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SUPPLEMENTARY INFORMATION

Supplementary Table S1 | **Pivotal clinical trials investigating ICB in various tumour settings**

Disease	Treatment (target)	Results	FDA approval status	Reference
Histology agnostic				
Progressive metastatic CRC and other cancers (dMMR or non-MMR)	Pembrolizumab (PD-1)	• dMMR CRC: ORR 40%; PFS 78% • Non-dMMR CRC: ORR 0%; PFS 11% • dMMR non-CRC: ORR 71%; PFS 67%	Approved in May 2017 (accelerated approval; trial ongoing) for adult and paediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumours that have progressed after prior treatment (and for which no satisfactory alternative treatments remain), independent of the tumour's original location. The pivotal data for approval included patients from the KEYNOTE-016 (*n* = 58), KEYNOTE-164 (*n* = 61), KEYNOTE-012 (*n* = 6), KEYNOTE-028 (*n* = 5), and KEYNOTE-158 (*n* = 19) trials. Pembrolizumab was administered at 200 mg every 3 weeks or 10 mg/kg every 2 weeks until disease progression, unacceptable toxicity, or for a maximum of 24 mo.	S1
Advanced-stage dMMR cancers (12 different tumour types)	Pembrolizumab	ORR 53%; CR rate 21%; 2-year PFS 53%; 2-year OS 64%		S2
Unresectable or metastatic MSI-H or dMMR solid tumours	Pembrolizumab	• ORR 39.6%; responses lasted >6 mo. for 78% • ORRs similar for CRC (36%) and other cancer types (46%)		S3
Melanoma				
Unresectable or metastatic melanoma	Ipilimumab (CTLA-4) plus dacarbazine vs dacarbazine plus placebo	Median OS 11.2 mo. vs 9.1 mo.; 1-year OS 47.3% vs 36.3%; 2-year OS 28.5% vs 17.9%; 3-year OS 20.8% vs 12.2%	Approved in March 2011 for unresectable or metastatic melanoma; expanded to paediatric patients aged ≥12 years in July 2017	S4
Unresectable or metastatic *BRAF*-wild-type melanoma	Nivolumab (PD-1) plus placebo vs dacarbazine plus placebo	Median PFS 5.1 mo. vs 2.2 mo.; 1-year OS 72.9% vs 42.1%	Accelerated approval in December 2014 for unresectable or metastatic melanoma after ipilimumab or BRAF-targeted therapy, and in combination with ipilimumab for $BRAF^{V600}$-wild-type tumours in October 2015 and independent of *BRAF* status in January 2016	S5
Unresectable or metastatic melanoma	Nivolumab vs chemotherapy (dacarbazine or paclitaxel plus carboplatin)	ORR 31.7% vs 10.6%	Accelerated approval in December 2014 for unresectable or metastatic melanoma after ipilimumab or BRAF-targeted therapy, and in combination with ipilimumab for $BRAF^{V600}$-wild-type tumours in October 2015, and independent of *BRAF* status in January 2016	S6
Resected stage III or IV melanoma	Ipilimumab vs placebo	Median RFS 26.1 mo. vs 17.1 mo.; 3-year RFS 46.5% vs 34.8%	Approved October 2015 for the adjuvant treatment of stage III melanoma (pathologic involvement of regional lymph nodes >1 mm)	S7
Unresectable or metastatic melanoma	Pembrolizumab every 2 weeks vs pembrolizumab every 3 weeks vs ipilimumab	ORR 33.7% vs 32.9% vs 11.9%; 6-mo. PFS 47.3% vs 46.4% vs 26.5%; 1-year OS 74.1% vs 68.4% vs 58.2%	Accelerated approval in September 2014 for unresectable or metastatic melanoma after ipilimumab or BRAF-targeted therapy 3-weekly schedule); approved as initial treatment in December 2015	S8
Unresectable or metastatic melanoma	Nivolumab plus ipilimumab vs ipilimumab plus placebo	ORR 61% vs 11%; median DoR not reached; median PFS not reached	Accelerated approval in December 2014 for unresectable or metastatic melanoma after ipilimumab or BRAF-targeted therapy, and in combination with ipilimumab for $BRAF^{V600}$-wild-type tumours in October 2015, and independent of *BRAF* status in January 2016	S9
Unresectable or metastatic melanoma	Nivolumab plus ipilimumab vs nivolumab vs ipilimumab	ITT: median PFS 11.5 mo. vs 2.9 mo. vs 6.9 mo.; median OS not reached vs 37.6 mo. vs 19.9 mo.; 3-year OS 58% vs 52% vs 34%	Accelerated approval in December 2014 for unresectable or metastatic melanoma after ipilimumab or BRAF-targeted therapy, and in combination with ipilimumab for $BRAF^{V600}$-wild-type tumours in October 2015, and independent of *BRAF* status in January 2016	S10

