# Supplementary Online Content

Maiorano BA, Di Maio M, Cerbone L, Maiello E, Procopio G, Roviello G; MeetURO Group. Significance of PD-L1 in metastatic urothelial carcinoma treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Netw Open.* 2024;7(3):e241215. doi:10.1001/jamanetworkopen.2024.1215



This supplementary material has been provided by the authors to give readers additional information about their work.

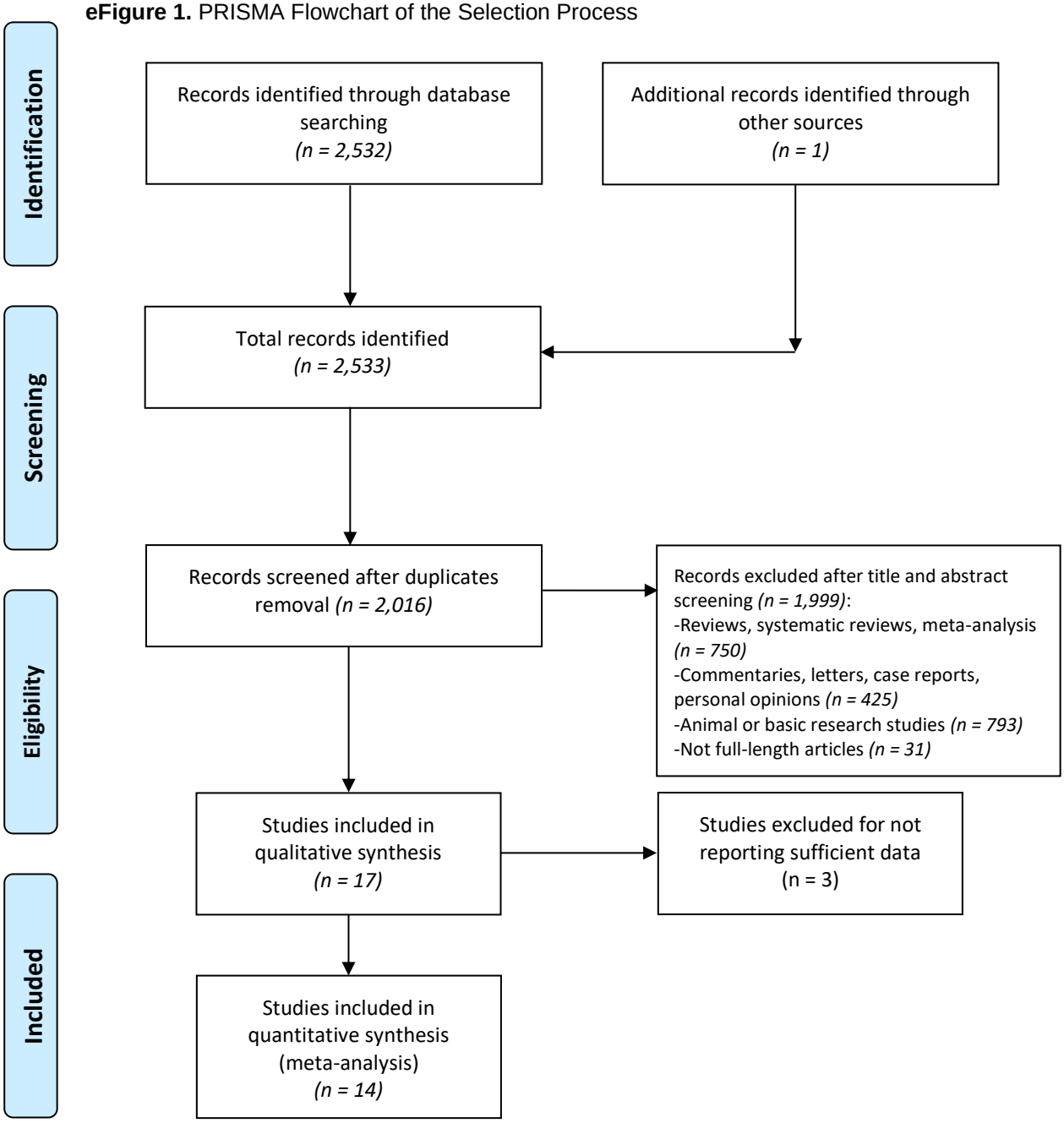
**eTable 1.** Search Strings for the Used Electronic Databases

