**Supplementary Online content**

Xing P et al. Incidence rates of immune-related adverse events and their correlation with response in advanced solid tumours treated with NIVO or NIVO+IPI: a systematic review and meta-analysis

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**Supplemental References**

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

**Supplemental Method. Search strategy.**

**Embase**

#1 ‘nivolumab’/exp

#2 ‘nivolumab’

#3 ‘ipilimumab’

#4 #1 **OR** #2 **OR** #3

#5 #4 **AND** ([article]/lim **OR** [article in press]/lim)

#6 #5 **AND** [clinical trial number]/lim **AND** [humans]/limit **AND** [clinical study]/lim

#7 #6 **AND** [1-1-2015]/sd **NOT** [1-5-2019]/sd

**PubMed**

#1 nivolumab

#2 ipilimumab

#3 clinical trials as topic [Mesh] **OR** (clinical **AND** trial **AND** topic) **OR** clinical trials as topic **OR** trial

#4 #2 **AND** #3

#5 Animals [Mesh] **NOT** human [Mesh]

#6 #4 **NOT** #5

#7 #6 **AND** (“2000/01/01”[Date-Publication] : “2019/05/01”[Date-Publication])

**Central Register of Controlled Trials of the Cochrane Library**

#1 nivolumab

#2 ipilimumab

#3 #1 **OR** #2 in trial

**Supplemental Table 1. Characteristics of the included studies.**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Trial ID** | **NCT** | **Type of tumour** | **Phase** | **Treatment** | **Dosing schedule** | **No. of patient** | **AE report criteria** | **Evaluator** | **Criteria for ORR** | **ORR** |
| 2014-Topalian-J Clin Oncol1 | CA209-003 | NCT00730639 | Melanoma | NA | NIVO | 0.1, 0.3, 1.0 mg/kg q2w | 107 | Treatment-related; ≥3% of patients | Investigator | RECIST v1.0 with modification | 31% |
| 2015-Borghaei-N Engl J Med2 | CheckMate 057 | NCT01673867 | NSCLC | III | NIVO | 3 mg/kg, q2w | 292 | Treatment-related; ≥10% of patients; select TRAE | Investigator | RECIST v1.1 | 19% |
|  |  |  |  |  | Docetaxel | 75 mg/m2, q3w | 290 | Treatment-related; ≥10% of patients; select TRAE | Investigator | RECIST v1.1 | 12% |
| 2015-Brahmer-N Engl J Med3 | CheckMate 017 | NCT01642004 | NSCLC | III | NIVO | 3 mg/kg, q2w | 135 | Treatment-related; ≥5% of patients; select TRAE | Investigator | RECIST v1.1 | 20% |
|  |  |  |  |  | Docetaxel | 75 mg/m2, q3w | 137 | Treatment-related; ≥5% of patients; select TRAE | Investigator | RECIST v1.1 | 9% |
| 2015-McDermott-J Clin Oncol4 |  | NCT0730639 | RCC | I | NIVO | 1, 10 mg/kg q2w | 34 | Treatment-related; ≥3% of patients | Investigator | RECIST v1.0 with modification | 29% |
| 2015-Hamanishi-J Clin Oncol5 |  | UMIN000005714 | Ovarian cancer | II | NIVO | 1, 3 mg/kg q2w | 20 | Treatment-related; ≥20% of patients | BICR | RECIST v1.1 | 15% |
| 2015-Larkin-N Engl J Med6 | CheckMate 067 | NCT01844505 | Melanoma | III | NIVO | 3 mg/kg, q2w | 316 | Treatment-related; ≥5% of patients | Investigator | RECIST v1.1 | 44% |
|  |  |  |  |  | NIVO+IPI | NIVO 1 mg/kg, IPI 3 mg/kg, q3w for 4 cycles; then NIVO 3 mg/kg q2w | 314 | Treatment-related; ≥5% of patients | Investigator | RECIST v1.1 | 58% |