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Unresectable or metastatic melanoma	Ipilimumab 10 mg/kg vs 3 mg/kg	Median OS 15.7 m vs 11.5 m	Approved in March 2011 for unresectable or metastatic melanoma; expanded to paediatric patients aged ≥12 years in July 2017	S11
Resected stage III or IV melanoma	Nivolumab vs ipilimumab	12-month RFS: 70.5% vs 60.8%	Approved in December 2017 for the adjuvant treatment of lymph node-positive or metastatic melanoma	S12
Lung cancer				
Advanced-stage squamous-cell NSCLC	Nivolumab vs docetaxel	ORR 20% vs 9%; median PFS 3.5 mo. vs 2.8 mo.; median OS 9.2 mo. vs 6.0 mo.; 1-year OS 42% vs 24%	Approved in March 2015 for advanced-stage squamous-cell NSCLC that has progressed on or after platinum-based chemotherapy	S13
Advanced-stage non-squamous-cell NSCLC	Nivolumab vs docetaxel	ORR 19% vs 12%; median OS 12.2 mo. vs 9.4 mo.; 1-year OS 51% vs 39%; 18-mo. OS 39% vs 23%	Approval expanded in October 2015 to include advanced-stage non-squamous NSCLC that has progressed on or after platinum-based chemotherapy	S14
Advanced-stage NSCLC	Pembrolizumab 2mg/kg vs pembrolizumab 10mg/kg vs docetaxel	• ITT: median PFS 3.9 mo. vs 4.0 mo. vs 4.0 mo.; median OS 10.4 mo. vs 12.7 mo. vs 8.5 mo. • PD-L1$^+$ tumours (≥50% positivity): median PFS 5.0 mo. vs 5.2 mo. vs 4.1 mo.; median OS 14.9 mo. vs 17.3 mo. vs 8.2 mo.	Approved in October 2015 for advanced-stage PD-L1$^+$ NSCLC (≥50% positivity) that has progressed on or after platinum-based chemotherapy; approval expanded to tumours with ≥1% PD-L1 positivity in October 2016	S15
Advanced-stage, *EGFR*/*ALK*-wild-type, PD-L1$^+$ NSCLC	Pembrolizumab (200 mg fixed dose every 3 weeks) vs platinum-based chemotherapy	ORR 44.8% vs 27.8%; median DoR not reached vs 6.3 mo.; median PFS 10.3 mo. vs 6 mo.; 6-months OS 80.2% vs 72.4%	Approved in October 2016 for the first-line treatment of advanced-stage, *EGFR*/*ALK*-wild-type, PD-L1$^+$ NSCLC (≥50% positivity)	S16
Advanced-stage NSCLC	Atezolizumab (PD-L1) vs docetaxel	ORR 13.6% vs 13.4%; median DoR 16.3 mo. vs 6.2 mo.; median OS 13.8 mo. vs 9.6 mo.	Approved in October 2016 for advanced-stage NSCLC that has progressed on or after platinum-based chemotherapy	S17
Advanced-stage, *EGFR*/*ALK*-wild-type non-squamous-cell NSCLC	Pembrolizumab plus carboplatin and pemetrexed vs carboplatin and pemetrexed	ORR 55% vs 29%	Accelerated approval of pembrolizumab plus carboplatin and pemetrexed granted in May 2017 for the first-line treatment of advanced-stage, *EGFR*/*ALK*-wild-type non-squamous-cell NSCLC, irrespective of PD-L1 expression	S18
Locally advanced, unresectable NSCLC	Durvalumab (PD-L1) vs placebo (after chemoradiotherapy)	ORR 28.4% vs 16.0%; median PFS 16.8 mo. vs 5.6 months; 1-year PFS 55.9% vs 35.3%; 18-mo. PFS 44.2% vs 27.0%; median time to death or distant metastasis 23.2 mo. vs 14.6 mo.	Approved in February 2018 for the consolidation treatment of unresectable stage III NSCLC that has not progressed after chemoradiotherapy	S19
Urological cancers				
Metastatic castration resistant prostate cancer (after progression on docetaxel)	Ipilimumab 10 mg/kg vs placebo (after bone-directed radiotherapy)	Median OS 11.2 mo. vs 10 mo.	Not yet approved	S20
Advanced-stage clear-cell RCC (previously treated)	Nivolumab vs everolimus	ORR 25% vs 5%; median PFS 4.6 mo. vs 4.4 mo.; median OS 25 mo. vs 19.6 mo.	Approval in November 2015 for metastatic RCC that has progressed after antiangiogenic therapy	S21
Advanced-stage, platinum-resistant urothelial carcinoma	Atezolizumab	• ITT: ORR 15% • PD-L1 positivity ≥5%: ORR 26% • PD-L1 positivity ≥1%: ORR 18%	Approval in May 2016 for advanced-stage urothelial carcinoma that has progressed during or following, or within 12 mo. of, platinum-containing chemotherapy	S22
Advanced-stage urothelial carcinoma (untreated)	Atezolizumab	ORR 23%; CR rate was 9%; median PFS 2.7 mo.; median OS 15.9 mo.	Approval in April 2017 for advanced-stage urothelial carcinoma in patients who are not eligible for cisplatin chemotherapy	S23
Advanced-stage, platinum-resistant urothelial carcinoma	Nivolumab	• ITT: ORR 19.6% • PD-L1 positivity ≥5%: ORR 28.4% • PD-L1 positivity ≥1%: ORR 23.8% • PD-L1 positivity <1%: ORR 16.1%	Approval in February 2017 for advanced-stage urothelial carcinoma that has progressed during or following, or within 12 mo. of, platinum-containing chemotherapy	S24
Advanced-stage, platinum-resistant urothelial carcinoma	Pembrolizumab vs chemotherapy (paclitaxel, docetaxel, or vinflunine)	• ITT: median OS 10.3 mo. vs 7.4 mo. • PD-L1$^+$ tumours (combined positive score ≥10%): median OS 8.0 mo. vs 5.2 mo.	Accelerated approval in May 2017 for advanced-stage urothelial carcinoma that has progressed during or following, or within 12 mo. of, platinum-containing chemotherapy	S25

Advanced-stage, platinum-resistant urothelial carcinoma	Durvalumab	• ITT: ORR 17.8%; CR rate 3.7%. • PD-L1-high tumours: ORR 27.6% • PD-L1-low/negative tumours: ORR 5.1%	Accelerated approval in May 2017 for advanced-stage urothelial carcinoma that has progressed during or following, or within 12 mo. of, platinum-containing chemotherapy	S26
Gastrointestinal cancers				
Advanced-stage hepatocellular carcinoma	Nivolumab	ORR 20% in the dose-expansion phase and 15% in the dose-escalation phase	Accelerated approval in September 2017 for advanced-stage hepatocellular carcinoma previously treated with sorafenib	S27
Recurrent or metastatic MSI-H or dMMR CRC	Nivolumab	ORR 31.1%; 12-week disease control rate 69%; median DoR not reached at a median follow-up duration of 12 mo.	Accelerated approval in August 2017 for adult and paediatric patients (aged ≥12 years) with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	S28
Advanced-stage gastric or GEJ cancer after at least two prior standard chemotherapy regimens	Pembrolizumab	• ITT: ORR 11.2% ; CR rate 1.9% • PD-L1^{+} tumours (≥1% positivity): ORR 15.5%; CR rate 2.0% • PD-L1^{-} tumours: ORR 5.5%; CR rate 1.8%	Accelerated approval in September 2017 for recurrent, advanced-stage, PD-L1^{+} gastric or GEJ cancer after ≥2 therapies including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2-targeted therapy	S29
Advanced-stage gastric or GEJ cancer after at least two prior standard chemotherapy regimens	Nivolumab vs placebo	Median OS 5.3 mo. vs 4.1 mo.; 1-year OS 26.2% vs 10.9%	Approved in Japan for recurrent locally advanced or metastatic, gastric or GEJ adenocarcinoma; not yet approved by the FDA	S30
Other cancers				
HNSCC	Nivolumab vs therapy of investigator's choice	ORR 26.1% vs 0%; median PFS 1.9 mo. vs 1.8 mo.; median OS 9.5 mo. vs 6.2 mo.	Approved in November 2016 for recurrent or metastatic HNSCC that has progressed on or after platinum-based therapy	S31
HNSCC	Pembrolizumab	ORR 18%; 6-mo. PFS 23%; 6-mo. OS 59%	Accelerated approval in August 2017 recurrent or metastatic HNSCC that has progressed on or after platinum-based therapy	S32
Hodgkin lymphoma	Pembrolizumab	ORR 69%; CR rate 22.4%	Accelerated approval in March 2017 for classical Hodgkin lymphoma that has progressed after ≥3 prior lines of therapy	S33
Hodgkin lymphoma	Nivolumab	ORR 65%; CR rate 7%; median DoR 8.7 mo. (in a combined analysis of data from phase II CheckMate 205 trial and the phase I CheckMate 039 trial)	Accelerated approval in May 2017 for classical Hodgkin lymphoma that has progressed after auto-HSCT and post-transplantation brentuximab vedotin	S34,S35

Auto-HSCT, autologous haematopoietic stem cell transplantation; CR, complete response; CRC, colorectal cancer; CTLA-4, cytotoxic T lymphocyte protein 4; dMMR, mismatch-repair deficient; DoR, duration of response; GEJ, gastroesophageal junction; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; ICB, immune-checkpoint blockade; ITT, intention-to-treat population; mo., months; MSI-H, microsatellite instability-high; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; RCC, renal cell carcinoma; RFS, recurrence-free survival.

