.5% 12.5% 2.6% 6.6% 1.2% 12.5% 12.5% 12.5% 2.6% 1.2% 1.5% 1.2% 1.5% 1.2% 1.5% 1.2% 1.2% 1.2% 1.5% 1.2%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1, 12] 0.57 [0.41, 0.80] 0.56 [0.51, 0.84] 0.72 [0.58, 0.83] 0.79 [0.64, 1, 0.6] 0.76 [0.54, 1, 0.6] 0.76 [0.54, 1, 0.6] 0.76 [0.54, 1, 0.6] 0.77 [0.53, 0.79] 1.01 [0.79, 1, 29] 0.55 [0.32, 0.93] 0.80 [0.57, 1, 12] 0.76 [0.54, 1, 0.6] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 [0.59, 0.91] 57 [0.24, 0.96] 57 [0.24, 0.96] 57 [0.24, 0.96] 57 [0.29, 1, 11]	Hazard Ratio IV, Fixed, 95% Cl Hazard Ratio PD I/PDL1 inhibitor better Hazard Ratio IV, Fixed, 95% Cl Hazard Ratio
t for overall effect: Z = 2.71 (P = 0.007) al (95% Cl) 100.0% 0.69 [0.58, 0.82] erogeneity: Chi ² = 1.14, df = 3 (P = 0.77); P = 0%	Study or Subgroup 1.8.1 ape, <65 years	$\begin{array}{c} \text{logIHazard Ratiol} \\ & -0.1905 \\ & -0.5574 \\ & -0.4238 \\ & -0.234 \\ & -0.279 \\ \text{df} = 6 \ (P=0.45); \ P=0 \\ & -0.224 \\ & -0.279 \\ \text{df} = 6 \ (P=0.45); \ P=0 \\ & -0.234 \\ & -0.234 \\ & -0.234 \\ & -0.284 \\ & -0.2$	SE 0.155 0.1703 0.1271 0.02772 0.133 0.123 0.1231 0.1271 0.1272 0.1272 0.1272 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.166 6% = 15% (P = 0.1 SE W 105 105 122 7 822 822 822 822 822 8242 1242	Weight 8,2% 6,7% 12,1% 16,4% 12,1% 11,0% 6,6% 6,3.6% 12,5% 6,3.6% 6,3.6% 12,5% 6,3.6% 6,3.6% 6,8% 36,4% 100.0% 2,1, P = 59 H eight IV 2,6% 0,0.5% 0,0.5% 3.0% 0,0.5%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.83] 0.79 [0.64, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 0.35, 1.74] 0.75 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 [0.59, 0.91] 55 [0.30, 1.02] 74 [0.58, 0.87] 67 [0.47, 0.96] 57 [0.29, 1.11] 67 [0.47, 0.96] 55 [0.47, 0.96]	Hazard Ratio IV. Fixed, 95% Cl Hazard Ratio Hazard Ratio IV. Fixed, 95% Cl Hazard Ratio
at (95% CI) 100.0% 0.69 [0.58, 0.82]	Study or Subgroup 1.8.1 age, <65 years Bellmunt et al (2021) Gegermont et al (2020) Yeally et al (2021) Saciento et al (2020) Zimmer et al (2020) Wakelee et al (2021) Subtotal (95% CI) Heterogeneity. Chi ² = 5.73, Test for overall effect Z = 6. H.8.2 age, ≥65 years Bellmunt et al (2021) Subtotal (95% CI) Heterogeneity. Chi ² = 5.94, Test for subarroup Inter et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 14.11 Test for subarroup Inter et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 0.27 Test for verall effect Z = 6. Test for subarroup Inter et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 0.12 Test for overall effect Z = 6. Study or Subarroup Inter et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 0.12 Test for overall effect Z = 7. Test for subarroup Inter et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 0.12 Test for overall effect Z = 7. Test for subarroup Inter et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 0.12 Test for overall effect Z = 7. Test for overall effect Z = 7. Test for subarroup Inter et al (2020) Subtotal (95% CI) Heterogeneity. Chi ² = 0.12 Test for overall effect Z = 7. Test