| Electronic databases | Search string |
|---|---|
| Pubmed | ("Immune checkpoint inhibitor" OR “Immune checkpoint inhibitors” OR ICI OR avelumab OR durvalumab OR atezolizumab OR nivolumab OR pembrolizumab) AND ("urothelial cancer" OR "urothelial carcinoma" OR uroth* OR “bladder cancer” OR “bladder carcinoma” OR bladd*)<br>Filters: English |
| Web of Science | ALL=(((Immune checkpoint inhibitor) OR (Immune checkpoint inhibitors) OR (ICI) (avelumab) OR (durvalumab) OR (atezolizumab) OR (nivolumab) OR (pembrolizumab)) AND ((urothelial cancer) OR (urothelial carcinoma) OR (bladder cancer) OR (bladder carcinoma)) |
| Scopus | ((“Immune checkpoint inhibitor” OR “Immune checkpoint inhibitors” OR “ICI” OR “avelumab” OR “durvalumab” OR “atezolizumab” OR “nivolumab” OR “pembrolizumab”) AND (“urothelial cancer” OR “urothelial carcinoma” OR “bladder cancer” OR “bladder carcinoma”))<br>AND ( LIMIT-TO ( LANGUAGE , "English" ) ) |

**eTable 2.** PICOS Structure for Study Selection

| | |
|---|---|
| **P**atients | Patients metastatic urothelial carcinoma treated with immune checkpoint inhibitors (ICIs) |
| **I**ntervention | ICIs in PD-L1 positive patients |
| **C**omparison | PD-L1 negative patients |
| **O**utcome(s) | Overall survival (OS), overall response rate (ORR), progression-free survival (PFS) |
| **S**tudy Design | Phase I-III clinical trials |

**eFigure 1.** PRISMA Flowchart of the Selection Process



**eTable 3.** Baseline Characteristics of the Included Studies

| Author's name - year | Trial | Line | Primary endpoint | ICI Therapy | Dosage | Control Group |
|---|---|---|---|---|---|---|
| Rosenberg 2016 [13] | IMvigor 210 (Cohort 2) | 2 | ORR | Atezolizumab | 1200 mg q3w | None |
| Bellmunt 2017 [14] | KEYNOTE-045 | 2 | OS, PFS (overall, PD-L1$^{+}$) | Pembrolizumab | 200 mg q3w | CT |
| Sharma 2017 [15] | CheckMate 275 | 2 | ORR (overall, PD-L1$^{+}$) | Nivolumab | 3 mg/kg q2w | None |
| Sharma 2016 [16,17] | CheckMate 032 | 2 | ORR | Nivolumab (NIVO3) | 3 mg/kg q2w | None |
| | | | | Nivolumab + Ipilimumab (NIVO3+IPI1) | Nivo 3 mg/kg, Ipi 1 mg/kg | |
| | | | | Nivolumab + Ipilimumab (NIVO1+IPI3) | Nivo 1 mg/kg, Ipi 3 mg/kg | |
| Powles 2017 [18] | STUDY 1108 | 2 | Safety, ORR | Durvalumab | 10 mg/kg q2w | None |
| Patel 2018 [19] | JAVELIN Solid Tumor (mUC EC) | 2 | Safety | Avelumab | 10 mg/kg q2w | None |
| Balar 2017 [20] | IMvigor 210 (cohort 1) | 1 (cis-unfit) | ORR | Atezolizumab | 1200 mg q3w | None |
| Galsky 2020 [21] | IMvigor 130 | 1 | PFS, OS (Atezo +CT vs. CT) → OS (Atezo vs. CT) | Atezolizumab + CT | Atezo 1200 mg q3w | CT + PBO |
| | | | | Atezolizumab | | |
| Balar 2017 [22] | KEYNOTE-052 | 1 (cis-unfit) | ORR | Pembrolizumab | 200 mg q3w | None |
| Powles 2021 [23] | KEYNOTE-361 | 1 | OS, PFS | Pembrolizumab | Pembro 200 mg q3w | CT |
| | | | | Pembrolizumab + CT | | |
| Rosenberg 2020 [24] | EV-103 | 1 (cis-unfit) | Safety | Pembrolizumab + Enfortumab vedotin | Pembro 200 mg q3w | None |
| Powles 2020 [25] | DANUBE | 1 | OS PD-L1+ (Durva vs. CT), OS overall (Durva + Treme vs. CT) | Durvalumab | Durva 1500 mg q4w, treme 75 mg q4w | CT |
| | | | | Durvalumab + Tremelimumab | | |
| van der Heijden 2023 [26] | CheckMate 901 | 1 | OS, PFS | Nivolumab + CT | Nivo 360 mg q3w x 6 → Nivo 480 mg q4w | CT |
| Powles 2023 [27] | EV-302/ KEYNOTE-A39 | 1 | OS, PFS | Pembrolizumab + enfortumab vedotin | Pembro 200 mg q3w | CT |
| Powles 2020 [28] | JAVELIN Bladder 100 | 1M | OS (overall, PD-L1$^{+}$) | Avelumab | 10 mg/kg q2w | BSC |