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Supplementary Table S2 | **FDA-approved agents targeting the VEGF axis**

Agent	Activity	Approved indication (according to FDA hematology/oncology approvals database)	PFS benefit[a]	OS benefit[a]	ClinicalTrial.gov identifier for pivotal study (publication)
VEGF-neutralizing agents					
Ziv-aflibercept	VEGFR–Fc fusion protein soluble decoy receptor for VEGFA, VEGFB, and PlGF	Metastatic CRC (in combination with FOLFIRI)	2.2 mo.	1.4 mo.	NCT00561470 (S36)
Bevacizumab	Anti-VEGF-A antibody	Metastatic CRC (with fluorouracil, and leucovorin)	4.47 mo.	4.7 mo.	NA (S37)
		First-line treatment of metastatic CRC (with FOLFOX4)	2.6 mo.	2.2 mo.	NCT00025337; E3200 (S38)
		First-line treatment of advanced-stage NSCLC (with carboplatin and paclitaxel chemotherapy)	1.7 mo.	2.0 mo.	NCT00021060; E4599 (S39)
		Second-line treatment of glioblastoma (with irinotecan)	1.5 mo.	0.5 mo.	NCT00345163; AVF3708g (S40)
		Advanced-stage RCC (with IFNα)	4.8 mo.	2 mo.	NCT00738530; AVOREN (S41)
		Second-line treatment (with FOLFIRI) of metastatic CRC after progression on bevacizumab containing first-line treatment	1.6 mo.	1.4 mo.	NCT00499369; ML18147 (S42)
		Recurrent or persistent stage IVB cervical cancer (with paclitaxel and either cisplatin; or topotecan)	3.1; 2.1 mo.	3.3; 3.6 mo.	NCT00803062 (S43)
		Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (with paclitaxel, pegylated liposomal doxorubicin, or topotecan)	3.4 (5.7 with paclitaxel) mo.	3.3 (9.2 with paclitaxel) mo.	NCT00976911; AURELIA (S44)
		Platinum-sensitive recurrent ovarian cancer (with gemcitabine+carboplatin (OCEAN), or with paclitaxel+carboplatin (GOG-0213))	4.0 mo. (OCEAN) 3.4 mo. (GOG-0213)	0.7 mo. (OCEAN) 4.9 mo. (GOG-0213)	NCT00434642; OCEAN (S45) NCT00565851; GOG-0213 (S46)
		Glioblastoma that has progressed after chemoradiation (with lomustine)	2.7 mo.	0.5 mo.	NCT01290939; EORTC 26101 (S47)
Angiogenesis inhibitors with dual VEGFR TKI and TIE2 TKI activity					
Cabozantinib	MET, VEGFR2, and TIE2 TKI	Advanced-stage RCC that has progressed after VEGFR TKI treatment	3.6 mo.	4.9 mo.	NCT01865747; METEOR (S48)
		Advanced-stage medullary thyroid cancer	7.2 mo.	NA	NCT00704730; EXAM (S49)
Regorafenib	VEGFR2/3, RET, KIT, TIE2, PDGFR and RAF TKI	Advanced-stage GIST	3.9 mo.	NS	NCT01271712; GRID (S50)
		Metastatic CRC	0.2 mo.	1.5 mo.	NCT01103323; CORRECT (S51)
		HCC (after sorafenib)	1.9 mo.	2.9 mo.	NCT01774344; RESORCE (S52)
Sorafenib	VEGFR1–3, PDGFRα/β, FGFR1–4, KIT, RET, FLT3, CRAF, BRAF, and TIE2 TKI	Unresectable and/or metastatic RCC	2.7 mo.	2.6 mo.	NCT00073307 (S53)
		Advanced-stage HCC	2.8 mo.	2.8 mo.	NCT00105443 (S54)
		Locally recurrent or metastatic progressive DTC refractory to radioactive iodine treatment	5.0 mo.	NA	NCT00984282 (S55)
Antiangiogenic agents with activity against VEGFRs					
Axitinib	VEGFR1–3 and PDGFRβ TKI	Advanced-stage RCC	2.0 mo.	0.9 mo.	NCT00678392 (S56)
Lenvatinib	VEGFR1–3, PDGFRα, and FGFR1–4 TKI	Recurrent or metastatic radioactive iodine-refractory DTC	14.7 mo.	NS	NCT01321554; SELECT (S57)
		Advanced-stage RCC (in combination with everolimus)	9.1 mo.	10.1 mo.	NCT01136733 (S58)
Pazopanib	KIT, FGFR1/2, PDGFRβ, and VEGFR1–3 TKI	Advanced-stage soft-tissue sarcoma (after chemotherapy	3.0 mo.	1.9 mo.	NCT02049905 (S59)
		Advanced-stage RCC	5.0 mo.	2.4 mo.	NCT00334282 (S60)
Ramucirumab	Anti-VEGFR2 antibody	Second-line treatment of metastatic CRC (in combination with FOLFIRI)	1.2 mo.	1.6 mo.	NCT01183780; RAISE (S61)
		Platinum-resistant metastatic NSCLC (in combination with docetaxel)	1.5 mo.	1.4 mo.	NCT01168973; REVEL (S62)
		Advanced-stage gastric or gastroesophageal junction adenocarcinoma (in combination with paclitaxel), after progression on or after fluoropyrimidine-based or platinum-containing chemotherapy	1.5 mo.	2.2 mo.	NCT02359058; RAINBOW (S63)

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		Advanced-stage gastric or gastroesophageal junction adenocarcinoma	0.8 mo.	1.4 mo.	NCT00917384; REGARD (S64)
Sunitinib	VEGFR1–3, PDGFRα/β, KIT, RET, FLT3, and G-CSF-R TKI	Advanced-stage clear-cell RCC (in combination with IFNα)	6.6 mo.	4.9mo.	NCT00083889 (S65)
		GIST (after failure of imatinib)	4.2 mo.	1.5 mo.	NCT00075218 (S66)
		Advanced-stage PNET	4.9 mo.	NA	NCT00428597 (S67)
		High-risk clear-cell RCC after nephrectomy	14.4 mo. (DFS)	NA	NCT00375674 (S68)
Vandetanib	VEGFR1–3, EGFR, RET, and PDGFRα/β TKI	Unresectable, locally advanced, or metastatic MTC	11.3 mo.	16 mo.	NCT00410761 (S69)

CRC, colorectal cancer; DFS, disease-free survival; DTC, differentiated thyroid carcinoma; EGFR, epithelial growth factor receptor; FGFR, fibroblast growth factor receptor; FOLFIRI, folinic acid (leucovorin), 5-fluorouracil, and irinotecan; FOLFOX4, folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin; G-CSF-R, granulocyte colony-stimulating factor receptor; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; IFNα, interferon α; mo., months; MTC, medullary thyroid carcinoma; NA, not available; NS, not statistically significant; NSCLC, non-small-cell lung cancer; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PlGF, placenta growth factor; PNET, pancreatic neuroendocrine tumour; RCC, renal cell carcinoma; TIE2, angiopoietin 1 receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. [a] Comparators varied between trials; see ClinicalTrials.gov database entries for details. When the outcomes are not available in ClinicalTrials.gov, we entered the value from final/most recent publication.