for overall (95% CI) Heterogeneity. Chi ² = 0.12 Test for overall effect Z = 7. Test for overall	log/Hazard Ratiol -0.1905 -0.5574 -0.4238 -0.3284 -0.2796 -0.2797 .0.2798 -0.2324 .0.2344 -0.2367 .0.2837 .0.311 .0.5668 .3.29 (F = 0.001) .0.3979 .0.3979 .0.3979 .0.3979 .0.5668 .0.3979 .0.5668 .0.39, df=1 (P = 0.66); F =	SE 0.1555 0.1705 0.1705 0.1703 0.1723 0.1721 0.13261 0.172	Weight 8.2%, 6.12,1%, 16.4%, 2.1%, 11.0%, 6.63,6%, 6.6%, 6.6%, 1.2%, 6.6%, 1.2%,	Hazard Ratio IV. Fixed. 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.58, 0.83) 0.79 (0.61, 1.03) 0.76 (0.54, 1.06) 0.71 (0.61, 0.03) 1.01 (0.79, 1.29) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.71 (0.51, 0.05) 0.82 (0.71, 0.94) 0.74 (0.68, 0.81) 2% azard Ratio Fixed, 95% CI 73 (0.59, 0.91) 55 (0.32, 1.02) 71 (0.58, 0.87) 67 (0.47, 0.96) 57 (0.29, 1.11) 55 (0.47, 0.88)	Hazard Ratio IV, Fixed, 95% CI
ar (95% CI) 100.0% 0.69 [0.58, 0.82] ▼ erogeneity: Chi ² = 1.14, df = 3 (P = 0.77); I ² = 0% 0.01 0.1 1 1.0 100	Study or Subgroup 8.8.1 age, <65 years	log[Hazard Ratio] -0.1905 -0.5574 -0.3306 -0.7296 -0.2324 -0.2324 -0.279 .0.3006 -0.7296 -0.2424 -0.2324 .0.279 .01605 .0201 .00095 .0506 .02244 .0.307 .0307 .0.248 .0.2837 .0.2837 .0.45 (P = 0.031); (P = 1 .78 (P = 0.037); P = 1 .78 (P = 0.0001) .68 (P < 0.00001)	SE 0.155 0.1705 0.1705 0.1703 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1271 0.1696 6% = 15% (P = 0.1 SE W 1052 7 0.0% 822 2 0.0% 2.0%	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 63.6% 12.5% 12.5% 63.6% 12.5% 63.6% 12.5% 63.6% 12.5% 63.6% 12.5% 12.5% 12.6% 0.0.5% 0.5% 0.05% 0.95%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 (0.41, 0.80) 0.65 [0.51, 0.84] 0.72 (0.58, 0.83) 0.79 [0.64, 1.03] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 0.35, 1.74] 0.74 [0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 [0.59, 0.91] 55 [0.32, 0.95] 67 [0.47, 0.96] 57 [0.24, 1.05] 55 [0.47, 0.89]	Hazard Ratio N, Fixed, 95% Cl + + + + + + + + + + + + +
D01 01 1 10 100	Study or Subgroup 18.1 age, <65 years	$\begin{array}{c} \mbox{log}[Hazard Ratio] \\ & -0.1905 \\ & -0.5574 \\ & -0.4238 \\ & -0.306 \\ & -0.234 \\ & -0.279 \\ \end{tabular} \\ & -0.279 \\ \end{tabular} \\ & -0.271 \\ & -0.2324 \\ & -0.2324 \\ & -0.2324 \\ & -0.2324 \\ & -0.2324 \\ & -0.2324 \\ & -0.2317 \\ \end{tabular} \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.248 \\ & -0.2837 \\ \end{tabular} \\ & -0.3311 \\ \end{tabular} \\ & -0.311 \\ & 0.5921 \\ \end{tabular} \\ & -0.3979 \\ \end{tabular} \\ & -0.5668 \\ \end{tabular} \\ & -0.3979 \\ \end{tabular} \\ & -0.5668 \\ \end{tabular} \\ &$	SE 0.1555 0.1273 0.1705 0.1273 0.1273 0.1273 0.1271 0.0 0.1251 0.1273 0.1211 % 0.1251 0.1713 0.1724 0.1725 0.1726 0.1718 0.1726 0.1727 0.1728 0.1721 % 0.1221 0.1121 % \$\$25 OW\$ \$\$25 OW\$ \$\$27 OW\$ \$\$22 2 \$\$200	Weight 8.2% 12.1% 16.4% 2.6% 63.6% 12.5% 2.6% 63.6% 12.5% 2.6% 6.8% 6.8% 36.4% 100.0% H 2.6% 0.5% 0.5% 0.5% 0.5% 0.5%	Hazard Ratio IV. Fixed, 95% CI 0.83 [0.61, 1.12] 0.57 [0.41, 0.80] 0.65 [0.51, 0.84] 0.72 [0.58, 0.83] 0.79 [0.64, 1.03] 0.76 [0.54, 1.06] 0.71 [0.63, 0.79] 1.01 [0.79, 1.29] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.71 [0.51, 0.35, 1.74] 0.75 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 [0.59, 0.91] 55 [0.30, 1.02] 74 [0.58, 0.87] 67 [0.47, 0.96] 57 [0.29, 1.11] 65 [0.47, 0.89] 60 [0.50, 0.71] 65 [0.47, 0.89]	Hazard Ratio IV. Fixed, 95% CI Hazard Ratio Hazard Ratio IV. Fixed, 95% CI Hazard Ratio