| 2015-Postow-N Engl J Med7 | Checkmate 069 | NCT01927419 | Melanoma | I | NIVO+IPI | NIVO 1 mg/kg, IPI 3 mg/kg, q3w for 4 cycles; then NIVO 3 mg/kg q2w | 95 | Treatment-related; ≥10% of patients; select TRAE | Investigator | RECIST v1.1 | 59% |
| 2015-Rizvi-Lancet Oncol8 | CheckMate 063 | NCT01721759 | NSCLC | II | NIVO | 3 mg/kg, q2w | 117 | Treatment-related; ≥5% of patients; immune-mediated TRAE | BICR | RECIST v1.1 | 15% |
| 2015-Motzer-N Engl J Med9 | CheckMate 025 | NCT01668784 | RCC | III | NIVO | 3 mg/kg, q2w | 410 | Treatment-related; ≥10% of patients | Investigator | RECIST v1.1 | 25% |
| 2015-Motzer-J Clin Oncol10 | NA | NCT01354431 | RCC | II | NIVO | 0.3 mg/kg, q3w | 60 | Treatment-related; ≥10% of patients; select TRAE | Investigator | RECIST v1.1 | 20% |
|  |  |  |  |  | NIVO | 2 mg/kg, q3w | 54 | Treatment-related; ≥10% of patients; select TRAE | Investigator | RECIST v1.1 | 22% |
|  |  |  |  |  | NIVO | 10 mg/kg, q3w | 54 | Treatment-related; ≥10% of patients; select TRAE | Investigator | RECIST v1.1 | 20% |
| 2015-Robert-N Engl J Med11 | CheckMate 066 | NCT01721772 | Melanoma | III | NIVO | 3 mg/kg, q2w | 210 | Treatment-related; ≥10% of patients; select TRAE of potential immunological etiology | Investigator | RECIST v1.1 | 40% |
| 2015-Gettinger-J Clin Oncol12 | CA209-003 | NCT00730639 | NSCLC | I | NIVO | 1 3 10 mg/kg | 129 | Treatment-related; ≥3% of patients | Not mentioned | RECIST v1.0 | 17% |
| 2015-Weber-Lancet Oncol13 | CheckMate 037 | NCT01721746 | Melanoma | III | NIVO | 3 mg/kg, q2w | 272 | Treatment-related; ≥5% of patients; select TRAE of potential immune-related | Investigator | RECIST v1.1 | 32% |
|  |  |  |  |  | Dacarbazine or chemo | dacarbazine 1000 mg/m², q3w, or carboplatin area under the curve 6 plus paclitaxel 175 mg/m² , q3w | 133 | Treatment-related; ≥5% of patients; select TRAE of potential immunological etiology | Investigator | RECIST v1.1 | 11% |
| 2016-Weber-Lancet Oncol14 | CheckMate 064 | NCT01783938 | Melanoma | II | NIVO+IPI | NIVO 3mg/kg q2w 6 cycles; then IPI 3mg/kg q3w; then NIVO 3 mg/kg q2w | 68 | Treatment-related; ≥5% of patients; select TRAE of potential immunological etiology | Investigator | RECIST v1.1 | 68% |
| 2016-Weber-Cancer Immunol Res15 | NA | NCT01176461 | Melanoma | I/II | NIVO | 3 mg/kg q2w | 92 | Treatment-related; >5% of patients | Not mentioned | mWHO and immune-related criteria | 29% |
| 2016-Nishio-ESMO open16 | NA | JapicCTI-132073 | NSCLC | II | NIVO | 3 mg/kg q2w | 76 | Treatment-related; ≥5% of patients; select treatment-related AE | BICR | RECIST v1.1 | 23% |
| 2016-Sharma-Lancet Oncol17 | CheckMate 032 | NCT01928394 | Urothelial carcinoma | I/II | NIVO | 3 mg/kg q2w | 78 | Treatment-related; ≥10 patients or grade 3/4 | Investigator | RECIST v1.1 | 24% |
| 2016-Gettinger-J Clin Oncol18 | CheckMate 012 | NCT01454102 | NSCLC | I | NIVO | 3 mg/kg q3w | 52 | Treatment-related; ≥5% of patients; TRAE | Investigator | RECIST v1.1 | 23% |
