Table SI. Selected studies representing NETs (n=22). Summary of the included studies, detailing sample size, patient demographics, tumour type, treatment regimen, treatment duration, key findings, survival outcomes (PFS and OS), and principal study limitations.

First author (year)	Number of patients	Median age, years (min., max. or range)	Male, %	PICO framework	Tumour		Treatment		Key findings	Survival rates	Limitations	(Refs.)
					Site	Type	Type	Duration				
Patel (2020)	32	60.5 (36, 81)	59%	*Population:* Patients with NETs that had at least one line of standard systemic therapy *Intervention:* Dual checkpoint inhibitors (DCI)-NIVO and IPI *Comparison:* With standard treatment *Outcome:* Determine the PFS and OS	Gastrointestinal; lung	56% with high-grade carcinoma	IPI plus NIVO	NIVO 240 mg IV every 2 weeks and IPI 1 mg/kg IV every 6 weeks on a continuous schedule	Improved PFS and OS with dual blockade; manageable toxicity profile	Median OS was 11 months, 95% confidence interval (6,∞), 16 adverse events for tumours grade 3-5	Small sample size; limited generalizability	(41)
Marabelle (2019)	233	60 (20, 87)	41.2%	*Population:* Patients with incurable non-colorectal solid tumours with disease progression on/or intolerance to prior standard therapy *Intervention:* Pembrolizumab *Comparison:* None *Outcome*: Determine the PFS and OS	Non-colorectal cancer (endometrial, gastric, cholangiocarcinoma, pancreatic, small intestine, ovarian, brain)	Disease stage: MX (0.4%); M0 (4.3%); M1 (91%); Unknown (4.3%)	Anti-programmed death-1 therapy with pembrolizumab	Pembrolizumab 200 mg once every three weeks for 35 cycles, approximately two years	In most tumour types, there were reductions in target lesion diameters (with almost 50% of the patients having experienced 30% or greater reductions from baseline). Patients with endometrial cancer had particularly positive outcomes,	The median PFS was 4.1 months, and the median OS was 23.5 months; data are not available for the number of deaths	63.8% of patients had treatment-related adverse events; no control group; possible selection bias as this is a 23 multicentre study	(42)

									with 70% experiencing a tumour size reduction of 30% or more			
Tawbi (2022)	714	63.0 (20-94)	59.3%	*Population:* Adults with advanced melanoma *Intervention:* Dual therapy: Relatlimab and NIVO *Comparison:* NIVO alone *Outcome:* Determine the PFS	Skin	Unresectable stage III or IV melanoma	Relatlimab and NIVO	5.6 months with Relatlimab-NIVO and 4.9 months with NIVO	Significant improvement in PFS with dual therapy as compared to single therapy	The median PFS was 10.1 months (dual therapy) vs. 4.6 months (NIVO); OS data not available: 3 deaths in the dual therapy group and two deaths in the NIVO group	High cost of treatment; limited long-term data available	(43)
Puca (2019)	228 (only the IHC group)	Not available	100%	*Population*: Patients with neuroendocrine prostate cancer *Intervention*: Targeted therapy based on DLL3-rovalpituzumab tesirine *Comparison*: Conventional therapy	Prostate	Benign prostate tissue; prostate adenocarcinoma; castration-resistant prostate adenocarcinoma; high-grade prostate cancer with neuroendocrine differentiation; small cell carcinoma	Rovalpituzumab tesirine	Continuous until progression or unacceptable toxicity	Promising efficacy in targeting DLL3; potential new treatment avenue	DLL3 expression was associated with worse OS compared to DLL3-negative cases (35 months vs. 81.5	Early-phase trial	(44)

				Outcome: Whether DLL3 expression is associated with the CRPC-NE phenotype in prostate cancer and to evaluate the antitumour activity of SC16LD6.5 in DLL3-expressing prostate cancer models						months); no data available for PFS and number of deaths		
Larkin (2019)	945	61 (18-88)	66%	*Population*: Adults with advanced melanoma *Intervention*: DCI-NIVO and IPI *Comparison:* Monotherapy with NIVO or IPI *Outcome:* Determine the OS	Skin	Stage III or stage IV melanoma, with known BRAF V600 mutation status	NIVO and IPI	Five years	DCI improved 5-year survival rates compared to monotherapy	In the DCI group, the median OS was 60.0 months, the median PFS 11.5 months and there were 53 deaths; in the NIVO group, the median OS was 36.9 months, the median PFS 6.9 months, and there were 45 deaths; compared with 19.9	High toxicity rates; high cost	(45)