t for overall effect: 7 = 4 23 (P < 0.0001)	ituty or Subgroup .8.1 age, <65 years	log[Hazard Ratio] -0.1905 -0.5574 -0.4238 -0.3284 -0.2796 -0.279 -0.279 .0.224 -0.2837 -0.243 -0.243 -0.244 -0.3667 -0.2837 .df=5 (P = 0.31); P = 1 .78 (P = 0.005) 1, df=12 (P = 0.29); P. .68 (P < 0.0001)	SE 0.1555 0.01273 0.10273 0.1273 0.1272 0.13261 0.2722 0.1721 0.1251 0.1251 0.1221 0.1261 0.1251 0.1261 0.1272 0.1261 0.1261 0.1261 0.1261 0.1718 0.10196 6% = 15% (P = 0.1 SE WW 105 105 6% 22 7 * 0% 822 0% 102 0% 102 0% 102 0% 102 103 104 105 105 105 105 105	Weight 8.2% 6.7% 6.1% 2.1% 16.4% 2.6% 6.3.6% 6.6% 1.1.0% 6.6% 6.6% 6.6% 7.2% 7.2% 100.0% 1.2% 6.1% 1.2% 6.3.6% 1.2% 6.3.6% 1.2% 100.0% 1.2% 100.0% 1.2% 100.0% 1.2% 100.0% 1.2% 100.0% 1.2% 100.0% 1.1% 100.0% 1.1% 100.0% 1.1% 100.0% 1.1%	Hazard Ratio IV. Fixed. 95% CI 0.83 (0.61, 1.12) 0.57 (0.41, 0.80) 0.56 (0.51, 0.84) 0.72 (0.58, 0.83) 0.79 (0.61, 1.03) 0.76 (0.54, 1.06) 0.71 (0.51, 0.03) 0.80 (0.57, 1.12) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.55 (0.32, 0.93) 0.80 (0.57, 1.12) 0.71 (0.51, 0.03) 0.82 (0.71, 0.94) 0.74 (0.68, 0.81] 2% azard Ratio Fixed, 95% CI 73 (0.59, 0.91) 55 (0.32, 1.02) 71 (0.58, 0.87] 67 (0.47, 0.96) 57 (0.29, 1.11) 55 (0.47, 0.89]	Hazard Ratio IV, Fixed, 95% CI
t for subgroup differences; Chi ² = 0.23, df = 1 (P = 0.63), l ² = 0% PD1/PDL1 inhibitor better Placebo better	tudy or Subgroup 8.1 age, <65 years	log[Hazard Ratio] -0.1905 -0.5574 -0.3306 -0.7296 -0.2324 -0.2324 -0.279 .0.3006 -0.7296 -0.2424 -0.2324 .0.279 .0.307 .0.2124 .0.2397 .0.367 .0.2437 .0.2637 .0.2837 .0.2837 .0.2837 .0.2837 .0.2837 .0.2837 .0.2837 .0.2837 .0.2837 .0.2837 .0.364 .0.2837 .0.2837 .0.364 .0.367 .0.311 .0.11 .0.5921 .0.329 .0.3297 .0.3297 .0.3297 .0.3297 .0.3297 .0.329 .0.71<(P = 0.007)	SE 0.155 0.1705 0.1705 0.1703 0.1271 0.1272 0.1373 0.1272 0.1272 0.1273 0.1272 0.1271 0.1272 0.1272 0.1272 0.1272 0.1261 0.1272 0.1261 0.1261 105 6% 2 0.0%	Weight 8.2% 6.7% 12.1% 16.4% 2.6% 6.3% 12.5% 6.6% 1.2% 6.6% 3.64% 100.0% 12.5% 100.0% 2.1% 6.6% 3.0% 0.05% 0.05% 0.05% 0.05%	Hazard Ratio IV. Fixed. 95% CI 0.83 [0.61, 1.12] 0.57 (0.41, 0.80) 0.65 [0.51, 0.84] 0.72 [0.58, 0.83] 0.79 [0.64, 1.03] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.76 [0.54, 1.06] 0.77 [0.63, 0.79] 1.01 [0.79, 1.29] 0.55 [0.32, 0.93] 0.80 [0.57, 1.12] 0.76 [0.54, 1.05] 0.82 [0.71, 0.94] 0.74 [0.68, 0.81] 2% azard Ratio Fixed. 95% CI 73 [0.59, 0.91] 55 [0.32, 1.05] 67 [0.47, 0.96] 57 [0.24, 1.05] 50 [0.58, 0.82] 0.71 [0.51, 0.82] 1.058 [0.58, 0.82]	Hazard Ratio N, Fixed, 95% Cl + + + + + + + + + + + + +