In format provided by Fukumura *et al.* (doi:10.1038/nrclinonc.2018.29)

Supplementary Table S3 | **Bevacizumab biosimilars under development**

Company	Biosimilar	Clinical development stage (disease setting)	Status and results	ClinicalTrial.gov identifier (publication)
Amgen/ Allergan	Mvasi (bevacizumab-awwb, ABP 215)	Phase III (NSCLC): Mvasi plus PC vs bevacizumab plus PC FDA approved[a] on 9/14/2017 for mCRC and advanced-stage NSCLC with chemotherapy	Completed: Mvasi and bevacizumab clinically equivalent in patients with advanced-stage NSCLC	NCT01966003 (S70)
Apobiologix	Not announced	In pipeline	Unknown	NA
AstraZeneca	FKB238	Phase III (NSCLC): FKB238 plus PC vs bevacizumab plus PC	Recruiting	NCT02810457
Biocad	BCD-021	Phase III (NSCLC): BCD 021 plus PC vs bevacizumab plus PC Approved in Russia	Completed; BCD-021 non-inferior to bevacizumab in patients with advanced-stage NSCLC	NCT01763645 (S71)
BioXpress	BX2314	In pipeline	Unknown	NA
BioXpress	BX0510	In pipeline	Unknown	NA
Boehringer Ingelheim	BI 695502	Phase III (NSCLC): BI 695502 plus PC vs bevacizumab plus PC	Active, not recruiting	NCT02272413
Celltrion Inc.	CT-P16	In pipeline	Unknown	NA
Coherus BioSciences	CHS-5217	In pipeline	Unknown	NA
Hetero	Cizumab	Data on clinical development not available Approved in India for mCRC	Unknown	Clinical Trial Registry India: CTRI/2015/05/005757
mAbxience	BEVZ92	Phase I (mCRC)	Active, not recruiting	NCT02069704
Oncobiologics	ONS-1045	Phase III	Clinical trial planning phase	NA
Pfizer	PF-06439535	Phase III (NSCLC): PF-06439535 plus PC vs bevacizumab plus PC	Active, not recruiting	NCT02364999
PlantForm	Not announced	In pipeline	Unknown	NA
Reliance Life Sciences	R-TPR-023	Approved in India for mCRC based on findings of a clinical trial in primary and mCRC	Clinical data not available	Clinical Trial Registry India: CTRI/2013/05/003699
Samsung Bioepis	SB8	Phase III (NSCLC): SB8 plus PC vs bevacizumab plus PC	Active, not recruiting	NCT02754882

On the basis of a systematic search of the PubMed and ClinicalTrials.gov databases using search terms 'biosimilar' and 'bevacizumab' and selected from the abbreviations list. mCRC, metastatic colorectal cancer; NA, not applicable; NSCLC, non-small-cell lung cancer; PC, paclitaxel and carboplatin chemotherapy. [a]On 14 September 2017, the US FDA approved Mvasi (bevacizumab-awwb) as a biosimilar to bevacizumab; Mvasi is the first bevacizumab biosimilar approved in the USA for the treatment of cancer.

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Supplementary Table S4 | **The influences of VEGF and ANG2 on different immune, endothelial, and cancer cells**

Cell type	Predominant VEGF receptor	Cellular response to VEGF	TIE2 expression	Cellular response to ANG2
DCs	VEGFR3 (REF. S72)	Inhibits the function and maturation of DCs[S73] Enables DCs to secrete angiogenic factors[S74]	Not known	Not known
Monocytes and macrophages	VEGFR1 VEGFR3 (REF. S75)	Drives recruitment of macrophages to the tumour[S76] Polarises macrophages towards a pro-tumour M2 phenotype[S76]	Yes[S77]	Promotes the recruitment of pro-tumour and pro-metastatic monocytes and macrophages Increased IL-10 production by subset of macrophages, enhancing an anti-inflammatory phenotype[S78] Upregulates ICAM1 expression on ECs, leading to enhanced adhesion of monocytes and macrophages[S79] Induces expression of CCL2, a monocyte chemoattractant[S80] Inhibits the release of TNF, restricting the antitumour activity of monocytes[S80]
T cells	VEGFR1 VEGFR2 (REF. S81,S82)	Inhibits T cell development[S83] Co-stimulates IFNγ production, and increase T cell chemotaxis[S81]	Not known	Suppresses T cell proliferation[S78]
T_{reg} cells	VEGFR2 NRP1 (REF. S82)	Fosters T_{reg} cell trafficking, proliferation, activation and maintenance of T_{reg} cells in the tumour site[S84] Chemotactic for T_{reg} cells[S85]	Not known	Promotes T_{reg} cell recruitment and expansion[S78] Increases VEGF production and thereby promotes angiogenesis[S86,S87]
ECs	VEGFR1 VEGFR2 VEGFR3 NRP1 (REF. S88)	Promotes EC proliferation[S88] Interaction with immune cells is context dependent Upregulation of EC adhesion molecules (ICAM1, VCAM1, E-selectin) that mediate interactions with NK cells[S89] Upregulation of CLEVER-1/stabilin-1 (increased T_{reg} cell and M2 macrophage infiltration)[S90] and FasL (CTL infiltration decreased)[S91] Increased immune cell infiltration by antiangiogenic therapies[94]	Yes[95]	Activities of ANG2 are context dependent: TIE2 antagonist in the context of VEGF signalling – destabilizes quiescent vessels and promotes angiogenesis[S93]; TIE2 agonist and inhibitor of angiogenesis in tumours with low expression of VEGF[S94] Dual VEGF–TIE2 blockade promotes PD-L1 expression[S95]
Tumour cells	VEGFR1 VEGFR2 NRP1 (REF. S96)	Increases the migration, mobility and invasiveness of tumour cells[S96]	Yes[S97]	Not known

ANG2, angiopoietin 2; CCL2, C-C-motif chemokine 2; CLEVER-1, common lymphatic endothelial and vascular endothelial receptor-1; DCs, dendritic cells; ECs, endothelial cells; FasL, FAS ligand (also known as tumour necrosis factor ligand superfamily member 6); ICAM1, intercellular adhesion molecule 1; IL-10, interleukin 10; IFNγ, interferon γ; NK, natural killer; NRP1, neuropilin-1; PD-L1, programmed cell death 1 ligand 1; TIE2, angiopoietin 1 receptor; TNF, tumour necrosis factor; T_{reg}, regulatory T; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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Supplementary Table S5 | **Preclinical studies investigating the roles of ANG2 signalling in cancer metastasis and invasion**