| 2016-Antonia-Lancet Oncol19 | CheckMate 032 | NCT01928394 | SCLC | I/II | NIVO | 3 mg/kg, q2w | 98 | Treatment-related; ≥10% of patients or grade 3/4 | Investigator | RECIST v1.1 | 10% |
|  |  |  |  |  | NIVO+IPI | NIVO 1 mg/kg, IPI 3 mg/kg, q3w for 4 cycles; then NIVO 3 mg/kg q2w | 61 | Treatment-related; ≥10% of patients or grade 3/4 | Investigator | RECIST v1.1 | 23% |
|  |  |  |  |  | NIVO+IPI | NIVO 3 mg/kg, IPI 1 mg/kg, q3w for 4 cycles; then NIVO 3 mg/kg q2w | 54 | Treatment-related; ≥10% of patients or grade 3/4 | Investigator | RECIST v1.1 | 19% |
| 2017-El-Khoueiry-Lancet Oncol20 | CheckMate 040 | NCT01658878 | HCC | I/II | NIVO | does-escalation | 48 | Treatment-related; ≥5% of patients | Investigator | RECIST v1.1 | 15% |
|  |  |  |  |  | NIVO | does-expansion | 214 | Treatment-related; ≥5% of patients | Investigator | RECIST v1.1 | 20% |
| 2017-Carbone-N Engl J Med21 | CheckMate 026 | NCT02041533 | NSCLC | III | NIVO | 3 mg/kg, q2w | 271 | Treatment-related; ≥10% of patients; select TRAE | BICR | RECIST v1.1 | 26% |
|  |  |  |  |  | Chemo | administered once every 3 weeks for up to six cycles | 270 | Treatment-related; ≥10% of patients; select TRAE | BICR | RECIST v1.1 | 33% |
| 2017-Hammers-J Clin Oncol22 | checkmate 016 | NCT01472081 | RCC | I | NIVO+IPI | NIVO 3 mg/kg q2w, IPI 1 mg/kg q3w; then NIVO 3 mg/kg q2w | 47 | Treatment-related; ≥20% of patients or ≥ 2 patients for grade 3/4; select TRAE | Investigator | RECIST v1.1 | 40% |
|  |  |  |  |  | NIVO+IPI | NIVO 1 mg/kg q2w，IPI 3 mg/kg q3w; then NIVO 3 mg/kg q2w | 47 | Treatment-related; ≥20% of patients or ≥ 2 patients for grade 3/4; select TRAE | Investigator | RECIST v1.1 | 40% |
| 2017-Hellmann-Lancet Oncol23 | CheckMate 012 | NCT01454102 | NSCLC | I | NIVO+IPI | NIVO 3 mg/kg, q2w; IPI 1 mg/kg, q12w | 38 | Treatment-related; ≥10% of patients or grade 3/4; select TRAE | Investigator | RECIST v1.1 | 47% |
|  |  |  |  |  | NIVO+IPI | NIVO 3 mg/kg, q2w; IPI 1 mg/kg, q6w | 40 | Treatment-related; ≥10% of patients or grade 3/4; select TRAE | Investigator | RECIST v1.1 | 38% |
| 2017-Overman-Lancet Oncol24 | CheckMate 142 | NCT02060188 | CRC (dMMR/MSI-H) | II | NIVO | 3 mg/kg, q2w | 74 | Treatment-related; ≥10% of patients or grade 3/4 | BICR | RECIST v1.1 | 36% |
| 2017-Yamazaki-Cancer Sci25 | NA | JapicCTI-142533 | Melanoma | II | NIVO | 3 mg/kg q2w | 24 | Treatment-related; ≥10% of patients; select TRAE | BICR | RECIST v1.1 | 35% |
| 2017-Sharma-Lancet Oncol26 | CheckMate 275 | NCT02387996 | Urothelial carcinoma | II | NIVO | 3 mg/kg, q2w | 270 | Treatment-related; ≥10% of patients; select TRAE | BICR | RECIST v1.1 | 20% |
| 2017-Kudo-Lancet Oncol27 | ATTRACTION01 | JapicCTI-142422 | Oesophageal squamous-cell | II | NIVO | 3 mg/kg, q2w | 65 | Treatment-related; ≥10% of patients or grade 3/4 | BICR | RECIST v1.1 | 22% |
| 2017-Hida-Cancer Sci28 | NA | JapicCTI-132072 | NSCLC | II | NIVO | 3 mg/kg, q2w | 35 | Treatment-related; ≥ 5% of patients; select TRAE | BICR | RECIST v1.1 | 26% |