FIGURE 3 | (A) Forest plots of the fixed-effects meta-analysis for the effects of PD1/PDL1 inhibitors on RFS. (B) Forest plots of the fixed-effects meta-analysis for the effects of PD1/PDL1 inhibitors on RFS in gender. (C) Forest plots of the fixed-effects meta-analysis for the effects of PD1/PDL1 inhibitors on RFS in different age group. (D) Forest plots of the fixed-effects meta-analysis for the effects of PD1/PDL1 inhibitors on RFS in different PDL1 status.



exploring the efficacy of ICIs in adjuvant therapy for various tumor types. For example, the NCT02196961 trial is ongoing to explore the efficacy of ipilimumab or nivolumab in the adjuvant therapy of Merkel cell carcinoma (27), and the efficacy and safety of pembrolizumab are being confirmed for stage III or IV melanoma after resection in the phase III clinical trials SWOG S1404 (3, 27).

In addition, our results showed that PD1/PDL1 inhibitors did not improve OS in adjuvant therapy, which might be explained by the following reasons. In the study by Ascierto et al. (17), both the experimental and control groups were ICIs (nivolumab versus ipilimumab). In addition, effective immunotherapy or targeted therapy was subsequently used, leading to possible inherent crossover. In the study by Bellmunt et al. (14), the OS data were not complete because it was still in follow-up, and the use of ICIs in the late control group may have affected the OS. However, in the 2021 ASCO-Pacific study, durvalumab significantly improved OS in patients with unresectable stage III NSCLC following concurrent chemoradiotherapy. The difference in OS benefit may be due to the difference in efficacy between concurrent chemoradiotherapy and tumor resection.

The results of this meta-analysis revealed an increased risk of any grade AEs, fatigue, nausea, and pruritus in adjuvant therapy with PD1/PDL1 inhibitors relative to placebo, which is consistent with the safety results in advanced and metastatic cancer patients receiving PD1/PDL1 inhibitors (29–32). Therefore, these findings should be noted during the use of PD1/PDL1 inhibitors in the adjuvant therapy of solid tumors.

