Supplementary Table 1: Characteristics of studies included in the meta-analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| First author  (year) | Study name | Study Number | Phase | Indication  of immunotherapy | Combination therapy | Dose of  medication | N |
|
|
|  |  |  |  |  |  |  |  |
| Amaria 2018 | N/A | NCT02519322 | 2 | melanoma | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x3, then surgery, then N3 Q 2W | 11 |
| Antonia 2016 | CHECKMATE 032 | NCT01928394 | 1/2 | recurrent small cell lung cancer | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3Q2W | 61 |
| Antonia 2016 | CHECKMATE 032 | NCT01928394 | 1/2 | recurrent small cell lung cancer | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N3Q2W | 54 |
| Baas, 2021 | CheckMate 743 | NCT02899299 | 3 | malignant pleural mesothelioma | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3 Q2W + I1 Q6W | 303 |
| Boyer,2021 | KEYNOTE 598 | NCT03302234 | 3 | metastatic NSCLC | Pembrolizumab (P) (mg)+Ipilimumab (I) (mg/kg) | P 200 Q3W x35 + I1 Q6W x18 | 284 |
| Brastianos, 2021 | N/A | NCT02939300 | 2 | leptomeningeal carcinomatosis | Nivolumab (N) + Ipilimumab (I) (mg/kg) | \*See comments | 18 |
| Calabro, 2018 | NIBIT-MESO-1 | 2015-001995-23  NCT02588131 | 2 | pleural or peritoneal mesothelioma | Durvalumab (D) + Tremelimumab (T) (mg/kg) | D20+T1 Q4W x4 then D20 Q4W x9 | 40 |
| Cascone, 2021 | NEOSTAR | NCT03158129 | 2 | NSCLC | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3 Q2W X3 + I1 x1 | 21 |
| Chen 2020 | CO.26 Study | NCT02870920 | 2 | advanced colorectal cancer | Durvalumab (D) + Tremelimumab (T) (mg) | T75 Q4W x4 + D1500 Q4W | 119 |
| Cohen 2020 | GERCOR NIPICOL | NCT03350126 | 2 | MSI-H/MMR- metastatic CRC | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4, then N3Q2W | 57 |
| D'Angelo 2018 | A091401, NCTN | NCT02500797 | 2 | metastatic Sarcoma | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N3 Q2W | 42 |
| Di Giacomo 2021 | NIBIT-M2 | NCT02460068 | 3 | melanoma with brain mets | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 27 |
| Disselhorst 2019 | INITIATE | NCT03048474 | 2 | recurrent malignant pleural mesothelioma | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N240mg Q2W +I1 Q6W x4 | 35 |
| Edenfield 2021 | N/A | NCT02938793 | 2 | \*Rare cancers | Durvalumab (D) + Tremelimumab (T) (mg) | D1500mg Q4W x13+ T75 Q4W x7 then T75 Q12W x2 | 50 |
| Ferrarotto, 2020 | CIAO | NCT0314478 | N/A | Oropharyngeal cancer | Durvalumab (D) + Tremelimumab (T) (mg) | D1500+T75 Q4W x2 | 14 |
| Ferris, 2020 | EAGLE | N/A | 3 | recurrent or metastatic head and neck SCC | Durvalumab (D) + Tremelimumab (T) (mg/kg) | D20+T1 Q4W x4 then D10 Q2W | 247 |
| Gettinger 2021 | Lung-MAP  S1400I | NCT02785952 | 3 | Stage 4 squamous cell lung cancer | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N3 Q2W + I1 Q6W | 125 |
| Gubens 2019 | KEYNOTE-021 | NCT02039674 | 1/2 | NSCLC | Pembrolizumab (P) +Ipilimumab (I) (mg/kg) | P2+I1 Q3W then P2 Q3W | 45 |
| Hellmann 2019 | CheckMate 227 | NCT02477826 | 3 | advanced NSCLC | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3 Q2W + I1 Q6W | 583 |
