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Anti-tumour Treatment

Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook

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ABSTRACT

When the VEGF-A-targeting monoclonal antibody bevacizumab (Avastin®) entered clinical practice more than 15 years ago, it was one of the first targeted therapies and the first approved angiogenesis inhibitor. Marking the beginning for a new line of anti-cancer treatments, bevacizumab remains the most extensively characterized anti-angiogenetic treatment. Initially approved for treatment of metastatic colorectal cancer in combination with chemotherapy, its indications now include metastatic breast cancer, non-small-cell lung cancer, glioblastoma, renal cell carcinoma, ovarian cancer and cervical cancer. This review provides an overview of the clinical experience and lessons learned since bevacizumab's initial approval, and highlights how this knowledge has led to the investigation of novel combination therapies.

In the past 15 years, our understanding of VEGF's role in the tumor microenvironment has evolved. We now know that VEGF not only plays a major role in controlling blood vessel formation, but also modulates tumor-induced immunosuppression. These immunomodulatory properties of bevacizumab have opened up new perspectives for combination therapy approaches, which are being investigated in clinical trials. Specifically, the combination of bevacizumab with cancer immunotherapy has recently been approved in non-small-cell lung cancer and clinical benefit was also demonstrated for treatment of hepatocellular carcinoma. However, despite intense investigation, reliable and validated biomarkers that would enable a more personalized use of bevacizumab remain elusive.

Overall, bevacizumab is expected to remain a key agent in cancer therapy, both due to its established efficacy in approved indications and its promise as a partner in novel targeted combination treatments.

Introduction

Angiogenesis and VEGF as therapeutic targets in cancer

Cancer cells differ fundamentally from normal cells, as a result of having acquired hallmark capabilities that enable tumor growth and progression [1]. Due to their high metabolic demands, growing solid tumors depend on vascularization for provision of nutrients and oxygen and disposal of metabolic waste products. Vascularization can be promoted by angiogenesis, i.e. the generation of new blood vessels by sprouting from existing blood vessels. In normal physiology, angiogenesis plays a vital role in the generation of new vasculature during embryogenesis, but it is mostly quiescent in the adult body, with transient activation during wound healing and the female reproductive cycle. While angiogenesis is tightly controlled by an intricate interplay of pro- and anti-angiogenic factors, it can be activated by growing solid tumors; this so-called "angiogenic switch" is recognized as a hallmark of solid tumors [1]. Indeed, it was shown in animal models that blood vessels were essential to support tumor growth beyond the size allowed by oxygen diffusion alone [2].

Among tumor-secreted pro-angiogenic factors, Vascular Endothelial Growth Factors (VEGFs) and in particular VEGF-A, have been identified as key factors for inducing tumor angiogenesis. VEGFs activate VEGF signaling in endothelial cells by binding to VEGF receptor tyrosine

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kinases (VEGFR1-3) [3]. By these means, VEGF can stimulate the proliferation and survival of endothelial cells and increase the permeability of vessels, thereby supporting the metabolic demands of the growing tumor. Given the importance of angiogenesis in tumor biology, drug development efforts in the past decades have been dedicated to targeting angiogenesis, with VEGF-A as a therapeutic target for inhibition of angiogenesis and normalization of tumor vasculature [2,4]. The validity of this approach was confirmed by a host of *in vivo* studies in a range of tumor models, demonstrating that inhibition of angiogenesis with a VEGF monoclonal antibody suppressed tumor growth [2].