| 2017-Morris-Lancet Oncol29 | NCI9673 | NCT02314169 | Anal cancer | II | NIVO | 3 mg/kg q2w | 37 | All AEs | Investigator | RECIST v1.1 | 24% |
| 2017-Kang-Lancet30 | ATTRACTION02 | NCT02267343 | Gastric or gastro-oesophageal junction | III | NIVO | 3 mg/kg, q2w | 330 | Treatment-related; ≥2% of patients | Investigator | RECIST v1.1 | 11% |
| 2018-Omuro-Neuro Oncol31 | CheckMate 143 | NCT02017717 | Glioblastoma | I | NIVO | 3 mg/kg q2w | 10 | Treatment-related; ≥ 2 patients or grade 3/4 | Investigator | RANO criteria | 11% |
|  |  |  |  |  | NIVO+IPI | NIVO 1 mg/kg q2w, IPI 3 mg/kg q3w; then NIVO 3 mg/kg q2w | 10 | Treatment-related; ≥ 2 patients or grade 3/4 | Investigator | RANO criteria | 0% |
|  |  |  |  |  | NIVO+IPI | NIVO 1 mg/kg q2w, IPI 3 mg/kg q3w; then NIVO 3 mg/kg q2w | 20 | Treatment-related; ≥ 2 patients or grade 3/4 | Investigator | RANO criteria | 10% |
| 2018-Ma-J Clin Oncol32 | NCI-9742 | NCT02339558 | Nasopharyngeal Carcinoma | II | NIVO | 3 mg/kg q2w | 45 | Select treatment-related AE | Not mentioned | RECIST v1.1 | 20% |
| 2018-Long-Lancet Oncol33 |  | NCT02374242 | Melanoma with brain metastasis | II | NIVO+IPI | NIVO 1 mg/kg, IPI 3 mg/kg, q3w; then NIVO 3 mg/kg q2w | 35 | Treatment-related; ≥10% of patients or grade 3/4; select TRAE | Investigator | RECIST v1.1 | 49% |
|  |  |  |  |  | NIVO | 3 mg/kg, q2w | 25 | Treatment-related; ≥10% of patients or grade 3/4; select TRAE | Investigator | RECIST v1.1 | 24% |
|  |  |  |  |  | NIVO | 3 mg/kg, q2w | 16 | Treatment-related; ≥10% of patients or grade 3/4; select TRAE | Investigator | RECIST v1.1 | 19% |
| 2018-Tawbi-N Engl J Med34 | CheckMate 204 | NCT02320058 | Melanoma with brain metastasis | II | NIVO+IPI | NIVO 1 mg/kg, IPI 3 mg/kg, q3w; then NIVO 3 mg/kg q2w | 94 | Treatment-related; ≥5% of patients or grade 3/4 | Investigator | RECIST v1.1 | 50% |
| 2013-Wolchok-N Engl J Med35 | NA | NCT01024231 | Melanoma | I | NIVO+IPI |  | 53 | Select treatment-related AE | Investigator | mWHO and immune-related criteria | 40% |
| 2018-Lee-Lung Cancer36 | NA | NCT02175017 | NSCLC | II | NIVO | 3 mg/kg q2w | 100 | Treatment-related; ≥10 of patients or grade 3/4 | BICR | RECIST v1.1 | 20% |
| 2018-Quispel-Janssen-J Thorac Oncol37 | NA | NCT02497508 | Malignant pleural mesothelioma | II | NIVO | 3 mg/kg q2w | 34 | Treatment-related | Not mentioned | RECIST with modification | 24% |
| 2018-Hellmann-N Engl J Med38 | CheckMate 227 | NCT02477826 | NSCLC | III | NIVO+IPI | NIVO 3 mg/kg, q2w; IPI 1 mg/kg, q6w | 583 | Treatment-related; ≥10% of patients | BICR | RECIST v1.1 | 33% |
|  |  |  |  |  | NIVO | 3 mg/kg, q2w | 396 | Treatment-related; ≥10% of patients | BICR | RECIST v1.1 |  |
| 2018-Overman-J Clin Oncol39 | CheckMate 142 | NCT02060188 | CRC (dMMR/MSI-H) | II | NIVO+IPI | nivo 3 mg/kg, ipi 1 mg/kg, q3w | 119 | Treatment-related; >10% of patients; select TRAE | BICR | RECIST v1.1 | 49% |