| Hodi 2016 | CheckMate 069 | NCT01927419 | 2 | advanced melanoma | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 95 |
| Hodi 2018 | CheckMate 067 | NCT01844505 | 3 | advanced melanoma | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 314 |
| Janjigian 2018 | CheckMate 032 | NCT01928394 | 1/2 | metastatic esophagogastric cancer | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 49 |
| Janjigian 2018 | CheckMate 032 | NCT01928394 | 1/2 | metastatic esophagogastric cancer | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N3 Q2W | 52 |
| Kelley 2021 | N/A | NCT02519348 | 1/2 | HCC | Durvalumab (D) + Tremelimumab (T) (mg) | D1500+T75 Q4W x4 then D1500 Q4W | 84 |
| Kelly 2020 | N/A | NCT02340975 | 1/2 | gastric and GEJ adenocarcinoma | Durvalumab (D) + Tremelimumab (T) (mg/kg) | D20+T1 Q4W x4 then D10 Q2W | 71 |
| Kim 2020 | KCSG-LU16-07 | NCT03022500 | 2 | Pulmonary sarcomatoid carcinoma (recurrent or metastatic) | Durvalumab (D) + Tremelimumab (T) (mg) | D1500+T75 Q4W x4 then D750 Q2W | 18 |
| Lebbe 2019 | CheckMate 511 | NCT02714218 | 3b/4 | advanced melanoma | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N480mg Q4W | 180 |
| Lebbe 2019 | CheckMate 511 | NCT02714218 | 3b/4 | advanced melanoma | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N480mg Q4W | 178 |
| Lenz, H-J 2021 | CheckMate 142 | NCT04008030 | 2 | metastatic colorectal cancer | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N3 Q2W + I1 Q6W | 45 |
| Long 2018 | N/A | NCT02374242 | 2 | melanoma with brain metastasis | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 35 |
| Long 2021 | KEYNOTE-029 | NCT02089685 | 2 | advanced melanoma | Pembrolizumab (P) +Ipilimumab (I) (mg) | I 50 Q6W x4 + P 200 Q3W upto 24 mo | 51 |
| Long 2021 | KEYNOTE-029 | NCT02089685 | 2 | advanced melanoma | Pembrolizumab (P) +Ipilimumab (I) (mg) | I 100 Q12W x4 + P 200 Q3W upto 24 mo | 51 |
| McGregor 2021 | N/A | NCT03333616 | 2 | advanced rare genitourinary malignancy | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N480mg Q4W | 55 |
| Motzer, 2019 | CheckMate 214 | NCT02231749 | 3 | advanced RCC | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N3 Q2W | 547 |
| Namikawa, 2020 | ONO-4538-17 | JAPIC-CTI 152869 | 2 | melanoma | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 30 |
| O'Reilly, 2019 | N/A | NCT02558894 | 2 | metastatic pancreatic ductal adenocarcinoma | Durvalumab (D) + Tremelimumab (T) (mg) | D1500 mg +T75 mg Q4W x4 then D1500 mg | 32 |
| Overman 2018 | CheckMate 142 | NCT02060188 | 2 | MSI-H/MMR- metastatic CRC | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N3 Q2W | 119 |
| Owonikoko 2021 | CheckMate 451 | NCT02538666 | 3 | Extensive SCLC | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N240mg Q2W | 279 |
| Pakkala, 2020 | N/A | NCT02701400 | 2 | Relapsed SCLC | Durvalumab (D) + Tremelimumab (T) (mg) | D 1500+T75 Q4W x12 months | 9 |
| Patel 2020 | SWOG 1609  DART | NCT02834013 | 2 | Non pancreatic neuro endocrine tumors | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N240mg Q2W + I1 Q6W | 32 |