Angiogenesis-independent roles of VEGF in cancer development and progression

The tumor microenvironment is a complex and interactive environment, composed of diverse cell types including endothelial cells, pericytes, immune cells and fibroblasts, as well as the extracellular matrix. Cancer cells influence their microenvironment by releasing extracellular signals, to induce tumor angiogenesis, stimulate cancer cell proliferation and promote immune tolerance to avoid recognition by the immune system. Recent research has shown that VEGF signaling, in particular VEGF-A induced signaling, has additional angiogenesis-independent roles in supporting tumor progression such as effects on: (i) cancer cells; promoting cancer cell proliferation, migration and invasiveness through the activation of vascular endothelial growth factor receptor (VEGFR) 1 signaling; (ii) cancer stem cells; promoting stemness through the activation the VEGFA/neuropilin-1 pathway and self-renewal through VEGFR2/STAT3 signaling; (iii) immune cells; immune suppression in the tumor microenvironment through VEGFR signaling in hematopoietic cells (VEGFR1), dendritic cells (VEGFR3), macrophages (VEGFR1 and VEGFR3), T cells (VEGFR-1 and VEGFR-2) and regulatory T cells (VEGFR1, VEGFR2 and NRP1) [5–8]. Specifically, VEGF signaling supports immune suppression by a wide range of mechanisms, including aberrant hematopoiesis, impaired maturation and function of dendritic cells and T cells, inhibition of trafficking and survival of activated T cells, as well as promoting the activity of immunosuppressive cells such as regulatory T cells and myeloid- derived suppressor cells [8]. Considering its role in promoting cancer immune tolerance, targeting of VEGF/VEGFR has been recognized as an approach to enhance antitumor immunity in cancer patients, particularly in combination with cancer immunotherapies.

Development of bevacizumab, the first therapy targeting VEGF

The first available anti-angiogenic therapy was bevacizumab (Avastin®, F. Hoffmann La-Roche AG, Switzerland), a humanized monoclonal antibody that binds to all circulating, soluble VEGF-A isoforms. By binding to VEGF-A, bevacizumab prevents the interaction of VEGF-A with VEGFR and thereby inhibits the activation of VEGF signaling pathways that promote neovascularization. *In vivo* studies demonstrated that bevacizumab inhibits vessel growth, induces regression of newly formed vessels, and normalizes the vasculature to facilitate the delivery of cytotoxic chemotherapy and also has direct effects on tumor cells [2]. Based on its mode of action, clinical development of bevacizumab was focused on tumor types known to be driven by angiogenesis. Specifically, an important role of VEGF in cancer progression was supported by the association of elevated intra-tumoral VEGF expression levels with poorer prognosis or more aggressive disease in several solid tumor types, including metastatic colorectal cancer (mCRC) [9], non-small-cell lung cancer (NSCLC) [10], metastatic breast cancer (mBC) [11,12], glioblastoma multiforme (GBM) [13] and ovarian cancer (OC) [14]. Furthermore, renal cell carcinoma (RCC) specifically is recognized as a highly vascular cancer, with dysregulation of hypoxia-inducible factor (HIF) resulting in particularly high levels of VEGF expression [15]. Clinical studies with bevacizumab have been conducted in a wide range of indications [16], including the first pivotal studies demonstrating the clinical value of bevacizumab in mCRC and NSCLC, and subsequent pivotal studies in RCC, mBC, GBM, OC and cervical cancer (CC) (Table 1). These studies demonstrated clinical benefits of bevacizumab, mainly used in combination with chemotherapy, across a wide range of solid tumor types. This review provides an overview of clinical experience and lessons learned in the 15 years since the initial approval of bevacizumab. Furthermore, promising results obtained in clinical studies with bevacizumab as part of novel combination treatment approaches are highlighted.

Clinical experience with bevacizumab

Initially approved for treatment of mCRC in the United States (US) and the European Union (EU) in 2004 and 2005, respectively, bevacizumab is now approved in a range of solid tumor indications (Fig. 1), and currently marketed in 134 countries worldwide. As one of the first therapies targeting the tumor microenvironment [2], the addition of bevacizumab to standard-of-care chemotherapy provided a novel and effective therapeutic option in a range of advanced cancers with poor prognosis, which had seen only minor improvements in treatment options before the advent of targeted therapies (Table 1). Although more than a dozen other anti-angiogenic therapies - mostly small molecule multi-kinase inhibitors targeting the VEGF and/or other pro-angiogenic or oncogenic signaling pathways - have been approved in the meantime [16–18], bevacizumab remains the most widely used and most thoroughly characterized angiogenesis inhibitor. Since 1997, more than 37 000 patients have been treated with bevacizumab in manufacturer-sponsored clinical trials across a broad range of indications (Table 2) [19]. Overall, it is estimated that more than 3 500 000 patients have received bevacizumab as part of their cancer treatment. The clinical impact of bevacizumab in each approved indication is discussed in more detail below.

