Supplementary Table 1 | **Selected** **Anti-CTLA-4/PD-1/PD-L1 and radiotherapy combination trials.** Study selection based on those which included >20 patients and which have reported response rates. Reference list independent from main text below.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Reference, Name, NCT (if abstract) | Population | Phase, design | N | Drug | RT | Toxicity | Response |
| (Hiniker, Reddy et al. 2016) 1 | Stage IV melanoma | I | 22 | Ipilimumab (IPI) 3 mg/kg q3w 4 cycles | Various, conventional and SBRT, BED10 28 – 112.5 Gy10 | 16/22 completed all IPI3 discontinued IPI due to AE no unexpected toxicity | 3 PR3 CR |
| (Twyman-Saint Victor, Rech et al. 2015) 2 | Metastatic melanoma | I,Dose-escalated SBRT | 22 | IPI 3 mg/kg q3w 4 cycles, start 3-5 days after SBRT completion | Lung or bone: 8 Gy x2-3Liver or s/c: 6 Gy x2-3Over 9-13 days (for 3 f) | 6 G3 toxicities 6, 8 Gy x2, 6 Gy x3; 4 G3 toxicities 8 Gy x3no G4 toxicity | 18% PRmedian OS 10.7 months |
| (Tang, Welsh et al. 2017) 3 | Advanced solid tumours | I,3+3cohorts depending on site and schedule | 35 | IPI 3 mg/kg q3w 4 cycles | SBRT C1D2 (“concomitant”) or C2D7 (“sequential”)50 Gy/4f or 60 Gy/10fSplit between lung and liver irradiation | 2 DLT: concurrent liver group and sequential liver group12/35 (34%) G3 toxicity, no G4 | Median OS 10.2 months10% out of field PR |
| (Maity, Mick et al. 2018) 4 | Advanced solid tumours, anti-PD-1 naïve; NSCLC or melanoma progressing on anti-PD-1  | I,Stratified into 2 groups by tumour type,2 cohorts by RT dose | 24 | Pembrolizumab (PEMBRO) 200 mg q3w 6 cycles | 8 Gy x317 Gy x1Start 1 week after first dose PEMBRO | 8 G3 AEs, not related to treatment | 2 PR in prior anti-PD-1 group1 CR in anti-PD-1 naïve group |
| (Luke, Lemons et al. 2018) 5 | Advanced solid tumours | I | 79 | PEMBRO 200mg q3w started within 7 days after final SBRT fraction, continue to PD or toxicity | SBRT to 2-4 metastases30-50 Gy in 3-5 fractions depending on site, alternate day.Partial irradiation if >65 cm3 | 6/73 DLT(9.7% of 62 patients with 6 month follow up) | ORR 13.2%Median OS 9.6 months |
| (Formenti, Rudqvist et al. 2018) 6 | Metastatic NSCLC | II | 39 | IPI 3 mg/kg 4 cycles | 6 Gy x59 Gy x3 | 21/39 (54%) received planned IPI | ORR 18%2 CR5 PR |
| (Antonia, Villegas et al. 2018), PACIFIC 7 | Stage III NSCLC post radical CRT | III, Placebo- controlled | 713 | Durvalumab (DURVA) 10mg/kg q2w vs. placebo | Majority (92%) 54-66 Gy | G3-4 AE: 30.5% treatment, 26.1% placeboDiscontinuation due to AE 15.4% treatment, 9.8% placebo | Prolonged OS, HR 0.68, 2y OS 66.3 vs. 55.6% |
| (Kwon, Drake et al. 2014), CA184-043 8 | Castrate-resistant prostate cancer, post-docetaxel, ≥ 1 bone metastasis  | III,Placebo- controlled | 799 | IPI 10 mg/kg vs. Placebo. 4 doses q3w ± maintenance. | 8 Gy /1f within 2 days of starting IPI. 1-5 fields | G3-4 AE: 59% IPI, 41% placebo. Discontinuation due to AE: 35% IPI, 16% placebo | OS (primary endpoint) not significant. PFS benefit, subgroups benefit. |
| (Slovin, Higano et al. 2013) 9 | Metastatic castrate-resistant prostate cancer | I-II, Open-labelDose escalation monotherapy, add radiotherapy | 71 | IPI 3 or 10 mg/kg, 4 doses q3w(+ further 3 if SD/PR) | 8 Gy /1f 24-48 h before starting IPI | G3-4 AE: 32%, GI and hepatitis. Discontinuation due to AE in 2/7 3mg/kg + RT; 8/34 10mg/kg + RT | 1/16 CR with IPI 10mg/kg alone1/28 CR with IPI 10mg/kg + RT |
| (Theelen, H.Peulen@Nki.Nl et al. 2018) NCT02492568. PEMBRO-RT 10 | Advanced NSCLC | II,Randomized PEMBRO ± SBRT | 74 | PEMBRO 200 mg q3w | 3 x 8 Gy within 7 days before starting PEMBRO | G≥3 toxicity in 22% control and 17% experimental | ORR 19% in PEMBRO alone, 41% PEMBRO + SBRT |