| Patel 2021 | SWOG 1609  DART | NCT02834013 | 2 | high grade neuroendocrine neoplasm | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N240mg Q2W +I1 Q6W | 19 |
| Pelster 2020 | PROSPER | NCT01585194 | 2 | metastatic uveal melanoma | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 35 |
| Piulats 2021 | GEM-1402 | NCT02626962 | 2 | metastatic uveal melanoma | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W x2 then Q6W | 52 |
| Planchard, 2020 | ARCTIC | NCT02352948 | 3 | metastatic NSCLC | Durvalumab (D) + Tremelimumab (T) (mg/kg) | D20+T1 Q4W x3 then D10 Q2W x17 | 174 |
| Powles 2020 | DANUBE | NCT02516241 | 3 | locally advanced or metastatic urothelial cancer | Durvalumab (D) + Tremelimumab (T) (mg) | D1500mg + T75mg Q4W x4 then D1500mg Q4W | 342 |
| Ready, 2019 | CheckMate 568 | NCT02659059 | 2 | advanced NSCLC | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3 Q2W + I1 Q6W | 288 |
| Rizvi 2020 | MYSTIC | NCT02453282 | 3 | metastatic NSCLC | Durvalumab (D) +Tremelimumab (T) (mg/kg) | D20+T1 Q4W x4 | 371 |
| Sarfaty 2021 | N/A | NCT03430895 | 2 | metastatic, non-urothelial urinary tract cancer | Durvalumab (D) + Tremelimumab (T) (mg) | D1500mg + T75mg Q4W x4 then D1500mg Q4W | 13 |
| Sharma 2019 | CheckMate 032 | NCT01928394 | 1/2 | metastatic urothelial carcinoma | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N3 Q2W | 104 |
| Sharma 2019 | CheckMate 032 | NCT01928394 | 1/2 | metastatic urothelial carcinoma | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 92 |
| Sharma 2020 | CheckMate 650 | NCT02985957 | 2 | metastatic castration resistant prostate cancer | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N480mg Q4W | 90 |
| Singh 2021 | N/A | NCT02880020 | 2 | advanced GIST | Nivolumab (N) (mg) + Ipilimumab (I) (mg/kg) | N240mg Q2W +I1 Q6W | 16 |
| Siu 2019 | CONDOR | NCT02319044 | 2 | reccurent or metastatic head and neck SCC | Durvalumab (D) + Tremelimumab (T) (mg/kg) | D20+T1 Q4W x4 then D10 Q2W | 133 |
| Tawbi 2021 | CheckMate 204 | NCT02320058 | 2 | melanoma with brain metastasis | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 119 |
| Wagner 2021 | SWOG 1609  DART | NCT02834013 | 2 | metastatic or unresectable angiosarcoma | Nivolumab (N)(mg) +Ipilimumab (I) (mg/kg) | N24 Q2W +I1 Q6W | 16 |
| Yau 2020 | CheckMate 040 | NCT01658878 | 1/2 | Advanced HCC | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N240 mg Q2W | 50 |
| Yau 2020 | CheckMate 040 | NCT01658878 | 1/2 | advanced HCC | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N240mg Q2W | 49 |
| Yau 2020 | CheckMate 040 | NCT01658878 | 1/2 | advanced HCC | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N3 Q2W + I1 Q6W | 49 |
| Zamarin 2020 | NRG GY003 | NCT02498600 | 2 | recurrent or persistent ovarian cancer | Nivolumab (N) +Ipilimumab (I) (mg/kg) | N3+I1 Q3W x4 then N3 Q2W | 51 |
| Zimmer 2020 | IMMUNED | NCT02523313 | 2 | resected stage IV melanoma | Nivolumab (N) + Ipilimumab (I) (mg/kg) | N1+I3 Q3W x4 then N3 Q2W | 56 |
|  |  |  |  |  |  |  |  |