| 2018-Motzer-N Engl J Med40 | CheckMate 214 | NCT02231749 | RCC | III | NIVO+IPI | NIVO 3 mg/kg, IPI 1 mg/kg, q3w; then NIVO 3 mg/kg q2w | 425 | Treatment-related; ≥15% of patients | BICR | RECIST v1.1 | 42% |
| 2018-D'Angelo-Lancet Oncol41 | Alliance A091401 | NCT02500797 | Sarcoma | II | NIVO | 3 mg/kg, q2w | 43 | Treatment-related; ≥10% of patients or grade 3/4/5 | Investigator | RECIST v1.1 | 16% |
|  |  |  |  |  | NIVO+IPI | NIVO 3 mg/kg, IPI 1 mg/kg, q3w | 42 | Treatment-related; ≥10% of patients or grade 3/4/5 | Investigator | RECIST v1.1 | 7% |
| 2018-Janjigian-J Clin Oncol42 | CheckMate 032 | NCT01928394 | Esophagogastric | III | NIVO | 3 mg/kg, q2w | 59 | Treatment-related; ≥15% of patients | BICR | RECIST v1.1 | 7% |
|  |  |  |  |  | NIVO+IPI | NIVO 1 mg/kg, IPI 3 mg/kg, q3w for 4 cycles; then NIVO 3 mg/kg q2w | 49 | Treatment-related; ≥15% of patients | BICR | RECIST v1.1 | 20% |
|  |  |  |  |  | NIVO+IPI | NIVO 3 mg/kg, IPI 1 mg/kg, q3w for 4 cycles; then NIVO 3 mg/kg q2w | 52 | Treatment-related; ≥15% of patients | BICR | RECIST v1.1 | 4% |
| 2019-Wu-J Thorac Oncol43 | CheckMate 078 | NCT02613507 | NSCLC | III | NIVO | 3 mg/kg, q2w | 338 | Treatment-related; ≥10% of patients; select TRAE | Investigator | RECIST v1.1 | 17% |
|  |  |  |  |  | Docetaxel |  | 166 | Treatment-related; ≥10% of patients; select TRAE | Investigator | RECIST v1.1 | 4% |
| 2019-Lebbe-J Clin Oncol44 | Checkmate 511 | NCT02714218 | melanoma | IIIb/IV | NIVO+IPI | NIVO 3 mg/kg, IPI 1 mg/kg, q3w; then NIVO 480 mg q4w | 180 | Treatment-related; ≥10% of patients; select TRAE ≥5% of patients | Investigator | RECIST v1.1 | 46% |
|  |  |  |  |  | NIVO+IPI | NIVO 1 mg/kg, IPI 3 mg/kg, q3w; then NIVO 480 mg q4w | 178 | Treatment-related; ≥10% of patients; select TRAE ≥5% of patients | Investigator | RECIST v1.1 | 51% |
| 2019-Disselhorst-Lancet Respir Med45 | INITIATE | NCT03048474 | Malignant pleural mesothelioma | II | NIVO+IPI | NIVO 240 mg q2w, IPI 1 mg/kg q6w; then NIVO 240 mg q2w | 35 | Treatment-related; ≥ 10% of patients or grade 3/4 | BICR | mRECIST | 29% |
| 2019-Neal Ready-J Clin Oncol46 | CheckMate 568 | NCT02659059 | NSCLC | II | NIVO+IPI | NIVO 3 mg/kg q2w, IPI 1 mg/kg q6w | 288 | Treatment-related; ≥ 10% of patients; select TRAE | Investigator | RECIST v1.1 | 30% |
| 2019-Ferris-N Engl J Med47 | CheckMate 141 | NCT02105636 | HNSCC | III | NIVO | 3 mg/kg, q2w | 240 | Treatment-related; ≥5% of patients; select TRAE | Investigator | RECIST v1.1 | 13% |
|  |  |  |  |  | Methotrexate, docetaxel, or cetuximab |  | 121 | Treatment-related; ≥5% of patients; select TRAE | Investigator | RECIST v1.1 | 6% |
| 2019-Scherpereel-Lancet Oncol48 | IFCT-1501 MAPS2 | NCT02716272 | Malignant pleural mesothelioma | II | NIVO | 3 mg/kg q2w | 63 | Treatment-related; ≥10 of patients or grade 3/4 | BICR | RECIST v1.0 | 18% |
|  |  |  |  |  | NIVO+IPI | NIVO 3 mg/kg q2w, IPI 1 mg/kg q6w | 62 | Treatment-related; ≥10 of patients or grade 3/4 | BICR | RECIST v1.0 | 26% |