Tumor cells can escape the immune system by activating the T-cell suppression pathway, which is the immune checkpoint pathway. One of the most important pathways is the PD1 pathway (33-35). PD1 is expressed on the surface of T cells in the tumor microenvironment and binds to two ligands (PDL1 and PDL2), resulting in inactivation of the T cells' tumor-specific immune response, thus allowing the tumor to progress (36-38). PD1/PDL1 inhibitors are antagonists targeting PD1 or PDL1 sites. Therefore, the use of these two drugs will activate the immune response of T cells to tumors (39, 40), thereby inhibiting the growth of tumor cells. MRD is usually present after resection of solid tumors, which is the main cause of tumor recurrence (39, 41). Tumor load is greatly reduced after tumor resection; thus, immune cells are more likely to come into contact with the remaining tumor cells and kill them. PD1/PDL1 inhibitors have the potential to eliminate MRD and thus may reduce the risk of recurrence in patients after tumor resection. In addition, for patients that are in poor physical condition during the perioperative period, clinicians may opt to use an immunotherapy with a lower incidence of adverse events compared to radiotherapy or chemotherapy.

We performed the first meta-analysis of the efficacy and safety of PD1/PDL1 inhibitors in adjuvant therapy. Apart from nivolumab in melanoma, no ICIs have been approved for adjuvant therapy, and the results of our meta-analysis may provide evidence for new clinical applications of ICIs in the future and opens a new avenue for systemic adjuvant therapy. At present, the study content of this topic cannot be applied to

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Eggermont et al (2018)	475	509	453	502	28.2%	1.03 [1.00, 1.07]	•
Kelly et al (2021)	510	532	243	260	20.2%	1.03 [0.99, 1.06]	•
Zimmer et al (2020)	54	56	49	51	3.2%	1.00 [0.93, 1.08]	+
Bajorin et al (2021)	347	351	332	348	20.6%	1.04 [1.01, 1.06]	+
Choueiri et al (2021)	470	496	452	498	27.9%	1.04 [1.01, 1.08]	t
Total (95% CI)		1944		1659	100.0%	1.03 [1.02, 1.05]	
Total events	1856		1529				
Heterogeneity: Chi ² = 1.12,	df = 4 (P = 1	0.89); I ^z	= 0%				
Test for overall effect: Z = 3.	.91 (P < 0.0	001)					PD1/PDL1 inhibitor better Placebo better

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.12.1 Diarrhoea							
Kelly et al (2021)	88	532	39	260	8.4%	1.10 [0.78, 1.56]	
Eggermont et al (2018)	97	509	84	502	13.6%	1.14 [0.87, 1.48]	
Zimmer et al (2020)	9	56	1	51	0.2%	8.20 [1.08, 62.46]	
Bajorin et al (2021)	59	351	38	348	6.1%	1.54 [1.05, 2.25]	
Subtotal (95% CI)		1448		1161	28.2%	1.26 [1.05, 1.51]	•
Fotal events	253		162				
Heterogeneity: Chi² = 5.45, Test for overall effect: Z = 2	df = 3 (P = .46 (P = 0.0	0.14); I² 1)	= 45%				
1.12.2 Fatigue							
<elly (2021)<="" al="" et="" td=""><td>90</td><td>532</td><td>29</td><td>260</td><td>6.2%</td><td>1.52 [1.03, 2.24]</td><td></td></elly>	90	532	29	260	6.2%	1.52 [1.03, 2.24]	
Eggermont et al (2018)	189	509	167	502	27.0%	1.12 [0.94, 1.32]	+
Zimmer et al (2020)	12	56	13	51	2.2%	0.84 [0.42, 1.67]	
Bajorin et al (2021)	61	351	42	348	6.8%	1.44 [1.00, 2.07]	-
Subtotal (95% CI)		1448		1161	42.1%	1.21 [1.05, 1.40]	◆
Total events	352		251				
Heterogeneity: Chi ² = 4.15,	df = 3 (P =	0.25); I ^z	= 28%				
Test for overall effect: Z = 2	.70 (P = 0.0	07)					
1.12.3 Nausea							
Kelly et al (2021)	47	532	13	260	2.8%	1.77 [0.97, 3.21]	
Eggermont et al (2018)	58	509	43	502	6.9%	1.33 [0.91, 1.93]	T •-
Zimmer et al (2020)	5	56	5	51	0.8%	0.91 [0.28, 2.96]	
Bajorin et al (2021)	24	351	13	351	2.1%	1.85 [0.96, 3.57]	
Subtotal (95% CI)		1448		1164	12.7%	1.48 [1.12, 1.96]	\bullet
Fotal events	134		74				
Heterogeneity: Chi² = 1.74, Test for overall effect: Z = 2	df = 3 (P = .79 (P = 0.0	0.63); I² 05)	= 0%				
1.12.5 Pruritus							
<elly (2021)<="" al="" et="" td=""><td>53</td><td>532</td><td>9</td><td>260</td><td>1.9%</td><td>2.88 [1.44, 5.74]</td><td></td></elly>	53	532	9	260	1.9%	2.88 [1.44, 5.74]	
Eggermont et al (2018)	90	509	51	502	8.2%	1.74 [1.26, 2.40]	
Zimmer et al (2020)	6	56	2	51	0.3%	2.73 [0.58, 12.93]	
Bajorin et al (2021)	81	351	40	348	6.4%	2.01 [1.42, 2.84]	
Subtotal (95% CI)		1448		1161	16.9%	1.99 [1.60, 2.49]	
Fotal events	230		102				
Heterogeneity: Chi ² = 1.93,	df= 3 (P =	0.59); I²	= 0%				
Fest for overall effect: Z = 6	.09 (P < 0.0	0001)					
otal (95% CI)		5792		4647	100.0%	1.39 [1.27, 1.53]	•
Total events	969		589				
Heterogeneity: Chi ² = 29.03	3, df = 15 (P	= 0.02)	; I ^z = 48%	ò			
Fest for overall effect: Z = 6	.91 (P < 0.0	0001)					PD1/PDL1 inhibitor better Placebo better
		1 00 1	0.00	0.000	17 00 01	~	