\* Melanoma: N1+I3 Q3W x4 then N480mg Q4W, NSCLC: N3 Q2W + I1 Q6W, Small cell lung CA+ CA Breast: N1+I3 Q3W x4 then N240mg Q2W, Other solid tumors: N3+I1 Q3W x4 then N480mg Q4W

Abbreviations: NSCLC: non-small cell lung cancer; MSI-H: microsatellite instability-high; MMR: mismatch repair; CRC: colo-rectal cancer; SCC: squamous cell cancer; HCC: hepatocellular carcinoma; GEJ: gastroesophageal cancer; RCC: renal cell cancer; GIST: gastrointestinal stromal tumor; Q: every ; W: weekly; N: number

Supplementary Table 2: Pooled incidence of treatment related adverse events in nivolumab plus ipilimumab group

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Number of study arms | Pooled incidence (95% C.I.) | I2 |
| All grade colitis | 10 | 6.9 (4.0 - 11.7) | 84% |
| Grade ≥ 3 colitis |  | - |  |
| All grade diarrhea | 34 | 27.5 (23.9 - 31.1) | 82% |
| Grade ≥ 3 diarrhea | 34 | 5.2 (4.1 - 6.5) | 52% |
| All grade amylase | 14 | 8.9 (7.1 - 11.2) | 32% |
| Grade ≥ 3 amylase | 14 | 3.0 (2.2 - 4.2) | 0 |
| All grade lipase | 23 | 11.9 (9.4 - 14.9) | 66% |
| Grade ≥ 3 lipase | 23 | 7.6 (6.1 - 9.4) | 36% |
| All grade ALT | 27 | 14.7 (11.5 - 18.6) | 80% |
| Grade ≥ 3 ALT | 28 | 7.4 (5.7 - 9.6) | 63% |
| All grade AST | 27 | 14.2 (11.2 - 17.9) | 78% |
| Grade ≥ 3 AST | 28 | 6.3 (4.7 - 8.9) | 63% |
| All grade Bilirubin | 4 | 4.4 (2.0 - 9.5) | 60% |
| Grade ≥ 3 Bilirubin | 4 | 0.7 (0.2 - 2.4) | 10% |
| All grade ALP | 9 | 8.7 (5.5 - 13.5) | 58% |
| Grade ≥ 3 ALP | 9 | 2.1 (1.3 - 3.4) | 64% |
| All grade liver related adverse events | 6 | 2.4 (1.8 - 3.2) | 75% |
| Grade ≥ 3 liver related adverse events | 6 | 11.6 (8.9 - 15.1) | 30% |

Abbreviations: CI: confidence interval; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase

Supplementary Table 3: Pooled incidence of GI treatment related adverse events in durvalumab plus tremelimumab group

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Number of study arms | Pooled incidence (95% C.I.) | I2 |
| All grade colitis | - | - | - |
| Grade ≥ 3 colitis | - | - | - |
| All grade diarrhea | 14 | 15.7 (11.4 - 21.1) | 79% |
| Grade ≥ 3 diarrhea | 14 | 4.0 (2.4 - 6.6) | 65% |
| All grade amylase | 9 | 8.6 (4.2 - 17.0) | 79% |
| Grade ≥ 3 amylase | 9 | 3.4 (1.7 - 6.7) | 45% |
| All grade lipase | 9 | 8.0 (4.1 - 15.2) | 76% |
| Grade ≥ 3 lipase | 9 | 6.1 (3.4 - 10.9) | 59% |
| All grade ALT | 5 | 6.4 (1.5 - 23.8) | 96% |
| Grade ≥ 3 ALT | 5 | 1.6 (0.7 - 3.8) | 28% |
| All grade AST | 5 | 9.4 (1.5 - 40.8) | 96% |
| Grade ≥ 3 AST | 5 | 3.3 (1.8 - 5.8) | 13% |
| All grade Bilirubin | - | - | - |
| Grade ≥ 3 Bilirubin | - | - | - |
| All grade ALP | 3 | 18.9 (1.2 - 82.1) | 94% |
| Grade ≥ 3 ALP | 3 | 5.2 (0.7 - 31.2) | 69% |

Abbreviations: CI: confidence interval; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase

Supplementary Table 4: Pooled incidence of treatment related adverse events in pembrolizumab plus ipilimumab group

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Number of study arms | Pooled incidence (95% C.I.) | I2 |
| All grade colitis | - | - | - |
| Grade ≥ 3 colitis | - | - | - |
| All grade diarrhea | 4 | 24.7 (17.7 - 33.4) | 58% |
| Grade ≥ 3 diarrhea | 4 | 3.1 (1.8 - 5.3) | 0% |
| All grade amylase | - | - | - |
| Grade ≥ 3 amylase | - | - | - |
| All grade lipase | - | - | - |
| Grade ≥ 3 lipase | - | - | - |
| All grade ALT | 3 | 10.8 (6.9 - 16.3) | 27% |
| Grade ≥ 3 ALT | 3 | 2.8 (1.5 - 5.2) | 0% |
| All grade AST | 3 | 12.4 (9.4 - 16.1) | 0% |
| Grade ≥ 3 AST | 3 | 1.6 (0.7 - 3.5) | 0% |
| All grade Bilirubin |  | - |  |
| Grade ≥ 3 Bilirubin |  | - |  |
| All grade ALP |  | - |  |
| Grade ≥ 3 ALP |  | - |  |