AE=adverse event. ORR=objective response rate. TRAE=treatment-related adverse event. BICR=Blinded independent central review. NIVO=nivolumab. IPI=ipilimumab. NIVO+IPI=nivolumab+ipilimumab. RECIST=response evaluation criteria in solid tumours. NSCLC=non-small cell lung cancer. RCC=renal cell carcinoma. HCC=hepatocellular carcinoma. CRC=colorectal carcinoma. HNSCC=head and neck squamous cell carcinoma.

**Supplemental Table 2. Incidences of Categorical irAEs according to system organ class.**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **All grades** | | | |  | | **Grade 3 or higher** | | | |
| **NIVO**  **(95% CI)** | **NIVO+IPI**  **(95% CI)** | **OR**  **(95% CI)** | **P** | |  | **NIVO**  **(95% CI)** | **NIVO+IPI**  **(95% CI)** | **OR**  **(95% CI)** | **P** |
| Skin | 24.48 (20.84-28.52) | 50.56 (42.52-58.57) | 0.44 (0.39-0.49) | <0.001 | |  | 0.99 (0.66-1.49) | 3.47 (2.23-5.36) | 0.28 (0.18-0.42) | <0.001 |
| Gastrointestinal | 10.73 (8.85-12.97) | 33.55 (27.18-40.58) | 0.32 (0.28-0.36) | <0.001 | |  | 1.20 (0.81-1.76) | 9.93 (6.83-14.22) | 0.13 (0.09-0.17) | <0.001 |
| Endocrine | 10.09 (8.59-11.81) | 27.55 (22.70-33.01) | 0.33 (0.28-0.38) | <0.001 | |  | 0.41 (0.19-0.88) | 4.07 (3.03-5.43) | 0.13 (0.08-0.23) | <0.001 |
| Hepatic | 4.87 (3.53-6.69) | 20.10 (14.39-27.35) | 0.28 (0.24-0.33) | <0.001 | |  | 1.26 (0.84-1.89) | 10.06 (7.12-14.03) | 0.12 (0.09-0.16) | <0.001 |
| Pulmonary | 4.23 (3.38-5.28) | 7.77 (5.83-10.29) | 0.54 (0.43-0.67) | <0.001 | |  | 0.91 (0.52-1.59) | 1.66 (1.11-2.46) | 0.61 (0.36-1.04) | 0.07 |
| Renal | 1.98 (1.34-2.93) | 5.14 (3.51-7.47) | 0.46 (0.34-0.64) | <0.001 | |  | 0.22 (0.10-0.48) | 1.65 (0.99-2.75) | 0.14 (0.06-0.33) | <0.001 |