BSC: best supportive care; CT: chemotherapy; ICI: immune checkpoint inhibitor; ORR: overall response rate; OS: overall survival; PD-L1: programmed cell death-ligand 1; PFS: progression-free survival q2/3/4w: every 2/3/4 weeks; 1M: first-line maintenance

**eTable 4.** Subgroup Analyses for ORR

| Subgroups | ORR, OR (95% CI) | Total | Subgroup differences |
|---|---|---|---|
| *ICIs mechanism of action* | | | |
| Anti-PD1 | 1.71 (1.19-2.46) | 1.83 (1.39-2.4) | *P=0.69* |
| Anti-PD-L1 | 1.91 (1.28-2.87) | | |
| *Line of therapy* | | | |
| First line | 1.97 (1.21-3.21) | 1.83 (1.39-2.4) | *P=0.73* |
| Second line | 1.83 (1.23-2.72) | | |
| Maintenance | 1.48 (0.86-2.56) | | |
| *Single ICIs vs combo* | | | |
| ICI single agent | 1.70 (1.27-2.27) | 1.94 (1.47-2.56) | *P=0.08* |
| ICI combinations | 2.74 (1.75-4.27) | | |

CI: confidence interval; ICI: immune checkpoint inhibitor; ORR; overall response rate; PD-(L)1: programmed cell death (ligand) 1

**eTable 5.** Subgroup Analyses for OS

| Subgroups | OS, HR (95% CI) | Total | Subgroup differences |
|---|---|---|---|
| *ICIs mechanism of action* | | | |
| Anti-PD1 | 0.70 (0.55-0.90) | 0.68 (0.55-0.84) | *P=0.92* |
| Anti-PD-L1 | 0.69 (0.48-0.98) | | |
| *Line of therapy* | | | |
| First line | 0.68 (0.52-0.88) | 0.68 (0.55-0.84) | *P=0.07* |
| Second line | 0.75 (0.54-1.03) | | |
| Maintenance | 0.40 (0.25-0.62) | | |
| *Single ICIs vs combo* | | | |
| ICI single agent | 0.77 (0.55-1.10) | 0.69 (0.55-0.86) | *P=0.29* |
| ICI combinations | 0.61 (0.48-0.79) | | |

CI: confidence interval; ICI: immune checkpoint inhibitor; OS; overall survival; PD-(L)1: programmed cell death (ligand) 1