Abbreviations: CI: confidence interval; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase

Supplementary Table 5: Pooled incidence of treatment related adverse events of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg regimen

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Number of study arms | Pooled incidence (95% C.I.) | I2 |
| All grade colitis | 7 | 11.0 (7.4 - 16.2) | 58% |
| Grade ≥ 3 colitis | 7 | 8.3 (5.7 - 11.9) | 36% |
| All grade diarrhea | 14 | 34.3 (28.8 - 40.3) | 78% |
| Grade ≥ 3 diarrhea | 14 | 7.7 (6.4 - 9.3) | 4% |
| All grade amylase | 9 | 10.0 (7.6 - 13.0) | 33% |
| Grade ≥ 3 amylase | 9 | 4.5 (1.9 - 10.5) | 76% |
| All grade lipase | 10 | 14.9 (10.7 - 20.5) | 72% |
| Grade ≥ 3 lipase | 10 | 10.2 (7.9 - 13.2) | 29% |
| All grade ALT | 12 | 20.6 (15.2 - 27.4) | 81% |
| Grade ≥ 3 ALT | 13 | 10.6 (7.5 - 14.8) | 67% |
| All grade AST | 12 | 18.7 (13.5 - 25.2) | 80% |
| Grade ≥ 3 AST | 13 | 8.2 (4.9 - 13.2) | 75% |
| All grade Bilirubin |  | - |  |
| Grade ≥ 3 Bilirubin |  | - |  |
| All grade ALP | 3 | 9.0 (5.9 - 13.4) | 0% |
| Grade ≥ 3 ALP | 3 | 1.0 (0.2 - 3.7) | 0% |
| All grade Liver related adverse events | 3 | 22.3 (13.7 - 34.1) | 79% |
| Grade ≥ 3 Liver related adverse events | 3 | 13.2 (8.6 - 19.6) | 53% |

Abbreviations: CI: confidence interval; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase

Supplementary Table 6: Pooled incidence of GI treatment related adverse events of Nivolumab 3 mg/kg plus ipilimumab 1mg/kg regimen

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Number of study arms | Pooled incidence (95% C.I.) | I2 |
| All grade colitis | 3 | 3.2 (2.3 - 4.6) | 0% |
| Grade ≥ 3 colitis | 3 | 2.1 (1.3 - 3.2) | 0% |
| All grade diarrhea | 16 | 22.0 (19.1 - 25.2) | 62% |
| Grade ≥ 3 diarrhea | 16 | 3.2 (2.6 - 4.0) | 0% |
| All grade amylase | 3 | 6.9 (4.0 - 11.5) | 46% |
| Grade ≥ 3 amylase | 3 | 2.0 (1.0 - 3.8) | 0% |
| All grade lipase | 11 | 9.6 (7.4 - 12.4) | 39% |
| Grade ≥ 3 lipase | 11 | 5.6(4.4 - 7.1) | 0% |
| All grade ALT | 12 | 10.4 (8.1 - 13.2) | 43% |
| Grade ≥ 3 ALT | 12 | 5.0 (3.9 - 6.3) | 0% |
| All grade AST | 12 | 10.1 (7.7 - 13.2) | 51% |
| Grade ≥ 3 AST | 12 | 4.7 (3.4 - 6.4) | 20% |
| All grade Bilirubin | - | - | - |
| Grade ≥ 3 Bilirubin | - | - | - |
| All grade ALP | - | - | - |
| Grade ≥ 3 ALP | - | - | - |
| All grade liver related adverse events | 3 | 27.5 (18.5 - 38.7) | 71% |
| Grade ≥ 3 liver related adverse events | 3 | 10.0 (6.9 - 14.2) | 0 |

Abbreviations: CI: confidence interval; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase

Supplementary Table 7: Toxicity characteristics, impact on therapy and interventions reported in the included trials