Metastatic colorectal cancer

Colorectal cancer is one of the most common cancers and patients frequently present with metastatic disease. Prior to the availability of targeted therapies, treatment options for patients with mCRC were limited to chemotherapeutic agents. In 2004, AVF2107g, the first phase 3 study evaluating bevacizumab in first-line treatment of mCRC demonstrated significantly longer survival of patients with the addition of bevacizumab to chemotherapy (irinotecan, fluorouracil and leucovorin) compared to chemotherapy alone (10.6 vs 6.2 months, hazard ratio [HR] 0.66; $p < 0.001$) [20,21] (Table 1). These results led to the approval of bevacizumab as the first targeted therapy for patients with mCRC (Fig. 1). Several additional randomized studies with bevacizumab in mCRC followed, showing benefit of bevacizumab in combination with newer chemotherapy regimens (fluorouracil/leucovorin or capecitabine/oxaliplatin [XELOX]) in the first-line setting (AVF0780g and NO16966) and in combination with leucovorin/fluorouracil and oxaliplatin [FOLFOX] in the second-line setting (E3200), as well as the persistent benefit with bevacizumab treatment in multiple lines (e.g. ML18147) [22–25].

While other anti-angiogenic agents are approved in mCRC, their use is limited to later treatment lines, [26]. Several targeted therapies have become available in mCRC, including epidermal growth factor receptor (EGFR) inhibitors for KRAS, NRAS and BRAF wild-type mCRC, as well as BRAF and HER2 inhibitors for mCRC with BRAF mutations or human epidermal growth factor receptor 2 (HER2)-amplifications, respectively [22,28]. Furthermore, the use of immune checkpoint inhibitors is a novel treatment approach for mCRC with microsatellite instability and DNA mismatch repair deficiency. Since its approval over a decade ago, bevacizumab remains a standard-of-care therapy in mCRC, recommended in combination with chemotherapy for induction and as maintenance treatment [22,28].

Table 1
Overview of pivotal clinical trials with bevacizumab in approved indications.