NIVO=nivolumab. NIVO+IPI=nivolumab+ipilimumab. OR=odds ratio. CI=confidence interval

**Supplemental Table 3. Sensitivity analysis of the correlation between irAEs and ORR in NIVO**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Omitted studies | No. of  omitted arms | Skin irAEs | |  | Gastrointestinal irAEs | |  | Endocrine irAEs | |  | Hepatic irAEs | |  | Pulmonary irAEs | |  | Renal irAEs | |
| P | r |  | P | r |  | P | r |  | P | r |  | P | r |  | P | r |
| Anal cancer | 1 | <0.001 | 0.79 |  | 0.004 | 0.59 |  | 0.05 | 0.44 |  | 0.29 | 0.25 |  | 0.03 | -0.47 |  | 0.85 | 0.04 |
| HNSCC | 1 | <0.001 | 0.78 |  | 0.01 | 0.54 |  | 0.06 | 0.42 |  | 0.50 | 0.16 |  | 0.001 | -0.64 |  | 0.34 | -0.22 |
| Melanoma | 7 | 0.009 | 0.63 |  | 0.07 | 0.47 |  | 0.08 | 0.48 |  | 0.31 | 0.27 |  | 0.74 | 0.09 |  | 0.45 | 0.20 |
| NSCLC | 9 | <0.001 | 0.83 |  | 0.04 | 0.56 |  | 0.26 | 0.34 |  | 0.26 | 0.35 |  | 0.13 | -0.43 |  | 0.27 | 0.33 |
| RCC | 3 | <0.001 | 0.80 |  | 0.007 | 0.58 |  | 0.06 | 0.46 |  | 0.33 | 0.24 |  | 0.04 | -0.46 |  | 0.94 | 0.02 |
| Urothelial carcinoma | 2 | <0.001 | 0.82 |  | 0.009 | 0.56 |  | 0.04 | 0.47 |  | 0.36 | 0.22 |  | 0.03 | -0.48 |  | 0.92 | -0.02 |

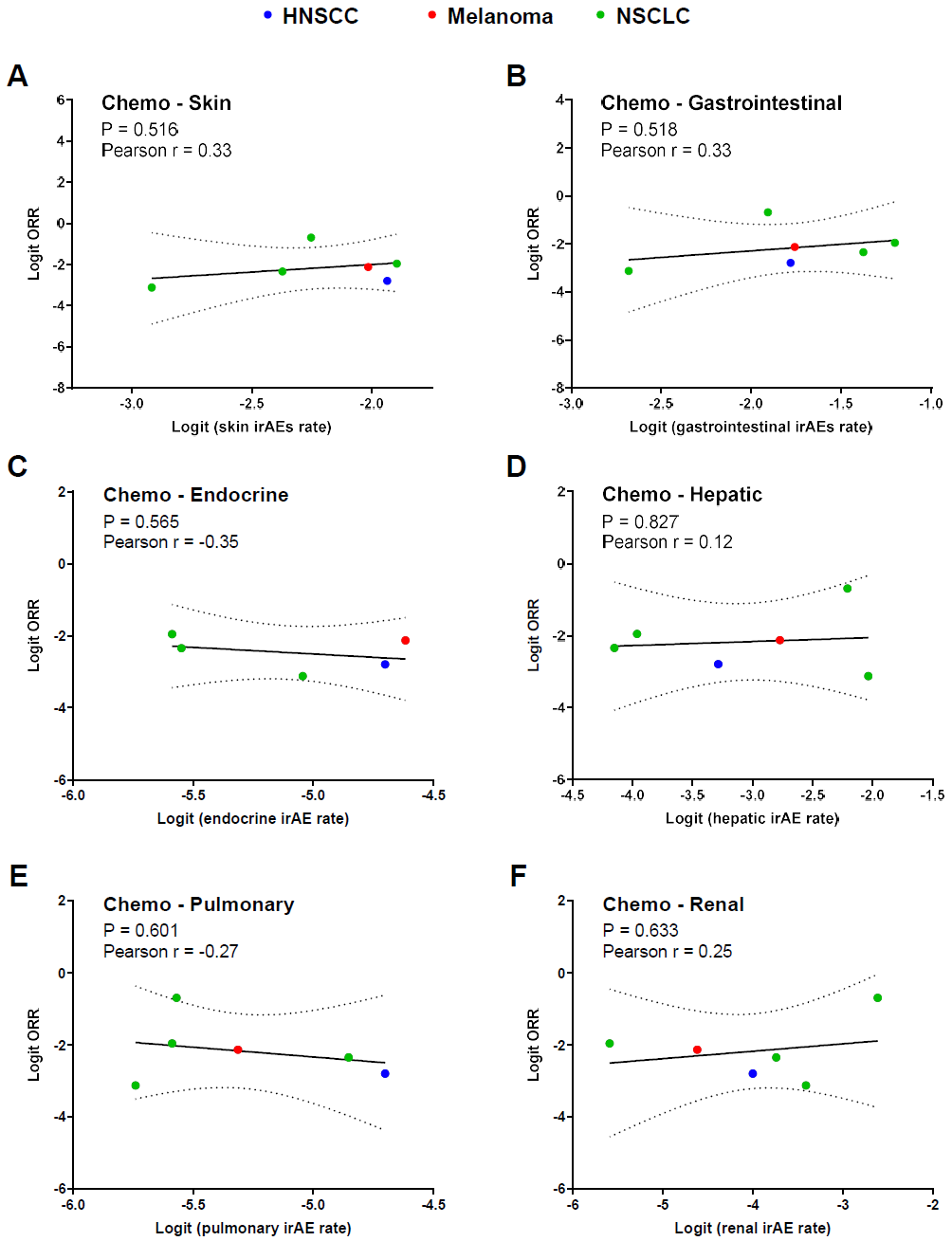
irAE=immune-related adverse event. ORR=objective response rate. HNSCC=head and neck squamous cell carcinoma. NSCLC=non-small cell lung cancer. RCC=renal cell carcinoma.