Agent	Cancer (mouse model)	Results	Reference
ANG2 inhibition			
3.19.3 (anti-ANG2 mAb) or LC06 derivative[S98] (anti-ANG2 mAbs)	Metastatic breast cancer (MMTV-PyMT), PNET (RIP1-Tag2)	ANG2 blockade decreased angiogenesis, tumour growth and metastasis	S99
	Breast cancer (4T1), lung cancer (Lewis lung carcinoma)	ANG2 inhibition decreased metastatic growth in models of post-surgical adjuvant therapy	S100
	Breast cancer with lung metastasis (4T1)	Pericyte depletion plus ANG2 inhibition restored vascular integrity, decreased tumour growth, and reduced metastasis	S101
VEGF plus ANG2			
3.19.3 and DC101 (anti-VEGFR2 mAb)	PNET (RIP1-Tag2), metastatic breast cancer (MMTV-PyMT)	Dual ANG2/VEGFR2 causes hypoxia but not increased metastasis in PNETs	S102
ANG2 overexpression			
Commercially available MMP2 inhibitor	Glioblastoma (U87MG, U373MG, T98G)	Overexpression of ANG2 leads to increased MMP2 levels and enhanced glioblastoma cell invasion, which was reduced by MMP2 inhibition	S103
NA	PDAC (MiaPaca-2 and Capan-1)	ANG2 overexpression leads to lymphangiogenesis and lymphatic metastasis	S104
NA	Breast cancer (MCF-7)[a]	ANG2 overexpression leads to increased lymph-node invasion and increased tumour metastasis	S105
NA	Glioblastoma (U87)	ANG2 overexpression induces glioblastoma cell invasion through the Fak/Bcar1/Erk1/2 and Jnk, and via $\alpha_5\beta_1$ integrin	S106,S107

On the basis of a systematic search of the PubMed database using selected search terms from the abbreviations list. ANG2, angiopoietin 2; Bcar1, Breast cancer anti-oestrogen resistance protein 1 (also known as p130cas); Erk1/2, extracellular signal regulated kinase 1 and/or 2; Fak, focal adhesion kinase 1; Jnk, Janus kinase; mAb, monoclonal antibody; MMP2, matrix metalloproteinase 2 (also known as 72 kDa type IV collagenase); NA, not applicable; PDAC, pancreatic adenocarcinoma; PNET, pancreatic neuroendocrine tumour; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2. [a]Results of a study of human breast cancers showed overexpression of ANG2 correlates with a high risk of nodal invasion, and poor disease-free and overall survival outcomes[S108].

In format provided by Fukumura *et al.* (doi:10.1038/nrclinonc.2018.29)

Supplementary Table S6 | **Clinical studies on the prognostic and predictive potential of ANG2**

Agent (target)	Disease	Results	Reference
ANG2 levels as a potential predictive biomarker			
Pan-VEGFR TKIs			
Sorafenib (VEGFR1–3, PDGFRα/β, FGFR1–4, KIT, RET, FLT3, CRAF, BRAF, and TIE2)	Advanced-stage HCC	Circulating ANG2 and VEGF levels were independent predictor of survival	S109
Sunitinib (VEGFR1–3, PDGFRα/β, KIT, RET, FLT3, G-CSF-R)	Metastatic RCC	Low baseline levels of circulating ANG2 and high baseline MMP2 levels associated with tumour response	S110
No antiangiogenic treatment			
Surgery	Breast cancer	Tumour ANG2 mRNA expression correlated with lymph-node invasion and unfavourable overall survival	S108
Surgery	Advanced-stage HCC	Tumour ANG2 expression negatively correlated with progression-free survival	S111
Unclear, archival samples	Metastatic melanoma	High circulating soluble ANG2 level is a biomarker of disease progression and metastasis in melanoma and correlates with greater tumour load and unfavourable overall survival	S112
Platinum-based chemotherapy	Ovarian cancer	High serum ANG2 levels predictive of poor recurrence-free and overall survival	S113
Unclear, archival samples	Neuroendocrine tumours	Circulating ANG2 levels correlated with metastatic vs localized disease and unfavourable overall survival	S114
Unclear, archival samples	Pancreatic adenocarcinoma	Circulating ANG2 levels correlated with extent of lymphatic metastasis and survival	S104
Unclear, archival samples	Small-cell lung cancer	High baseline circulating levels of ANG2 correlated with worse survival	S115
Unclear, archival samples	Breast cancer	Tumour ANG2 mRNA overexpression associated with unfavourable recurrence-free survival	S101
Unclear, archival samples	Glioblastoma	High tumour ANG2/*ANGPT2* expression correlated with unfavourable survival	S116
Standard of care (RT + temozolomide)	Glioblastoma	High tumour *ANGPT2* expression across molecular subtypes and treatment settings	S117
Unclear, archival samples	Oral squamous cell carcinoma	Tumour ANG2 protein expression positively correlated with angiogenesis and overall survival	S118
NA	Lung cancer	Serum ANG2 levels correlated with tumour stage; ANG2 levels were higher if lymph node metastasis was present; high ANG2 levels portended a worse prognosis	S119
ANG2 levels as a candidate biomarker for the outcome anti-VEGF therapy			
Anti-VEGFA antibody therapy			
Bevacizumab (VEGFA)	Glioblastoma	ANG2 levels increased at disease recurrence/progression	S120
	Metastatic colorectal cancer	Low ANG2 level were predictive of a better outcome with bevacizumab therapy	S121
	Advanced-stage gastric cancer	ANG2 levels prognostic of overall survival and liver metastasis, but were not predictive of bevacizumab efficacy	S122
VEGFR-TKI therapy			
AZD2171 (VEGFR1–3)	Glioblastoma	ANG2 levels initially dropped and then increased after AZD2171 therapy	S123
Sunitinib	RCC	ANG2 levels increased after disease progression on sunitinib	S124
ANG2 levels as a candidate biomarker for the outcome of anti-VEGF therapy plus ICB			
Ipilimumab (CTLA-4) plus bevacizumab, or nivolumab or pembrolizumab (PD-1)	Metastatic melanoma	High circulating ANG2 levels before ICB correlated with poor treatment response and survival; ICB alone increased serum ANG2 levels early after treatment initiation, whereas ipilimumab plus bevacizumab treatment decreased serum concentrations	S125

On the basis of a systematic search of the PubMed and Google scholar databases and the *Journal of Clinical Oncology* website using selected search terms from the abbreviations list. ANG2, angiopoietin 2; CTLA-4, cytotoxic T lymphocyte protein 4; FGFR, fibroblast growth factor receptor; G-CSF-R, granulocyte colony-stimulating factor receptor; HCC, hepatocellular carcinoma; ICB, immune-checkpoint blockade; MMP2, matrix metalloproteinase 2 (also known as 72 kDa type IV collagenase); PD-1, programmed cell death protein 1; PDGFR, platelet-derived growth factor receptor; RCC, renal cell carcinoma; TIE2, angiopoietin 1 receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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Supplementary Table S7 | **Preclinical studies of inhibitors of ANG2 or ANG1/2 signalling**