**A**

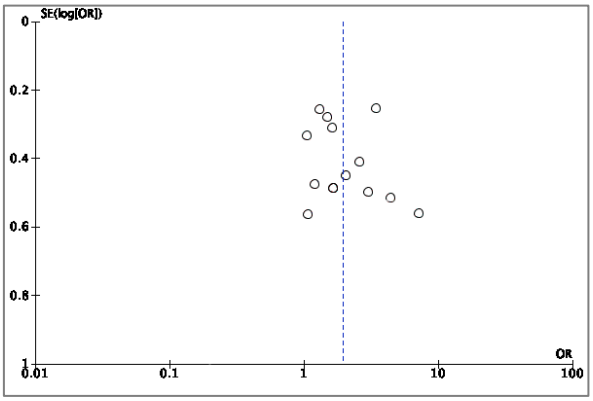
| | Confounding bias | Selection bias | Classification intervention bias | Deviation from intended intervention | Missing data bias | Measure outcome bias | Selected outcome bias | Overall bias |
|---|---|---|---|---|---|---|---|---|
| IMvigor 210 | + | + | + | + | + | ? | + | + |
| CheckMate 275 | + | + | ? | + | + | + | + | + |
| STUDY 1108 | + | ? | + | + | + | + | + | + |
| JAVELIN solid tumor (mUC EC) | + | + | + | + | + | + | + | + |
| KEYNOTE-052 | + | + | + | + | ? | + | + | + |
| EV-103 | + | + | + | + | ? | + | ? | ? |

**B**

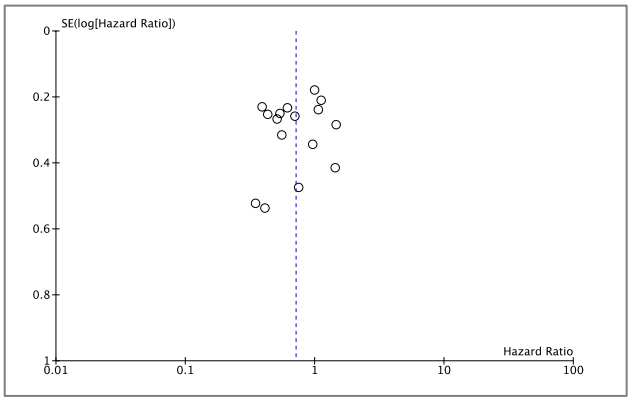
| | Selection bias | Allocation bias | Performance bias | Detection bias | Attrition bias | Reporting bias | Other bias |
|---|---|---|---|---|---|---|---|
| KEYNOTE-045 | + | ? | ? | + | + | + | + |
| IMvigor130 | + | + | + | + | + | + | + |
| CheckMate 032 | + | ? | ? | ? | + | + | + |
| KEYNOTE-361 | + | + | ? | + | + | + | + |
| DANUBE | + | + | + | ? | + | + | + |
| JAVELIN BLADDER 100 | + | ? | + | + | + | + | + |