										months, 2.9 months and 57 deaths respectively in the IPI group		
Jonasch (2021)	61	41 (19-66)	52%	*Population*: Adults with VHL-associated renal cell carcinoma *Intervention*: Belzutifan *Comparison*: Standard treatment *Outcome*: Determine tumour shrinkage and PFS rate	Kidney	Renal cell carcinoma (von Hippel-Lindau disease) tumour ≥10 mm in the longest diameter	Belzutifan	120 mg administered orally per day until progression or unacceptable toxicity	Belzutifan showed significant efficacy in reducing tumour size and delaying progression	Median OS was not reached; no data was available for PFS; 1 patient died, but it was considered to be unrelated to the trial drug	Limited to patients with von Hippel-Lindau disease	(46)
Morizane (2022)	170	64 (29-75)	68.8%	*Population*: Adults with neuroendocrine carcinoma *Intervention*: Etoposide and Cisplatin vs. Irinotecan and Cisplatin *Comparison*: Treatment regimens *Outcome*: Determine the OS and treatment response	Various (including lung, GI tract)	Advanced neuroendocrine carcinoma of the digestive system	Etoposide and Cisplatin vs. Irinotecan and Cisplatin	In the EP arm, etoposide was administered every three weeks; in the IP arm, irinotecan was administered every four weeks	Both EP and IP therapy remain standard first-line chemotherapy options. No significant difference in overall survival between the two regimens, but different side effect profiles	The median OS was 12.5 months in the EP arm vs. 10.9 months in the IP arm. The 1-year survival was 52.1% in the EP arm and 41.8% in the IP arm	Retrospective design; potential for bias	(47)

Amaria (2018)	23	55 (34-73)	75%	*Population*: Adults with high-risk melanoma *Intervention*: Neoadjuvant immune checkpoint blockade *Comparison*: Adjuvant therapy *Outcome*: Recurrence-free survival, OS	Skin	Clinical stage IIIB or IIIC of high-risk melanoma	Neoadjuvant immune checkpoint blockade	Median of 15.0 months in the NIVO monotherapy arm and 15.6 months in the combination therapy arm	Neoadjuvant therapy led to higher rates of recurrence-free survival compared to adjuvant therapy	2-year OS 15.6 months	Small sample size; single-centre study	(48)
Motzer (2022)	1,096	64.6	73.7%	*Population:* Patients with untreated advanced renal cell carcinoma *Intervention:* NIVO plus IPI; NIVO or SUN *Comparison:* SUN *Outcome:* OS and PFS	Kidney	Advanced renal cell carcinoma	NIVO, then patients were separated into two groups, first group continued treatment with NIVO as monotherapy, second group changed to SUN	NIVO (3 mg/kg) plus IPI (1 mg/kg) every three weeks for four cycles, then either NIVO monotherapy or SUN (50 mg) daily (four 6-week cycles)	Durable clinical benefits were observed with NIVO + IPI versus SUN at five years, the most extended phase 3 follow-up for a first-line checkpoint inhibitor-based combination in patients with aRCC. Conditional estimates indicate that most patients who remained alive or in response to NIVO + IPI at 3 years remained so at 5 years	OS median, 55.7 vs. 38.4 months; PFS median, 12.3 vs. 12.3 months; and objective response, 39.3 vs. 32.4%. (n=550 vs. 546)	Imbalances in clinical characteristics for survivors, potentially affecting outcomes	(49)
Ott (2020)	82	60	68%	*Population*: Patients with unresectable or metastatic	Various (including NETs, melanoma)	Multiple solid tumours	Combination of immunotherapy and vaccine	12 months	The personalized neoantigen vaccine Neo-PV-01 plus	The median OS for vaccinated	Single-arm design; no NIVO	(50)