Agent(s)	Cancer (model)	Results	Reference
Anti-ANG2 agents			
3.19.3 (mAb)	Hepatocellular carcinoma (PLCPRF/5) or pancreatic cancer (HPAC)	Decreased tumour growth; combination of MEDI3617 and bevacizumab resulted in greater inhibition of tumour growth compared with either monotherapy	S126
	Subcutaneous: colon epidermoid carcinoma (A431) or colon cancers (Lovo, SW480, Colo205) Orthotopic: breast cancers (MCF7, MDA-MB-231)	Decreased tumour growth	S127
LC06 and LC08 (mAbs)	Colon cancer (Colo205; subcutaneous) or choroidal neovascularization model	Decreased tumour growth, and reduced tumour MVD	S128
Nesvacumab (REGN910/ SAR307746; mAb)	Prostate (PC3), colon (Colo205), or epidermoid carcinoma (A431)	Decreased tumour growth	S129
A11 (peptibody)	Colon cancer (HCT116/CCL-247) or retinal angiogenesis model	Induced tumour cell apoptosis and reduced tumour MVD	S130
LC06 (mAb)	Colon cancer (Colo205) or breast cancer (KPL-4)	Reduced tumour MVD, increased vascular maturity, and decreased tumour growth	S98
LC06 derivative (mAb)	Breast cancer (4T1) or lung cancer (Lewis lung carcinoma)	Decreased tumour growth in models of postsurgical adjuvant therapy	S100
CVX-060 (PF-04856884; anti-ANG2 peptibody)	Colon cancer (Colo205)	Reduced tumour MVD and decreased tumour growth	S131
Anti-ANG1/2 agents			
AMG 780 (anti-ANG1/2 mAb) and trebananib (AMG 386; anti-ANG1/2 peptibody)	Colon cancer (Colo205)	Decreased tumour growth and decreased viable tumour and tumour cell proliferation with AMG 780 than with trebananib	S132
Trebananib, L1-7(N) (anti-ANG2 peptibody), and mL4-3 (anti-ANG1 peptibody)	Colon cancer (Colo205)	Decreased tumour growth and reduced tumour MVD compared with ANG1 or ANG2 inhibition alone	S133
VE-PTP inhibition			
AKB-9778 (VE-PTP inhibitor that activates TIE2 signalling)	Breast cancers (4T1, E0771)	Increased vascular maturity, reduced metastasis, and prolonged survival	S134
TIE2 activator			
ABTAA (anti-ANG2 mAb that activates TIE2)	Glioma (GL261), lung cancer (Lewis lung carcinoma) or breast cancer (MMTV-PyMT)	Decreased tumour growth, prolonged survival, and enhanced the efficacy of chemotherapy	S135

On the basis of a systematic search of the PubMed and Google scholar databases and the *Journal of Clinical Oncology* website using selected search terms from the abbreviations list. ANG1, angiopoietin 1; ANG2, angiopoietin 2; mAb, monoclonal antibody; MST1R, macrophage-stimulating protein receptor; MVD, microvessel density; PDGFR, platelet-derived growth factor receptor; TIE2, angiopoietin 1 receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VE-PTP, vascular endothelial protein tyrosine phosphatase (also known as receptor-type tyrosine-protein phosphatase β).

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Supplementary Table S8 | **Clinical studies investigating ANG2 or dual ANG1/2 inhibitors**

Treatments	Disease	Results	Phase; status	ClinicalTrials.gov identifier (publication)
Anti-ANG2 or ANG1/2 mAbs				
Nesvacumab (REGN910/ SAR307746 (anti-ANG2 mAb)	Advanced-stage solid tumours	Safe at all doses tested; recommended phase II dose 20 mg/kg every 2 weeks	Phase I; completed	NCT01271972 (S136)
AMG 780 (anti-ANG1/2 mAb)	Advanced-stage solid tumours	AMG 780 administration possible up to 30 mg every 2 weeks	Phase I; terminated[a]	NCT01137552 (S137)
Combination of ANG2 inhibition and ICB				
MEDI3617 (anti-ANG2 mAb) and tremelimumab (anti-CTLA-4 mAb)	Metastatic melanoma	Ongoing	Phase I; active, not recruiting	NCT02141542
Anti-ANG2 or anti-ANG1/2 peptibodies				
Phase I studies				
CVX-060 (PF-04856884; anti-ANG2 peptibody)	Advanced-stage solid tumours	Limited toxicities observed	Phase I; completed	NCT00879684
Trebananib (AMG 386; anti-ANG1/2 peptibody that inhibits ANG1 to a greater degree than it does ANG2)	Advanced-stage solid tumours	Acceptable safety at 30 mg/kg weekly; efficacy observed as monotherapy	Phase I; completed	NCT00102830 (S138)
	Advanced-stage solid tumours	Drug well tolerated in paediatric patients	Phase I; completed	NCT01538095 (S139)
	Advanced-stage solid tumours	Acceptable safety at 30 mg/kg weekly; efficacy observed as a monotherapy	Phase I; complete	NCT02525536 (S140)
Trebananib + temsirolimus (mTOR inhibitor)	Advanced-stage solid tumours	MTD exceeded at 15 mg/kg and 20 mg/kg of trebananib	Phase I; completed	NCT01548482, (S141)
Trebananib + paclitaxel	Advanced-stage solid tumours	No results available	Phase I; completed	NCT01331941
		No drug–drug interaction between trebananib and paclitaxel	Phase Ib; completed	NCT01992341 (S142)
Trebananib and cytarabine	Adult acute myeloid leukaemia	Trebananib ± cytarabine well tolerated	Phase I; completed	NCT01555268 (S143)
Trebananib + pegylated liposomal doxorubicin or topotecan	Ovarian, fallopian tube, primary or peritoneal cancer	Acceptable toxicity of trebananib + pegylated liposomal doxorubicin or topotecan; associated with antitumour activity	Phase I; completed	NCT01253681 (S144)
		No results available	Phase I; completed	NCT00770536
Trebananib + paclitaxel and trastuzumab, or capecitabine and lapatinib	Locally recurrent or metastatic breast cancer	Trebananib 10 mg/kg (A1) and 30 mg/kg (A3) + paclitaxel and trastuzumab tolerable; ORR 80% (A1) and 88.2% (A3); PFS 14.5 mo. (A1) and 18.7 mo. (A3)	Phase I; completed	NCT00807859 (S145)
Trebananib + pemetrexed and carboplatin	Non-small-cell lung cancer	No results available	Phase 1b/II; completed	NCT01666977
Phase II studies				
CVX-060	Glioblastoma	Not applicable	Phase II; withdrawn prior to enrolment[b]	NCT01225510
Trebananib	Adult angiosarcoma or soft-tissue sarcoma	No PRs or CRs; protracted estimated PFS (3.5–5.5 mo.) observed in 4 of 16 patients (no comparator arm)	Phase II; completed	NCT01623869 (S146)
	Endometrial carcinoma	Insufficient single-agent activity	Phase II; completed	NCT01210222 (S147)
Trebananib + paclitaxel	Ovarian, fallopian tube, primary or peritoneal cancer	Trebananib combined with weekly paclitaxel tolerable; evidence of antitumour activity and a dose-response effect	Phase II; completed	NCT00479817 (S148)
Trebananib + FOLFIRI	Colorectal cancer	Estimated PFS unchanged with trebananib + FOLFIRI compared with placebo + FOLFIRI	Phase II; completed	NCT00752570 (S149)
Trebananib or placebo + cisplatin and capecitabine	Gastrointestinal cancer	Estimated PFS and ORRs similar with cisplatin and capecitabine ± trebananib	Phase II; completed	NCT00583674 (S150)
Trebananib + abiraterone	Metastatic castration-resistant prostate cancer	Well tolerated and acceptable safety profile	Phase II; active, not recruiting	NCT01553188 (S151)
Trebananib + docetaxel	Urothelial carcinoma	Not applicable	Phase II; withdrawn prior to enrolment[c]	NCT01907308
Trebananib + sunitinib (pan-VEGFR, pan-PDGFR, KIT, RET, FLT3, G-CSF-R TKI)	Advanced-stage renal cell carcinoma	Estimated PFS 13.9 mo. with sunitinib + 10 mg/kg trebananib vs 16.3 mo. with sunitinib + 15 mg/kg trebananib	Phase II; active, not recruiting	NCT00853372 (S152)
Trebananib ± bevacizumab	Recurrent glioblastoma	Trebananib was well tolerated but ineffective as a monotherapy; combination did not have enhanced efficacy over bevacizumab monotherapy	Phase I/II; completed Phase II; active, not recruiting	NCT01290263 (S153) NCT01609790