**eFigure 2.** Risk of Bias Tools for (A) Not-Randomized (ROBINS-I) and (B) Randomized Studies (ROB-2)

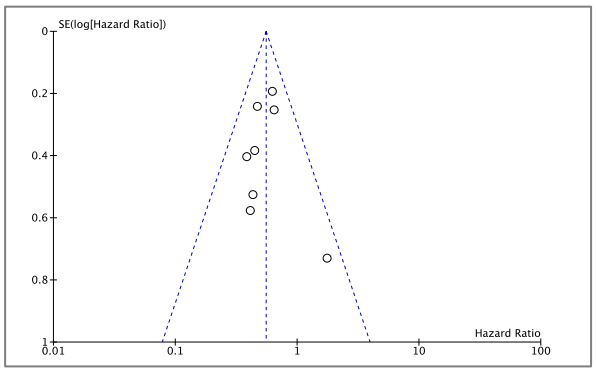
A




B

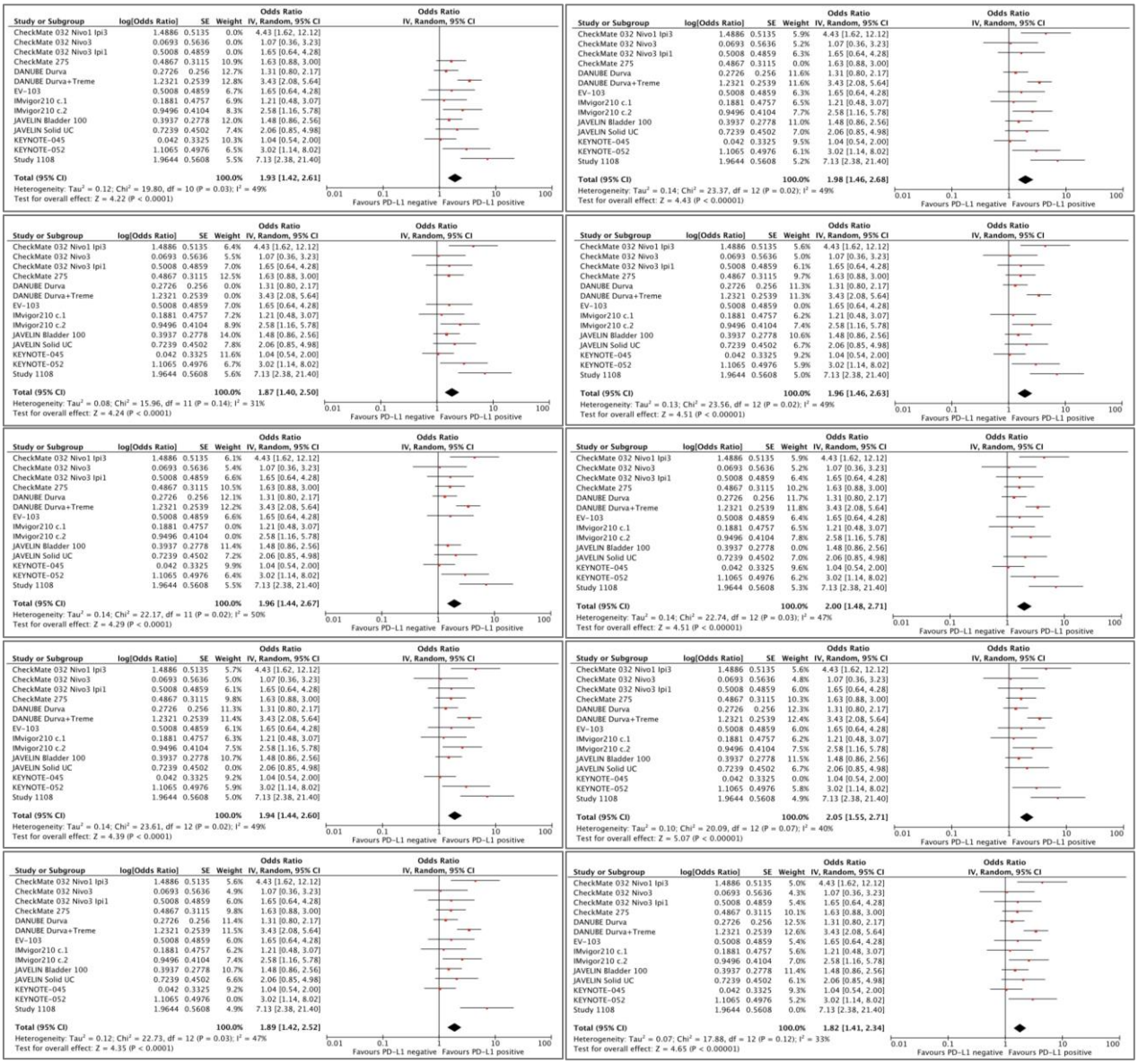