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author, year | Onset of toxicity | Duration of toxicity | Immunotherapy stopped/Delays | Intervention for Adverse Events |
| Amaria 2018 | N/A | N/A | Therapy interruption: 7/11(64%) | N/A |
| Antonia 2016 | N/A | N/A | N/A | N/A |
| Antonia 2016 | N/A | N/A | N/A | N/A |
| Baas, 2021 | N/A | N/A | Therapy stopped: 69/300(23%) | N/A |
| Boyer,2021 | N/A | N/A | Therapy stopped: 88/284(30.9%); Therapy interruption: 114/284 (40.1%) | N/A |
| Brastianos, 2021 | N/A | N/A | Therapy stopped: 2/18(11.11%)  AE: hepatitis and colitis in 1 patient each | N/A |
| Calabro, 2018 | N/A | N/A | Therapy stopped: 1/40 (0.025%)  AE: grade 4 liver toxicity | Steroids |
| Cascone, 2021 | N/A | N/A | N/A | N/A |
| Chen 2020 | N/A | N/A | N/A | N/A |
| Cohen 2020 | N/A | N/A | N/A | N/A |
| D'Angelo 2018 | N/A | N/A | Therapy stopped: 6/42(14%); Therapy interrupted: 35/42(83.3%) | N/A |
| Di Giacomo 2021 | N/A | N/A | N/A | N/A |
| Disselhorst 2019 | N/A | N/A | Therapy stopped: 1/38 (2.6%); Therapy interrupted: 2/38(5.2%), AE: colitis | Steroids |
| Edenfield 2021 | N/A | N/A | N/A | N/A |
| Ferrarotto, 2020 | N/A | N/A | N/A | N/A |
| Ferris, 2020 | N/A | N/A | Therapy stopped: 10/247(4.1%) | N/A |
| Gettinger 2021 | N/A | N/A | N/A | N/A |
| Gubens 2019 | N/A | N/A | Therapy stopped: 9/51(20%) | N/A |
| Hellmann 2019 | N/A | N/A | Therapy stopped: 48/391(12.3%) | N/A |
| Hodi 2016 | N/A | N/A | Therapy stopped: 35/142 (24.65%) | N/A |
| Hodi 2018 | N/A | N/A | Therapy stopped: 126/313(40%) | N/A |
| Janjigian 2018 | N/A | N/A | Therapy stopped: 10/49 (20%) | N/A |
| Janjigian 2018 | N/A | N/A | Therapy stopped: 7/52 (13%) | N/A |
| Kelley 2021 | N/A | N/A | Therapy stopped: 5/84 (6.1%) | N/A |
| Kelly 2020 | N/A | N/A | N/A | N/A |
| Kim 2020 | N/A | N/A | Therapy stopped: 1/18 (5.5%); AE: grade 3 amylase and grade 4 lipase elevation in a patient | N/A |
| Lebbe 2019 | Median time:  5.1-15.7 weeks | N/A | Therapy stopped: 43/180 (23.9%) | N/A |
| Lebbe 2019 | Median time: 2.4-9.1 weeks | N/A | Therapy stopped: 59/178 (33.1%) | N/A |
| Lenz, H-J 2021 | GI: 11.9 median, range (0.1-78.3) weeks; hepatic: 6.4 median, range (2.1-30.0) weeks | time to resolution: GI: 2.1 median, range (0.1-18.0) weeks: hepatic: 2.3 median, range (0.7-31.1) weeks | Therapy stopped: 1/45 (2%); AE: grade 3 diarrhea | Immunomodulators therapy: GI: 4/9 (44%), hepatic 1/5 (20%) |
| Long 2018 | N/A | N/A | Therapy stopped: 5/35 (14/2%);  AE: colitis | N/A |
| Long 2021 | N/A | N/A | N/A | N/A |
| Long 2021 | N/A | N/A | N/A |  |
| McGregor 2021 | N/A | N/A | N/A | N/A |
| Motzer, 2019 | within 30 days of last dose | N/A | Therapy stopped: 41/547 (7.49%): AE: diarrhoea (14/547; 2·6%); increased alanine aminotransferase (15/547; 2·7%); and increased aspartate aminotransferase (12/547; 2·2%) | Steroids |
| Namikawa, 2020 | N/A | N/A | Therapy stopped: 2/30 (6.66%) AE: grade 3 diarrhea | Symptomatic management |