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Phase III studies				
Trebananib + paclitaxel and carboplatin	Ovarian, fallopian tube, primary or peritoneal cancer	No results available	Phase III; terminated[d]	NCT01493505; TRINOVA-3
Trebananib + paclitaxel	Ovarian, fallopian tube, primary or peritoneal cancer	PFS2 1.6 mo. longer with trebananib + paclitaxel vs paclitaxel alone; OS 2.2 mo. longer with combination vs paclitaxel alone in patient with ascites	Phase III; completed	NCT01204749; TRINOVA-1 (S154)
Trebananib + pegylated liposomal doxorubicin	Ovarian, fallopian tube, primary or peritoneal cancer	Median PFS 7.6 mo. with trebananib vs 7.2 mo. with placebo; ORR 46% vs 21%; DOR 7.4 mo. vs 3.9 mo.	Phase III; terminated[b]	NCT01281254; TRINOVA-2 (S155)

On the basis of a systematic search of the PubMed database website using selected search terms from the abbreviations list. ANG1, angiopoietin 1; ANG2, angiopoietin 2; CRs, complete response; CTLA-4, cytotoxic T lymphocyte protein 4; FOLFIRI, folinic acid (leucovorin), 5-fluorouracil, and irinotecan; G-CSF-R, granulocyte colony-stimulating factor receptor; mAb, monoclonal antibody; mo., months; MTD, maximum tolerated dose; mTOR, mechanistic target of rapamycin; ORRs, objective response rates; OS, overall survival; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PRs, partial responses; TIE2, angiopoietin 1 receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. [a]Dose-escalation phase completed; dose-expansion phase not conducted owing to business decision. [b]Reasons unknown. [c]Sponsor's decision. [d]Administrator's decision

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Supplementary Table S9 | **Preclinical studies investigating combined inhibition of the ANG2 and VEGF pathways**

Agent(s)	Disease (model)	Results	Reference
VEGF and ANG2 neutralizing agents			
L1-10 (anti-ANG2 peptibody) + bevacizumab (anti-VEGFA mAb[a])	Subcutaneous colon cancer xenografts (LS 174T)	Dual targeting of VEGF and ANG2 achieved effective normalization (pericyte coverage, vascular integrity, adherence junctions and perfusion) at only one-tenth of the dose required with bevacizumab alone	S156
3.19.3 (anti-ANG2 mAb) + bevacizumab	Multiple subcutaneous xenograft models	Decreased tumour growth with 3.19.3; antitumour activity increased when combined with bevacizumab or chemotherapy	S157
3.19.3 + DC101 (anti VEGFR2 mAb)	PNET (RIP1-Tag2), breast cancer (MMTV-PyMT)	Dual ANG2/VEGFR inhibition has superior efficacy against PNETs compared with anti-VEGF alone, whereas only minor additive effects were observed in the breast cancer model	S102
DC101 + TIE2-based decoy receptor for ANG2	Glioblastoma (GL261, U87)	Tumour invasiveness was decreased under dual ANG2/VEGFR2 inhibition compared with DC101 alone	S158
Double antiangiogenic protein (DAAP; VEGFA and ANG1/2 decoy receptor), VEGF-Trap, or TIE2–Fc fusion	Subcutaneous melanoma (LLC and B16/F10), orthotopic colon cancer (CT-26), peritoneal human ovarian cancer (MDAH-2774)	Dual TIE2/VEGF inhibition decreased tumour growth, reduced vascular leakage, and lowered the frequency of ascites compared with VEGF or TIE2 blockade alone	S159
L1-7(N) + anti-VEGFA antibody (clone 26503; R&D Systems)	Subcutaneous colon cancer xenograft model (Colo205)	ANG2 inhibition complemented anti-VEGF therapy (substantial decreases in vessel sprouting, vessel density, and tumour growth)	S160
Trebananib (AMG 386; anti-ANG1/2 peptibody) + aflibercept (VEGFR1/2–Fc decoy receptor for VEGFA/B and PlGF)	Glioblastoma (GL261)	Dual ANG2/VEGF inhibition prolonged survival compared with anti-VEGF therapy alone	S116
Vanucizumab (dual anti-ANG2 and anti-VEGFA mAb)	Multiple orthotopic and subcutaneous xenograft models	Reduced tumour MVD, increased vascular maturity, and decreased tumour growth	S161
Vanucizumab or B20 (anti-VEGFA mAb)	Glioblastoma (murine GL261 and patient-derived MGG8)	Prolonged survival; reduced immunosuppression imparted by pro-tumour macrophages compared with IgG treated and anti-VEGF treated animals	S117
Vanucizumab	Subcutaneous colon cancer xenografts model (Colo205)	Decreased tumour growth	S162
Vanucizumab	Orthotopic breast cancer (MMTV-Py), melanoma (B16 ova), PNET models (RIP1-Tag2)	Decreased tumour growth and prolonged survival	S163
Sunitinib (VEGFR1–3, PDGFRα/β, KIT, RET, FLT3, G-CSF-R TKI), or CVX-060 (PF-04856884; anti-ANG2 peptibody) or regorafenib (VEGFR2/3, RET, KIT, TIE2, PDGFR and RAF TKI), or CVX-241 (dual anti-ANG2 and anti-VEGF peptibody) (± anti-PD-1)	Orthotopic breast (EMT-6, MDA-MB-231.LM2-4), colon (HCT116, HT29), RCC (RENCA) tumour models	Inhibition of tumour growth and metastasis, and prolongation of animal survival: markedly greater with anti-VEGF/ANG2 agents than with anti-VEGF or anti-ANG2 agents alone in breast and colon cancer models. Broad spectrum TKI (sunitinib) had the best efficacy in an RCC model	S164
VEGFR TKI with TIE2 inhibitory activity, or without such activity but combined with an anti-ANG2 agent			
CEP-11981 (pan-VEGFR and TIE2 TKI)	Subcutaneous: melanoma, glioblastoma, prostate carcinoma (models not specified) Orthotopic: solid (colon carcinoma, renal carcinoma, and glioblastoma) and haematological cancers (acute leukaemia)	Reduced tumour MVD and decreased tumour growth	S165
Pexmetinib (ARRY-614; p38 and TIE2 kinase inhibitor)	Plasmocytoma (RPMI 8226)	Decreased tumour growth	S166
Sorafenib (pan-VEGFR, pan-PDGFR, pan-FGFR, KIT, RET, FLT3, CRAF, BRAF, and TIE2 TKI) + DC101 (anti-VEGFR2 mAb)	Metastatic colon cancer (CT26)	Decreased angiogenesis, tumour growth, and metastasis	S167
Cediranib (AZD 2171; pan-VEGFR TKI) and MEDI3617 (anti-ANG2 mAb)	Glioblastoma (murine Gl261 and human U87)	Prolonged survival and enhanced antitumour immunity compared with cediranib treated and untreated control animals	S168
Regorafenib	Breast (MDA-MB-231), colon (Colo205), or RCC (786-O) tumour models	Reduced tumour MVD (breast & colon cancers), and decreased tumour growth	S169
Glesatinib (MGCD265; MET, TIE2, VEGFR1–3, and MST1R TKI)	Breast, kidney, pancreatic, and lung carcinoma models (not specified)	Decreased tumour growth	S170