| (McBride, Sherman et al. 2018). NCT02684253 11 | Metastatic HNSCC (included nasopharynx) | II, Randomized Nivolumab ± SBRT. Stratified by HPV/EBV | 53 | Nivolumab (NIVO) 3 mg/kg q2w | 3 x 9 Gy between 1st and 2nd doses of NIVO | G≥3 toxicity 15% NIVO alone, 11% NIVO + SBRT | ORR 26.9% NIVO alone, 22.2% NIVO + SBRT |
| (Yoshino, Bando et al. 2019)VOLTAGE.NCT02948348. 12 | Locally-advanced rectal cancer | I-IIStratified by microsatellite status2-stage | 42 | NIVO 240 mg q2w for 3-5 cycles, prior to surgical resection | 50.4 Gy /28f with concomitant capecitabine, prior to NIVO start | 1x G2 interstitial nephritis1x G3 myasthenia. | 11/37 pCR in MSS2/2 pCR in MSI-H |
| (Johnson, Ad et al. 2019)NCT03162731. 13 | Locally-advanced HNSCC | I,2-stage | 24 | NIVO 3 mg/kg q2w x 17 dosesIPI 1 mg/kg q6w x 6 doses | 70 Gy /35f start 2 weeks after IPI/NIVO | No DLT or acute G4 tox.G3 in-field toxicity in 50%, irAE in 50%. At >3 months post-RT, 1 discontinued due to irAE (G3 colitis), 1 death: carotid rupture, no evidence malignancy. 1 G3 oropharyngeal ulcer | At 7.4- 18.4 months, 10/12 alive with no evidence of disease |
| (Parikh, Clark et al. 2019)NCT03104439. 14 | MSS metastatic colorectal adenocarcinoma | II,Open-label, single arm | 40 | IPI 1 mg/kg q6w, NIVO 240 mg q2w | 8 Gy x3 starting at cycle 2 IPI/NIVO | 50% G≥3 AEs1 G5 AE: respiratory failure, possibly related to treatment | ORR 7.5% |
| (Kelly, Smith et al. 2019) 15 | Stage II-III oesiohageal and oesophago-gastric cancers | I | 16 | NIVO 240 mg q2w2 cycles before concomitant chemoradiotherapy. Week 1, 3, 5 chemoradiotherapy | Concomitant radiotherapy with carboplatin + paclitaxel, followed by oesophagectomy | G≥3 AEs 2/16No delays of surgery | pCR rate 40% |
| (Sloan, Gilbert et al. 2018) NCT02311920. 16 | GBM | I,6 patients per group, expansion cohort | 32 | (i) NIVO 3 mg/kg(ii) IPI 3 mg/kg(iii) Combination IPI (1 mg/kg) NIVO (3 mg/kg), start after radical CRT, during maintenance temozolamide | Radical chemoradiotherapy | 16% G4 toxicity1/6 DLT in each single-agent arm | Similar survival between arms |
| (Hong, Kim et al. 2019)NCT02844075. 17 | Stage Ib-III oesophageal squamous cell carcinoma | II,Single arm | 28 | PEMBRO 200 mg q3w for 5 weeks concomitant with CRT. After surgery, 2 years’ PEMBRO | Radical chemoradiotherapy 44.1 Gy /21f with weekly carboplatin and paclitaxel, followed by surgery | 26/28 received surgery3 deaths: haematemesis (1), acute lung injury (2)50% neutropenia, 31% liver enzyme elevation, not graded | 46.1% pCR in those who had surgery. 12 month OS: 82.1% |
| (Jabbour, Berman et al. 2019)NCT02621398. 18 | Locally-advanced NSCLC (stage III) | I, 3+3 | 23 | PEMBRO 100-200 mg. Initial cohorts: started post-CRT, later cohorts: concomitant with CRT. Q3w up to 18 cycles | Radical CRT 60 Gy /30f with concomitant weekly carboplatin and paclitaxel | No DLT (G4 pneumonitis within 21d of first dose).G≥3 irAE: 4/23 (18%). 1 G5 pneumonitis, 1 G3. | Median PFS for those who received ≥2 doses PEMBRO: 20.3 mo |
| (Welsh, Menon et al. 2019)NCT02444741 19 | Metastatic NSCLC | I-II,Randomized: PEMBRO ± RT | 103 | PEMBRO 200mg q3w up to 16 cycles | Lung radiotherapy:SBRT (n = 16) 50 Gy /4f or 70 Gy/10fConventional RT (n = 20) 45 Gy /15f | PEMBRO alone: 5 G3 toxicitiesPEMBRO + RT: 2 G4, 9 G3 | Out of field response: 22% PEMBRO + RT (SBRT: 38%, conventional RT 10%); 25 % PEMBRO alone |
| (Durm, Althouse et al. 2018)LUN14-179NCT02343952 20 | Unresectable stage III NSCLC | II, Single-arm | 93 | PEMBRO 200 mg q3w for up to 1 year, in patients without PD 4-8 weeks following CRT | CRT 59-66.6 Gy with concomitant carboplatin/paclitaxel, cisplatin/etoposide or cisplatin/pemetrexed | 84% received ≥ 4 cycles PEMBRO37% completed 1 year PEMBRO5 patients (5.4%) G≥3 pneumonitis. 1 G5 pneumonitis. | Median PFS 15.4 months1y OS 80.%, 2y OS 68.7% |