Study name and ID Reference	Study design	Patient population (N)[‡]	Treatment line	Treatment arms[§] (n)	Dose and regimen	Endpoints	Median PFS (mths) [#]	HR (95%CI) p-value	Median OS (mths) [#]	HR (95%CI) p-value
Metastatic colorectal cancer										
AVF2107g (NCT00109070) Hurwitz H et al (2004) NEJM [20] Hurwitz H et al (2005) JCO [21]	Phase 3 blinded randomized controlled	mCRC (N = 813)	1L	• Bev + IFL (n = 402)¢ • IFL (n = 411) • Bev + FL (n = 110) *treatment arm discontinued after first interim analysis demonstrating safety of IFL + Bev*	• Bev:5 mg/kg/every 2 wks • I: 125 mg/m^2 weekly for 4 wks/6 wks cycle • F: 500 mg/m^2 weekly for 4 wks/6 wks cycle • L: 20 mg/m^2 weekly for 4 wks/6 wks cycle	• 1°: OS • 2°: PFS, RR, DOR, SFTY, QoL	Bev + IFL vs IFL: 10.6 vs 6.2	0.54 (0.45–0.66) **p ≤ 0.0001**[*]	Bev + IFL vs CIFL: 20.3 vs 15.6 *(F/U at 385 deaths)*	0.66 (0.54–0.81) **p ≤ 0.0001**[*]
							Bev + FL vs IFL 8.8 vs 6.8	0.86 (0.60–1.24) p = 0.42	Bev + FL vs IFL 18.3 vs 15.1	0.82 (0.59–1.1-5) p = 0.25)
AVF0780g Kabbinavar F et al (2003) JCO [23]	Phase 2, open-label randomized controlled	mCRC (N = 104)	1L	• Bev_L + FU/LV (n = 35) • Bev_H + FU/LV (n = 33) • FU/LV (n = 36)	• Bev_L: 5 mg/kg/every 2 wks • Bev_H:10 mg/kg/every 2 wks • FU 500 mg/m^2 + LV 500 mg/m^{2}weekly, 6 wks/8 wks cycle	• 1°: PFS • 2°: OS, RR	Bev_L + FU/LV vs FU/LV: 9.0 vs 5.2	0.46 (0.34–0.73) **p = 0.005**[*]	Bev_L + FU/LV vs FU/LV: 17.7 vs 13.6	0.52 (NR) p = 0.73
							Bev_H + FU/LV vs FU/LV 7.2 vs 5.2	0.66 (0.54–0.81) p = 0.22	Bev_H + FU/LV vs FU/LV: 15.2 vs 13.6	1.01 (NR) p = 0.98
NO16966 (NCT00069095) Saltz LB et al (2008) JCO [24]	Phase 2 blinded randomized controlled	mCRC (N = 1400)	1L	• Bev_H + XELOX (n = 350) • Bev_L + FOLFOX (n = 349) • XELOX (n = 350) • FOLFOX-4 (n = 351)	• Bev_L: 5 mg/kg/every 2 wks • Bev_H:7.5 mg/kg/every 3 wks • XELOX: (CP: 1000 mg/m^2/bid/2 wks/3 wks cycle; OX: 130 mg/m^2/3 wks) • FOLFOX: (FU: 400 mg/m^2/; LV: 200 mg/m^2; OX: 200 mg/m^2) D1&2/q2 wks	• 1°: PFS • 2°: PFS, OS, BOR, TTF, TtR, DOR	Bev_H + XELOX vs XELOX: 9.4 vs 8.6	0.77 (0.63–0.94)[¤] **p = 0.00263**[¤*]	Bev_H + XELOX vs XELOX: 21.4 vs 19.2	0.84 (0.68–1.04) p = ns
							Bev_L + FOLFOX vs FOLFOX: 9.3 vs 7.4	0.89 (0.73–1.08)[¤] p = 0.18713[¤]	Bev_L + FOLFOX vs FOLFOX: 21.2 vs 20.3	0.89 (0.73–1.0-8) p = 0.077
							Bev + XELOX/FOLFOX vs XELOX/FOLFOX 9.4 vs 8.0 *(at median F/U 15.6mths)*	0.83 (0.72–0.95) **p = 0.0023**[*]	Bev + XELOX/FOLFOX vs XELOX/FOLFOX 21.3 vs 19.9 *(at median F/U 27.6 mths)*	0.89 (0.76–1.0-3) p = ns
E3200 NCI-2012–02417 (NCT00025337) Giantonio BJ et al (2007) JCO [25]	Phase 3 open-label randomized controlled	Advanced or metastatic CRC (N = 821)	2L	• Bev (n = 243) • Bev + FOLFOX (n = 287) • FOLFOX (n = 291)	• Bev: 10 mg/kg/every 2 wks • FOLFOX:(FU: 1000 mg/m^2; LV: 400 mg/m^2; OX: 85 mg/m^2/D1 only) D1&2/q2wks	• 1°: OS • 2°: PFS, RR (RECIST), SFTY	Bev + FOLFOX vs FOLFOX: 7.3 vs 4.7 *(at median F/U: 28mths)*	0.52 (0.42–0.65) **p ≤ 0.0001**[*]	Bev + FOLFOX vs FOLFOX: 12.9 vs 10.8 *(at median F/U: 28mths)* Bev: 10.2	0.75 (0.63–0.89) **p = 0.0011**[*]
ML18147 (NCT00700102)	Phase 3 open-label	mCRC, progressing within 3 mths after discontinuation of	2L	• Bev + chemo (n = 409)	• Bev: 5 mg/kg/every 2 wk or 7.5 mg/kg/every 3 wks	• 1°: OS (from randomization)	Bev + chemo vs chemo: 5.7 vs 4.1	0.68 (0.59–0.78) **p < 0.0001**[*]	Bev + chemo vs chemo: 11.2 vs 9.8	0.81 (0.69–0.94); **p = 0.0062**[*]

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Table 1 (*continued*)