C




**eFigure 3.** Funnel Plot of Selected Studies for (A) ORR, (B) OS, (C) PFS

A

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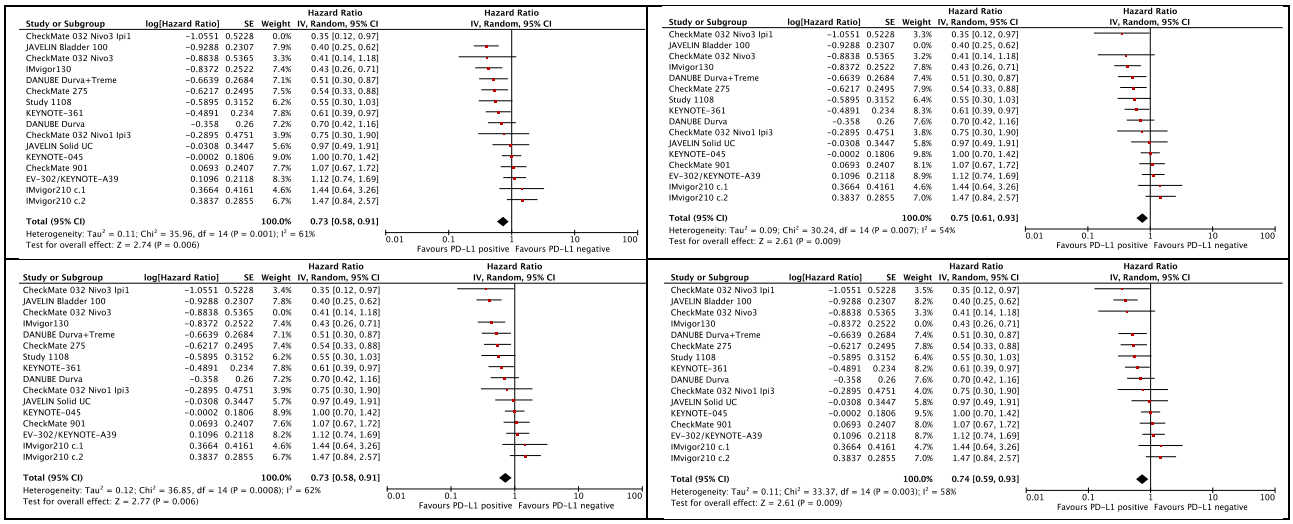