| O'Reilly, 2019 | N/A | N/A | N/A | N/A |
| Overman 2018 | GI: median 9.1, range (0.3-41) weeks; hepatic: median 7, range (1-42) weeks | time to resolution: GI median 1.5, range (0.1-28) weeks; hepatic: median 5, range (0.3-66) weeks | Therapy stopped: 2/119 (2%) | Immunomodulators therapy: GI AE: 6/27 (22.2%) and Hepatic AE:10/22 (45.45%) |
| Owonikoko 2021 | N/A | N/A | Therapy stopped: 1/265 (0.4%) AE: colitis | N/A |
| Pakkala, 2020 | N/A | N/A | N/A | N/A |
| Patel 2020 | N/A | N/A | N/A | N/A |
| Patel 2021 | N/A | N/A | N/A | N/A |
| Pelster 2020 | N/A | N/A | Therapy stopped: 10/35(29%) | Steroids: 7/35 (20%) |
| Piulats 2021 | N/A | N/A | N/A | N/A |
| Planchard, 2020 | N/A | N/A | N/A | N/A |
| Powles 2020 | N/A | N/A | Therapy stopped: 80/340 (24%) | Steroids: 90/340(26%) |
| Ready, 2019 | N/A | N/A | N/A | N/A |
| Rizvi 2020 | N/A | N/A | N/A | N/A |
| Sarfaty 2021 | N/A | N/A | Therapy interrupted: 3/13 (23.0%) | Steroids: 2/13 (15.3%): lipase elevation and colitis;  Infliximab: 1/13 (7.6%): colitis |
| Sharma 2019 | GI: median 7.4, range (0.3-20.7) weeks, hepatic: median11.3, range (3.0-96.0) weeks | N/A | Therapy stopped: 15/104 (14.4%) | Immunomodulator: GI: 7/8 (87.5%); hepatic: 5/7 (71.4%) |
| Sharma 2019 | GI: median 7.9, range (1.6-53.1) weeks, hepatic: median 9.1, range (4.6-42.7) weeks | N/A | Therapy stopped: 13/78 (16.67%) | Immunomodulator: GI: 14/15 (93.3%); hepatic: 6/9 (66.7%) |
| Sharma 2020 | N/A | N/A | N/A | N/A |
| Singh 2021 | N/A | N/A | N/A | N/A |
| Siu 2019 | N/A | N/A | N/A | N/A |
| Tawbi 2021 | N/A | N/A | Therapy stopped: 19/95 (20%) | NA |
| Wagner 2021 | N/A | N/A | Therapy stopped: 1/16 (6.25%) AE: grade 3-liver toxicity | N/A |
| Yau 2020 (A) | Diarrhea/colitis: median 8.4, IQR (7.9-22.3) weeks; hepatitis: median 5.6, IQR (3.4-9.3) weeks | Time to resolution: Diarrhea/colitis: median 4.3, IQR (3.1-5.7) weeks; hepatitis: median 6.6, IQR (2.0-15.0) weeks | N/A | Steroids: hepatic 7/10 (70%) |
| Yau 2020 (B) | Diarrhea/Colitis: median 10.1, IQR (N/A) weeks; hepatitis: median 8.1, range (3-11) weeks | Time to resolution: Diarrhea/Colitis: 3.9 weeks, IQR N/A; hepatitis: median 7.9, IQR (6.7-10.9) weeks | N/A | Steroids: hepatic 3/6 (50%) |
| Yau 2020 (C) | Diarrhea/Colitis: median 24.6, IQR (N/A) weeks; hepatitis: median 5.9, IQR (3.6-8.6) weeks | time to resolution: Diarrhea/Colitis: 1.9 weeks, IQR N/A ; hepatitis: median 6.1, IQR (3.9-not evaluable) weeks | N/A | Steroids: hepatic 2/3 (66%) |
| Zamarin 2020 | N/A | N/A | N/A | N/A |
| Zimmer 2020 | GI: median 4, range (0-17) weeks; hepatic: median 6, range (2-38) weeks; Pancreatic: median 8; range (0 - 31) weeks | GI: median1.4, IQR (0-159.7) weeks; hepatic: median 11, IQR (0.7-166.9) weeks; pancreatic: median 5∙4, IQR (0∙4 - 167∙1) weeks | N/A | N/A |

Abbreviations; N/A: not available; GI: gastrointestinal; AE: adverse event