				melanoma, smoking-associated NSCLC, and TCC of the bladder *Intervention*: NEO-PV-01 and NIVO *Comparison*: Vaccinated vs. unvaccinated patients *Outcome*: To evaluate the safety and tolerability of NEO-PV-01 in combination with NIVO					NIVO is feasible and safe. NEO-PV-01 plus NIVO stimulates durable neoantigen-specific T-cell reactivity. NEO-PV-01-specific T cells have cytotoxic potential NEO-PV-01 induces epitope spreading consistent with vaccine-mediated tumour cytotoxicity	patients was not reached in the melanoma and NSCLC cohorts, while the median OS for the bladder cancer cohort was 20.7 months. The 1-year OS rates for melanoma, NSCLC and bladder cancer patients were 96, 83 and 67%, respectively	monotherapy comparison cohort, significant pathologic responses observed after vaccination cannot definitively be linked to the vaccine	
Dummer (2020)	870	50 (18-89)	56%	*Population*: Patients with resected stage III melanoma with BRAF V600E or V600K mutations *Intervention*: Dabrafenib plus trametinib *Comparison*: With placebo	Skin	Resected stage III melanoma with BRAF V600E or V600K mutations	Oral dabrafenib (at a dose of 150 mg twice daily) plus trametinib (2 mg once daily) or two matched placebos	12 months	Dabrafenib plus trametinib improved OS compared to standard therapy. At five years, 52% of patients on dabrafenib plus trametinib were alive without relapse and 65% without	OS was not analysed since the required number of events to trigger the final OS analysis had	OS rate may be affected by the 47% of patients who also received anticancer therapy. Updated safety analyses were not performed	(51)

				Outcome: To evaluate relapse-free survival					distant metastasis, as compared with 36% with placebo treatment and 54% without distant metastasis	not been reached	at this data cutoff because no patients continued to receive therapy during the extended follow-up period, and reporting treatment-related adverse events after that point was at the investigator's discretion	
Eggermont (2018)	45	66 (50-86)	56%	*Population*: Patients with extensive-stage SCLC *Intervention*: Pembrolizumab *Comparison*: Chemotherapy *Outcome*: Overall survival, progression-free survival	Lung	SCLC	Pembrolizumab	Pembrolizumab 200 mg intravenously every three weeks was initiated within eight weeks of the last cycle of chemotherapy for two years	Pembrolizumab improved overall survival compared to chemotherapy alone	The median PFS was 1.4 months, with a 1-year PFS of 13%. The median OS was 9.6 months, with a 1-year OS of 37%	A single-arm study cannot determine whether a biomarker has prognostic or predictive utility; none of the observed differences were statistically significant	(52)
Taylor (2020)	137	65 (31-87)	61%	*Population:* Patients with progressive NETs *Intervention:*	Various (including pancreas, GI tract)	Metastatic renal cell carcinoma, endometrial cancer, squamous cell	Lenvatinib plus pembrolizumab	200 mg intravenously every three weeks	Lenvatinib plus pembrolizumab demonstrated a manageable safety	ORR week 24 was as follows: RCC, 63%;	Small sample size, a heterogeneous patient	(53)

				Lenvatinib plus Pembrolizumab *Comparison:* None *Outcome:* PFR, OS		carcinoma of the head and neck, melanoma, non-non-small-cell lung cancer, or urothelial cancer			profile and promising antitumour activity in patients with selected solid tumour types	endometrial cancer, 52%; melanoma, 48%; SCCHN, 36%; NSCLC, 33%; and urothelial cancer, 25%	population that was not randomly assigned, and the lack of a comparator treatment arm	
Olson (2021)	70	64 (27-87)	67%	*Population:* Patients with advanced melanoma who had progressed on anti-PD-1/L1 antibody as immediate prior therapy *Intervention:* Pembrolizumab plus low-dose IPI *Comparison:* With placebo *Outcome:* To determine the ORR of pembrolizumab with low-dose IPI following initial progression on an anti-PD-1/L1 antibody	Skin	Advanced melanoma	Pembrolizumab 200 mg plus IPI 1 mg/kg once every three weeks for four doses, followed by pembrolizumab monotherapy once every three weeks	Two years	Pembrolizumab plus low-dose IPI after anti-PD-1/L1 immunotherapy failure demonstrates significant antitumour activity and tolerability	The median PFS was 5.0 months, and the median OS was 24.7 months	There is no formal consensus to define progression on an anti-PD-1/L1 antibody as it exists currently	(54)
Chauhan (2018)	56	62	50%	*Population:* Patients with advanced NETs	Pancreas, small bowel, lung, rectum	NETs	CAPTEM	1,500 mg/m^2 Capecitabine was	CAPTEM regimen showed efficacy in	Median PFS on CAPTEM	Small sample size, missing data, and a	(55)