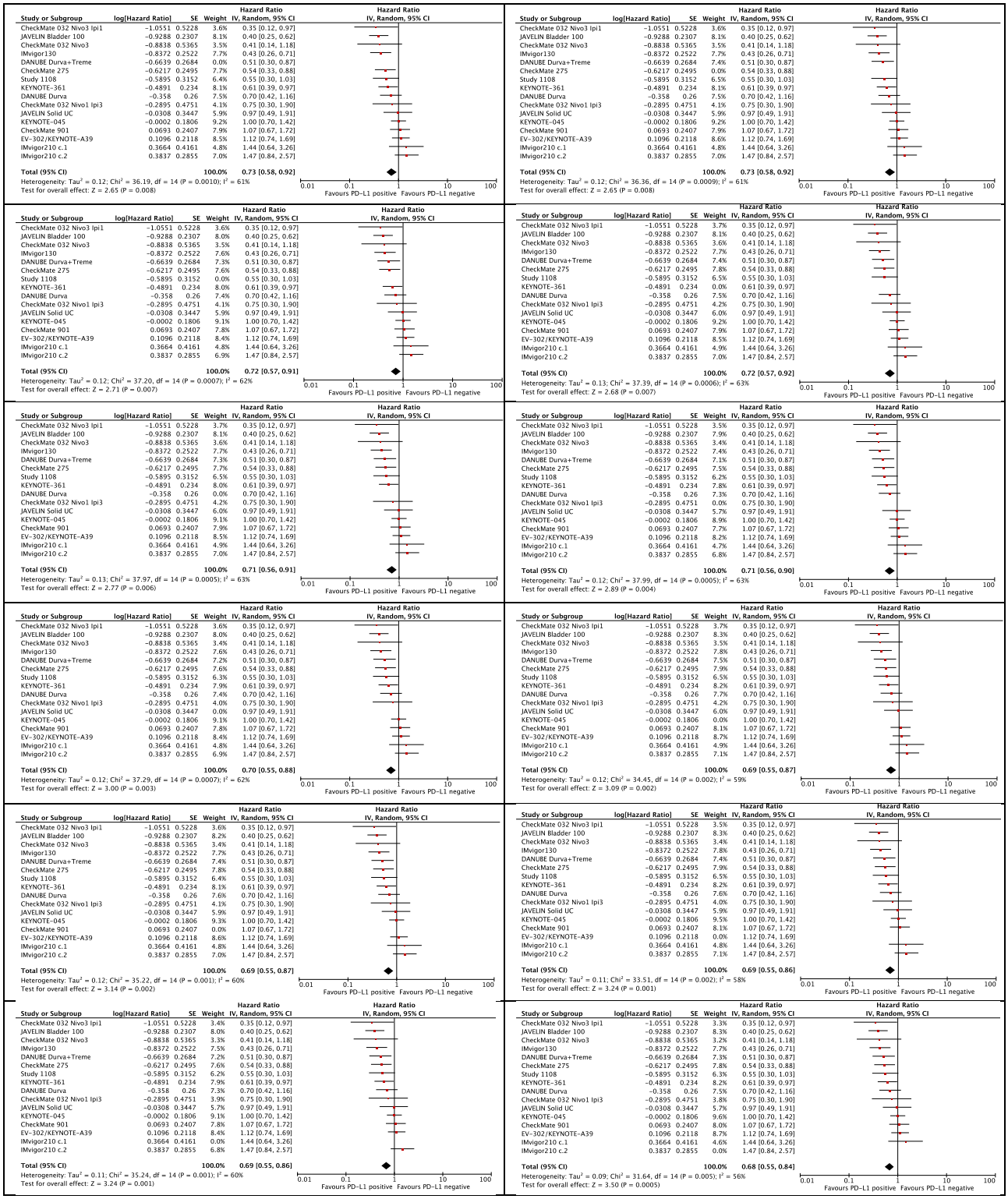

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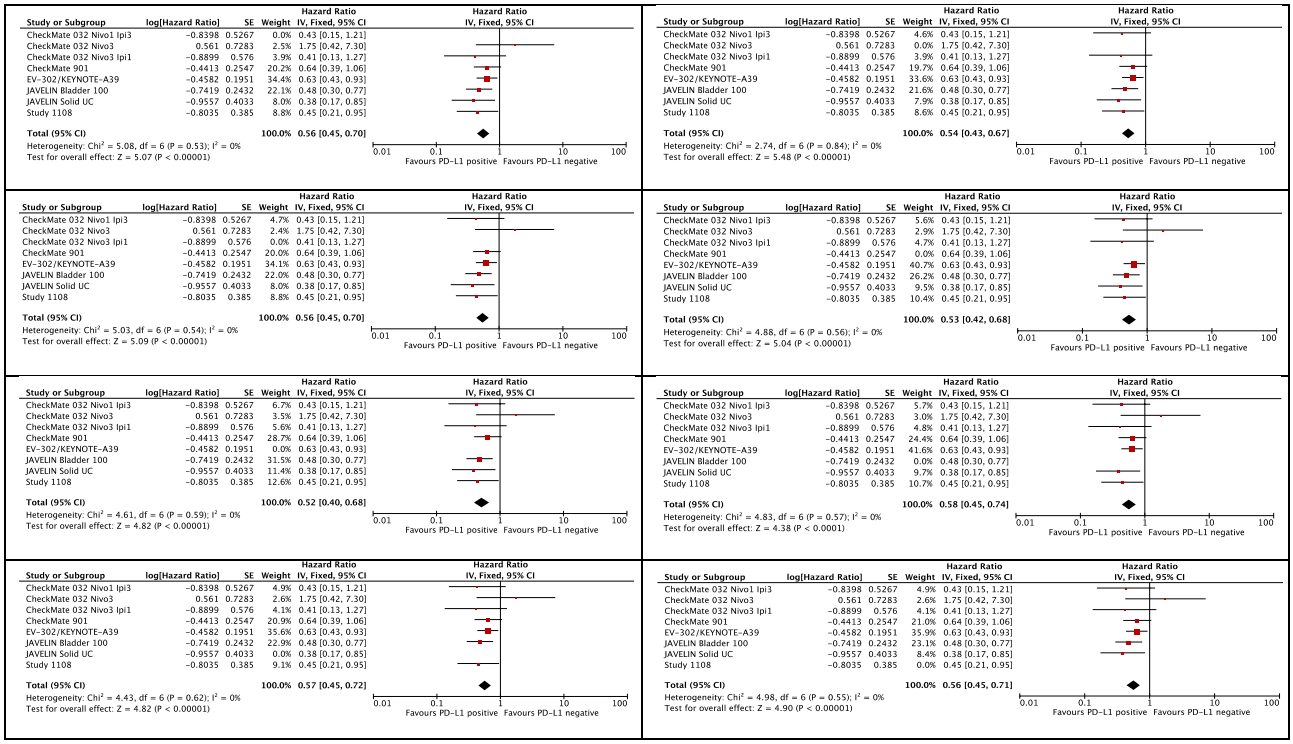


**eFigure 4.** Sensitivity Analysis for (A) ORR, (B) OS, and (C) PFS by Removing One Study at a Time