Study name and ID Reference	Study design	Patient population (N)[£]	Treatment line	Treatment arms[§] (n)	Dose and regimen	Endpoints	Median PFS (mths) [#]	HR (95%CI) p-value	Median OS (mths) [#]	HR (95%CI) p-value
Bennoua J et al. (2013) Lancet [22]	randomized controlled	1L treatment with bev + chemo (N = 820)		• Chemo (n = 411) *Chemo = oxaliplatin- or irinotecan-based, depending on previous 1L treatment, at discretion of investigator*		• 2°: PFS, OS (from start of 1L treatment), RR (RECIST), SFTY, on-treatment PFS	*(at median F/U: 9.6 and 11.1mths in bev + chemo and chemo groups, respectively)*		*(at median F/U: 9.6 and 11.1mths in bev + chemo and chemo groups, respectively)*	
Non-small cell lung cancer										
E4599 NCI-2012–02947 (NCT00021060) Sandler A et al (2006) NEJM [30]	Phase 2/3 open-label randomized controlled	Advanced (stage IIIB/IV)/ Recurrent/ Metastatic NSCLC (not squamous type) (N = 850)	1L	• Bev + PTX + CB (n = 417) • PTX + CB (n = 433)	• Bev: 15 mg/kg/every 3 wks • PTX: 200 mg/m^2 + CB: AUC6 every 3 wks	• 1°: OS • 2°: PFS, BMKR	Bev + PTX + CB vs PTX + CB: 6.2 vs 4.5 *(median F/U:19 mths,* min *18 mths, 779 events)*	0.66 (0.56–0.76) **p ≤ 0.001**[*]	Bev + PTX + CB vs PTX + CB: 12.3 vs 10.3 *(median F/U:19 mths,* min *18 mths, 649 deaths)*	0.79 (0.67–0.92) **p = 0.003**[*]
AVAiL /BO117704 (NCT00806923) Reck M et al, (2009), JCO, Reck M et al, (2010) AnnOnco [34,35]	Phase 3 open-label randomized controlled	Advanced (stage IIIB/IV)/ Recurrent/ Metastatic NSCLC (not squamous type) (N = 1043)	1L	• Bev_L + CIS + GEM (n = 345) • Bev_H + CIS + GEM (n = 351) • CIS + GEM (n = 347)	• Bev_L: 7.5 mg/kg/every 3 wks • Bev_H:15 mg/kg/every 3 wks • CIS: 80 mg/m^2 + GEM: 1250 mg/m^2 D1 + 8/q3 wks	• 1°: PFS • 2°: OS, TTF, RR, DOR, SFTY	Bev_L + CIS + GEM vs CIS + GEM: 6.7 vs 6.1	0.75 (0.62–0.91) **p = 0.0026**[*]	Bev_L + CIS + GEM vs CIS + GEM: 13.6 vs 13.1	0.93 (0.78–1.11) p = 0.420
							Bev_H + CIS + GEM vs CIS + GEM: 6.5 vs 6.1 *(at F/U* min *7 months or 430 events; 665 PFS events)*	0.82 (0.68–0.98) **p = 0.0301**[*]	Bev_H + CIS + GEM vs CIS + GEM:13.4 vs 13.1 *(at F/U: greater than 12.5 mths,* max *32 mths; 715 deaths)*	1.03 (0.86–1.2-3) p = 0.076[¥]
JO25567[¶] Seto, T et al (2014) Lancet [36]	Phase 2 open-label randomized controlled	Advanced (stage IIIB/IV or recurrent activated EGFR NSCLC (not squamous type) (N = 152)	1L	• Bev + ERL (n = 75) • ERL (n = 77)	• Bev: 15 mg/kg/every 3 wks • ERL: 150 mg/day	• 1°: PFS • 2°: OS, SFTY	Bev + ERL vs ERL: 16.0 vs 9.7	0.54 (0.36–0.79) **p = 0.0015**[*]	NR	NR
NEJ026[¶] Saito, H et al (2019) Lancet [37]	Phase 3 open-label randomized	Advanced (stage IIIB/IV or recurrent activated EGFR NSCLC (not squamous type) (N = 152)	1L	• Bev + ERL (n = 114) • ERL (n = 114)	• Bev: 15 mg/kg/every 3 wks • ERL: 150 mg/day	• 1°: PFS • 2°: OS, SFTY	Bev + ERL vs ERL: 16.9 vs 13.3 (median F/U 12.4 mths)	0.605 (0.42–0.89) **p = 0.016**[*]	NR	NR
IMpower150 GO29436 (NCT02366143) Socinski et al (2018)	Phase 3 open-label randomized	Stage IV NSCLC, including EGFR/ ALK alterations and low PD-L1	1L	• Bez + ATZ + PTX + CB (n = 400) • Bev + PTX + CB (n = 400)	• Bev: 15 mg/kg • ATZ: 1200 mg • PTX: 200 mg/kg + CB: AUC6	• 1°: PFS, PD • 2°: PFS, PD, OR, DOR, OS, BCHM, QoL	ATZ + Bev PTX + CB vs Bev PTX + CB	0.59 (0.50–0.70) **p < 0.001**[*]	ATZ + Bev PTX + CB vs Bev PTX + CB 19.2 vs 14.7 mths	0.78 (0.64–0.96) **p = 0.02**[*]