				Intervention: CAPTEM *Comparison:* Other chemotherapy regimens *Outcome*: OS, PFS				administered continuously from days 1 to 14 daily in two divided doses. Temozolomide was administered on days 10-14 in two divided doses	treating advanced NETs	in grade II and grade III NET of unknown primary was 10.8 and 7 months, respectively	nonrandomized patient population	
Topalian (2020)	39	68 (22, 88)	64.1%	*Population:* Patients with stage IIA-IV resectable MCC *Intervention:* 1 NIVO dose *Comparison:* Placebo *Outcome:* To evaluate the safety and potential efficacy of NIVO (anti-programmed death-1)	Skin	Merkel cell carcinoma	NIVO	Patients received NIVO 240 mg intravenously on days 1 and 15 and underwent surgery on day 29 (±7 days)	NIVO administered approximately four weeks before surgery in MCC was generally tolerable and induced pCRs and radiographic tumour regressions in approximately one-half of treated patients	Thirty-nine treated patients did not reach median OS; at 12 and 24 months after the first NIVO dose, OS rates were 93.2 and 79.4%, respectively	Relapses occurred among patients with non-pCR/MPR, suggesting that a period of postoperative anti-PD-1 may be appropriate only for some	(56)
Pavel (2024)	57	65.0 (39-82)	57.9%	*Population:* Adults with advanced NETs *Intervention:* LAN plus TMZ *Comparison:* Placebo or other systemic therapy	Pancreatic, Small intestinal, colorectal	NETs	LAN plus TMZ	LAN 120 mg/4 weeks with TMZ for the first six months. TMZ was administered for five	LAN plus TMZ is a treatment option for patients with progressive GEP-NET with a more aggressive biological profile showing a	At 12 months of follow-up, median PFS was 11.1 months	Small sample size; lack of randomization into the combination vs. monotherapy of TMZ	(57)

				Outcome: Tumour response rate, PFS				consecutive days every 28 days at 150 mg/m^2/day for one month, then increased to 200 mg/m^2/day	manageable safety profile		treatment; subgroup analyses resulted in small patient numbers, and hence, these data may only be interpreted as explorative	
Leidner (2023)	83	63 (28, 85)	56.6%	*Population*: Patients with advanced solid tumours *Intervention:* Monotherapy with single-agent NIZ985 *Comparison*: With NIZ985 TIW or QW plus spartalizumab *Outcome*: To assess the safety and tolerability of single-agent NIZ985 and NIZ985/natalizumab and to establish the maximum tolerated doses	Colon, pancreas, kidney, ovary, skin melanoma, bone, breast, eye, head and neck, liver, parotid gland, prostate, soft tissue, testis, thyroid	Advanced solid NETs	Monotherapy or combination	Single-agent NIZ985 administered subcutaneously twice weekly, two weeks on/2 weeks off, or once weekly, and NIZ985 TIW or QW administered subcutaneously plus spartalizumab (400 mg intravenously every four weeks)	NIZ985 was well tolerated in the single-agent and NIZ985/natalizumab regimens. The RDE was established at 1 µg/kg TIW. The combination's antitumour activity was observed against tumour types known to have a poor response to ICIs	Median PFS was 1.9 months in the PD-1-sensitive cohort and 1.6 months in the PD-1-resistant cohort	The study was limited only to solid tumours, not haematological malignancies. Also, more research is needed to reach stage conclusions	(58)
Reidy-Lagunes (2019)	20	57.5 (22-73)	50%	*Population*: Patients with advanced SSTR2 positive NETs	Lung, small bowel, pancreatic, gastric, rectal, kidney	NETs	Lu-satoreotide tetraxetan	Three months each cycle	Lu-satoreotide tetraxetan can deliver high radiation doses to NETs with favourable tumour-	Median PFS was 21.0 months; two-year OS was	The initial treatment schedule of this trial was associated with more severe	(59)