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Glesatinib	Multiple xenograft models	Tumour growth slowed with glesatinib plus a taxane or erlotinib compared with taxane or erlotinib treatment alone	S171

On the basis of a systematic search of the PubMed database website using selected search terms from the abbreviations list. ANG1, angiopoietin 1; ANG2, angiopoietin 2; FGFR, fibroblast growth factor receptor; mAb, monoclonal antibody; MST1R, macrophage-stimulating protein receptor; MVD, microvessel density; PDGFR, platelet-derived growth factor receptor; PlGF, placental growth factor; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
[a]Bevacizumab neutralises human VEGFA but not mouse VEGFA.

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Supplementary Table S10 | **Clinical studies of VEGF pathway inhibitors combined with ANG2 or dual ANG1/2 inhibitors**

Treatments	Disease	Phase; status	Results	ClinicalTrials.gov identifier (publication)
VEGF + ANG1/2 neutralizing agent				
Nesvacumab (REGN910/ SAR307746 (anti-ANG2 mAb) + aflibercept (VEGFR1/2–Fc decoy receptor for VEGFA/B and PlGF)	Solid tumours	Phase I; completed	Regimen well tolerated	NCT01688960 (S172)
Trebananib (AMG 386; anti-ANG1/ 2 peptibody) + bevacizumab (anti-VEGFA antibody)	Metastatic CRC	Phase II; unknown	ORR greater than historical rates with bevacizumab alone	NCT01249521 (S173)
	Glioblastoma	Phase I/II; completed	6-month PFS 24% with combined therapy vs 0% with trebananib alone	NCT01290263
	Adult glioblastoma, gliosarcoma, or oligodendroglioma	Phase II; active, not recruiting	6-month PFS 23% with combination therapy vs 41% with bevacizumab alone	NCT01609790
Trebananib + paclitaxel +/- bevacizumab	Locally recurrent and metastatic $HER2^-$ breast cancer	Phase II; completed	No prolongation of estimated PFS	NCT00511459 (S174)
Vanucizumab (dual anti-ANG2 and anti-VEGFA mAb) + RO7009789 (agonistic anti-CD40 mAb)	Advanced-stage solid tumours	Phase I; recruiting	Not available	NCT02665416
Vanucizumab or bevacizumab + mFOLFOX6	Untreated metastatic CRC	Phase II; completed	Not available	NCT02141295
CVX-241 (dual anti-ANG2 and anti-VEGF peptibody)	Advanced-stage solid tumours	Phase I; terminated (owing to the lack of significant pharmacological effects)	No safety concerns but terminated early by the sponsor	NCT01004822 (S175)
VEGFR TKI/antagonist + ANG-2 neutralizing agent				
Trebananib + sorafenib (pan-VEGFR, pan-PDGFR, pan-FGFR, KIT, RET, FLT3, CRAF, BRAF, and TIE2 TKI)	Advanced-stage RCC	Phase II; completed	Tolerable, but no PFS prolongation	NCT00467025 (S176)
	Advanced-stage, inoperable HCC	Phase II; completed	No improvement in PFS vs historical controls	NCT00872014 (S177)
CVX-060 (PF-04856884; anti-ANG2 peptibody) and axitinib (pan-VEGFR, pan-PDGFR, and KIT TKI)	Metastatic RCC	Phase II; terminated owing to poor tolerability	ORR 11.1%; treatment-related thromboembolic events observed	NCT01441414 (S178)
Trebananib + bevacizumab, sorafenib, sunitinib (pan-VEGFR, pan-PDGFR, KIT, RET, FLT3, G-CSF-R TKI) or AMG 706 (anti-ANG1/2 mAb)	Advanced-stage solid tumours	Phase I; completed	Antitumour activity was observed	NCT00861419 (S179)
CVX-060 + sunitinib	Advanced-stage RCC	Phase II; terminated owing to adverse safety signals	Owing to data safety signals in a separate clinical trial with CVX-060, all CVX-060 studies were discontinued	NCT00982657
Trebananib + bevacizumab, pazopanib (pan-VEGFR1–3, pan-PDGFR, pan-FGFR, KIT TKI), sorafenib, or sunitinib	Recurrent RCC	Phase II; active, not recruiting	Not available	NCT01664182
LY3127804 (anti-ANG2 mAb) ± ramucirumab (anti-VEGFR2 mAb) ± paclitaxel	Advanced-stage solid tumours	Phase I; completed	Not available	NCT02597036

On the basis of a systematic search of the PubMed, Google Scholar, ClinicalTrials.gov, and FDA Oncology databases, and the *Journal of Clinical Oncology* website using selected from the abbreviations list. ANG1, angiopoietin 1; ANG2, angiopoietin 2; CRC, colorectal cancer; FGFR, fibroblast growth factor receptor; G-CSF-R, granulocyte colony-stimulating factor receptor; HCC, hepatocellular carcinoma; mAb, monoclonal antibody; mFOLFOX6, modified FOLFOX, folinic acid (leucovorin), 5-fluorouracil, and oxaliplatin) regimen; mo., month; ORR, objective response rate; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PlGF, placental growth factor; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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