| (Campbell, Herbst et al. 2018)NCT02407171 21 | Metastatic NSCLC or melanoma | I-II,RT dose escalation; lung vs. non-lung irradiation | 24 | Immunotherapy naïve: PEMBRO 200 mg q3w until progression then SBRT. All patients: PEMBRO 200 mg q3w to progression | At progression on anti-PD-1 therapy: SBRT 30 Gy /5f, escalating to 30 Gy /3fStratified by site of irradiation (lung/ non-lung) | No DLTG≥3 AE: 3 irAEs, 2 G3 pneumonitis in lung RT. | Mean 19.8 (range 0-52) weeks PEMBRO post SBRT. |
| (van den Ende, de Clercq et al. 2019)PERFECTNCT03087864 22 | Resectable oesophageal adenocarcinoma | II,Single-arm | 39 | Atezolizumab (ATEZO) 1200 mg q3w | CRT 41.4 Gy /23fConcomitant carboplatin and paclitaxel | All CRT administered in 29/31 patientsAll ATEZO in 26/31G≥3 AE in 15/31irAE in 6/31 | pCR 9/23 (39%) |
| (Lin, Lin et al. 2019)DETERREDNCT02525757 23 | Locally-advanced NSCLC | II, 2-stage | 40 | Part 1: ATEZO 1200 mg q3w with adjuvant carboplatin-paclitaxel post CRTPart 2: concomitant ATEZO with carboplatin-paclitaxel then maintenance ATEZO | 60-66 Gy in 30-33 f | Concomitant (n =30): radiation pneumonitis 1 G3, 2 G2; 7 SAE related to ATEZO | Concomitant: 1y OS 70%. No significant difference by PD-L1 status |
| (Reardon, Kaley et al. 2019)NCT02336165 24 | MGMT-unmethylated glioblastoma | II, | 40 | Concomitant DURVA 10 mg/kg q2w | 60 Gy /30f after maximal safe resection | G≥3 AE in 14 (35%). | 12 month OS 60%, median OS 15.1 months |
| (Brar, Xie et al. 2019)NCT02311361 25 | Advanced pancreatic adenocarcinoma | I-II, | 51 | DURVA 1500 mg q4w ± tremelimumab 75 mg q4w | SBRT: 8Gy on day 1 DURVA ± treme or 5 Gy x5 followed by DURVA ± treme | No DLTG≥3 AE: lymphopenia, anaemia | 1 PR (DURVA concomitant with 8 Gy)2 PR (5 Gy x5 followed by DURVA + treme).ORR: 9.6% |
| (Mortier, Jamme et al. 2018)NCT02662725 26 | Metastatic melanoma with brain metastases | II,Single-arm | 57 | IPI 10 mg/kg q3w x4 then q12w to progression/toxicity | Dose not stated, SRS 3 days before 2nd dose IPI | Grades not stated:colitis (10.5%), hepatitis (10.5%), hypophysitis (8.77%) and headache (8.77%). 1 radionecrosis. | 49% disease controlmean OS 13.2 months |
| (Lopez-Martin, Arance et al. 2018)NCT02115139 27 | Metastatic melanoma with brain metastases, not SRS candidate | II,Single-arm | 58 | IPI 3 mg/kg q3w 4 cycles | Whole brain RT 30 Gy /10f | 55 completed RT31 completed IPITreatment-related SAE: 11 patients (19%), 10 expected IPI-related, 1 RT-related (headache and vomiting) | Median OS 5.8 months1y OS 31.8% |

Included: prospective interventional studies whose results have been reported in abstract or peer-reviewed form. Included adjuvant studies where IO treatment was given immediately after (Chemo)RT but not if after surgery (regardless of whether neoadjuvant (Chemo)RT was given). Only those with response data, >20 patients. AE: adverse event; ATEZO, atezolizumab; BED10: biologically equivalent dose for alpha/ß ratio of 10; CR: complete response; CRT: chemoradiotherapy; DLT: dose-limiting toxicity; DURVA, durvalumab; f: fractions; G: grade; GI: gastrointestinal; GTV: gross tumour volume; HNSCC: head and neck squamous cell carcinoma; HPV: human papillomavirus; HR: hazard ratio; HR+: hormone receptor-positive; IC: intracranial; IMRT: intensity-modulated radiotherapy; IPI, ipilimumab; irAE: immune-related adverse event; MSI-H: microsatellite instability high; MSS: microsatellite stable; NIVO, nivolumab; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; pCR: pathological complete response; PD: progressive disease; PEMBRO, pembrolizumab; PR: partial response; RCC: renal cell carcinoma; SAE: serious adverse event; SBRT: stereotactic body radiotherapy; SD: stable disease; SRS: stereotactic radiosurgery; WBRT: whole-brain radiotherapy.

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