				Intervention: Lu-satoreotide tetraxetan *Comparison*: Placebo *Outcome*: Progression-free survival, overall survival					to-normal organ dose ratios. Preliminary data on tumour response rates and PFS are encouraging and support a potential therapeutic role for radiolabeled somatostatin antagonists in treating NETs	85%, and three-year OS was 63%	hepatotoxicity than expected from SSTR2 agonists at the same or higher red marrow dose; extensive delay in treating a subgroup of patients with the second therapeutic dose, small sample size	
Iyer (2020)	32	65 (45-77)	53%	*Population:* Patients with advanced, grade 1-2 non-pancreatic NETs on a stable dose of somatostatin analogue *Intervention*: Nintedanib *Comparison*: Placebo *Outcome:* To determine the antitumour efficacy of nintedanib	Gastrointestinal tract	Non-functional gastroenteropancreatic NETs	Nintedanib	Dose of 200 mg twice daily in 28-day cycles; treatment was continued until disease progression, unacceptable toxicity	Nintedanib, in combination with octreotide LAR, showed activity in patients with advanced, pretreated, non-pancreatic NETs and had a manageable toxicity profile	The median PFS and OS were 11.0 months and 32.7 months, respectively	The authors cannot exclude any confounding effect of prior everolimus use. The small sample size and the number of patients with prior everolimus use preclude any meaningful comparisons	(60)

Rinke (2021)	79	65.7 (62.9-68.5)	54.4%	*Population:* Patients with neuroendocrine tumours *Intervention:* LAN *Comparison*: Single-agent checkpoint inhibition *Outcome:* To evaluate the long-term treatment response in patients with neuroendocrine tumours	Intestine, pancreas	NETs	45.6% of patients were administered LAN at a starting dose of 60 mg, 26.6% at a dose of 90 mg and 27.8% at a dose of 120 mg	Every four weeks for 24 months	Dual checkpoint inhibition showed enhanced efficacy compared to single-agent therapy	Overall tolerability of treatment was judged as 'very good' or 'good' by 94.6% at month 12 and by 83.3% of patients at month 24	The treating physician made all decisions concerning diagnosis and treatment; the high dropout rate was mainly due to the decreasing efficacy of treatment	(61)
Singh, 2024	226	61 (51-70)	54%	*Population:* Adults ≥15 years, newly diagnosed advanced grade 2-3, well-differentiated, SSTR+ GEP-NETs *Intervention:* (^{177}Lu)Lu-DOTA-TATE + octreotide 30 mg LAR; *Comparison*: High-dose octreotide 60 mg LAR; *Outcome:* PFS (primary), ORR, OS, QoL, safety	Pancreas 54%, small intestine 29%, rectum 5%, stomach 4%, other 7%	Grade 2 (65%), Grade 3 (35%), well-differentiated	Arm A: ^{177}Lu-Dotatate IV q8w x4 cycles + octreotide 30 mg LAR; Arm B: octreotide 60 mg LAR q4w	Median exposure 71.1 weeks (Lu-Dotatate) vs. 40.3 weeks (control); 88% completed all 4 cycles	Median PFS 22.8 months vs. 8.5 months (HR 0.28, P<0.0001); ORR 43% vs. 9%; durable responses (median DoR 23.3 months); QoL maintained; manageable safety (grade ≥3 AEs 35% vs. 27%); 1 case of MDS	OS not yet mature; 6-months PFS 78% vs 59%; high DCR 90.7% vs. 66.7%	Open-label design; central pathology not mandated (local Ki67); crossover from control to Lu-Dotatate confounded OS; immature OS; limited adolescent inclusion	(62)

SCLC, small cell lung cancer; NIVO, nivolumab; SUN, sunitinib; IPI, ipilimumab; IHC, immunohistochemistry; DLL3, delta-like protein 3; CRPC-NE, castration-resistant prostate cancer with neuroendocrine differentiation; DCI, dual checkpoint inhibition; VHL, Von Hippel-Lindau; EP, etoposide plus cisplatin; IP, irinotecan plus cisplatin; TCC, transitional cell carcinoma; SCLC, small cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck;

GI, gastrointestinal; CAPTEM, capecitabine and temozolomide; MCC, Merkel cell carcinoma; LAN, lanreotide; TMZ, temozolomide; GEP-NET, gastroenteropancreatic neuroendocrine tumour; SSTR2, somatostatin receptor type 2; LAR, long-acting release; LAN lanreotide autogel; OS, overall survival; PFS, progression-free survival; DCR, disease control rate; ORR, objective response rate; QoL, quality of life.