clinical practice, which needs to be verified by many large randomized clinical trials in the future. In addition, clinical decision-making requires a reasonable balance between the efficacy and toxicity of PD1/PDL1 inhibitors in adjuvant therapy. For future research on this topic, we think that the following aspects can be expanded on. First, to better play the role of PD1/PDL1 inhibitors in adjuvant therapy, we need to select appropriate patients, namely, the applicable population. Second, the specific regimen and dose selection of PD1/PDL1 inhibitors in adjuvant therapy still need to be further explored. Third, the efficacy predictors of PD1/PDL1 inhibitors in adjuvant therapy for cancer patients need to be explored and updated, such as blood indicators, which have guiding significance for when to stop and whether to continue using drugs. Fourth, the application of PD1/PDL1 inhibitors in combination with other therapies such as targeted therapy or radiotherapy in adjuvant therapy may also be a new breakthrough point in the future.

Our meta-analysis has several limitations. First, many ongoing clinical trials have not yet been completed. Second, due to the diversity of cancer types and adjuvant treatment options and the limited number of included studies, we were unable to conduct a subgroup analysis on the various cancer types and treatment options. This was one of the sources of the heterogeneity in the study results. In the future, more studies on the use of PD1/PDL1 inhibitors in the adjuvant treatment of



cancer patients will be conducted, and this will give the study greater statistical significance. Third, although the heterogeneity between the results of each analysis was not particularly significant, the study of Bellmunt et al. was the main source of heterogeneity after the heterogeneity test, which may be related to the PDL1 inhibitor in the experimental group. This suggests that there may be great heterogeneity between the efficacy and safety of PD1 and PDL1 inhibitors, and more studies are needed to confirm this.

6 CONCLUSION

Overall, the results of our meta-analysis revealed that the use of PD1/PDL1 inhibitors in adjuvant therapy was associated with better RFS compared to controls. Men or women older than or younger than 65 years of age can benefit from PD1/PDL1 inhibitors. Moreover, regardless of the expression status of PDL1, PD1/PDL1 inhibitors can reduce the risk of recurrence. However, the use of PD1/PDL1 inhibitors in adjuvant therapy

also increases the risk of adverse events such as fatigue, nausea, and pruritus. Our results provide a reference for the application of PD1/PDL1 inhibitors as adjuvant therapy for solid tumors. However, more studies are needed to demonstrate the efficacy and safety of PD1/PDL1 inhibitors in adjuvant therapy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization, YW, MP. Methodology, YJ, ZX. Software, JyW. Formal analysis, JsW, XyC. Writing-original draft

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SUPPLEMENTARY MATERIAL

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