**Supplemental Table 4. Sensitivity analysis of the correlation between irAEs and ORR in NIVO+IPI**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Omitted studies | No. of  omitted arms | Skin irAEs | |  | Gastrointestinal irAEs | |  | Endocrine irAEs | |  | Hepatic irAEs | |  | Pulmonary irAEs | |  | Renal irAEs | |
| P | r |  | P | r |  | P | r |  | P | r |  | P | r |  | P | r |
| CRC (dMMR/MSI-H) | 1 | 0.01 | 0.64 |  | 0.02 | 0.65 |  | 0.12 | 0.45 |  | 0.07 | 0.55 |  | 0.47 | 0.23 |  | 0.97 | 0.01 |
| Malignant pleural mesothelioma | 1 | 0.03 | 0.57 |  | 0.02 | 0.60 |  | 0.11 | 0.44 |  | 0.05 | 0.55 |  | 0.49 | 0.21 |  | 0.97 | 0.01 |
| Melanoma | 7 | 0.93 | -0.04 |  | 0.77 | 0.14 |  | 0.84 | -0.10 |  | 0.75 | -0.15 |  | 0.99 | 0.01 |  | 0.21 | 0.54 |
| NSCLC | 4 | 0.32 | 0.33 |  | 0.25 | 0.40 |  | 0.31 | 0.36 |  | 0.02 | 0.76 |  | 0.67 | 0.17 |  | 0.10 | 0.59 |
| RCC | 2 | 0.04 | 0.57 |  | 0.02 | 0.65 |  | 0.07 | 0.54 |  | 0.05 | 0.60 |  | 0.50 | 0.23 |  | 0.47 | 0.25 |

irAE=immune-related adverse event. ORR=objective response rate. dMMR/MSI-H=mismatch repair deficient/micro-satellite instability high. NSCLC=non-small cell lung cancer. RCC=renal cell carcinoma.

**Supplemental Figure 1. Correlation between irAEs and ORR of chemotherapy-contained regimen.** The correlation between ORR of chemotherapy-contained regimen and irAEs categorized by system organ class (A-F). HNSCC=head and neck squamous cell carcinoma.



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