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Table 1 (*continued*)

Study name and ID Reference	Study design	Patient population (N)[£]	Treatment line	Treatment arms[§] (n)	Dose and regimen	Endpoints	Median PFS (mths) [#]	HR (95%CI) p-value	Median OS (mths) [#]	HR (95%CI) p-value
NEJM [41]		expression (N = 1202)		• ATZ + PTX + CB (n = 404)	• *(all every 3 wks/4–6 wks cycle)*		8.3 vs 6.8			
Metastatic breast cancer[^]										
ECOG E2100 (NCT00028990) Miller K et al (2007) NEJM [43]	Phase 3 open-label randomized controlled	HER2-negative, mBC (N = 673)	1L	• Bev + PTX (n = 326) • PTX (n = 347)	• Bev: 10 mg/kg/every 2 wks • PTX: 90 mg/m^2 D1/8/15 every 28 days	• 1°: PFS • 2°: ORR, OS, SFTY, QoL	Bev + PTX vs PTX: 11.8 vs 5.9 *(FA: 624 PFS events)*	0.60 **p < 0.001**[*]	Bev + PTX vs PTX: 26.7 vs 25.2 *(FA: 483 deaths)*	0.88 p = 0.16
AVADO/BO17708 (NCT00333775) Miles DW et al (2010) JCO [45]	Phase 3 blinded randomized controlled	HER2-negative, locally recurrent/ metastatic breast cancer (N = 736)	1L	• Bev$_L$ + DTX (n = 248) • Bev$_H$ + DTX (n = 247) • DTX (n = 241)	• Bev$_L$: 7.5 mg/kg/every 3 wks • Bev$_H$: 15 mg/kg/every 3 wks • DTX: 100 mg/m^2 every 3 wks	• 1°: PFS • 2°: OS, BOR, DOR, TTF, SFTY, QoL	Bev$_L$ + DTX vs DTX: 9.0 vs 8.2	0.86 (0.72–1.04) p = 0.12 0.77	Bev$_L$ + DTX vs DTX: 30.8 vs 31.9	1.05 (0.81–1.36) p = 0.72
							Bev$_H$ + DTX vs DTX: 10.1 vs 8.2 *(median F/U: 25mths, 665 events)*	(0.64–0.93) **p = 0.006**[*]	Bev$_H$ + DTX vs DTX: 30.2 vs 31.9 *(FA: median F/U: 25mths, 394 deaths)*	1.03 (0.7–1.33) p = 0.85[¥]
RIBBON-1 BO20094 (NCT00262067) Robert et al (2011) JCO [46]	Phase 3 blinded randomized controlled	HER2-negative, recurrent or metastatic breast cancer (N = 1237)	1L	• Bev + CP $_1$ (n = 404) • Bev + PTX/DTX/ DOX/EPI (n = 413) • CP (n = 206) • PTX/DTX/DOX/EPI (n = 207)	• Bev: 15 mg/kg/every 3 wks • CP: 200 mg/m^2 14 days/3 wks • PTX: 200 mg/m^2/3 wks • DTX: 75/100 mg/m^2/3 wks • DOX: 50–60 mg/m^2/3 wks • EPI: 90–100 mg/m^2/3 wks	• 1°: PFS • 2°: OS, ORR, DOR, 1-year survival rate, SFTY	Bev + CP vs CP: 8.6 vs 5.7 *(median F/U: 15.6mths)*	0.69 0.56–0.84 **p < 0.001**[*]	Bev + CP vs CP: 29.0 vs 21.2	0.847 0.63–1.14 p = ns
							Bev + PTX/ DTX/DOX/EPI vs PTX/DTX/ DOX/EPI: 9.2 vs 8.0 *(median F/U: 19.2mths)*	0.64 0.52–0.80 **p < 0.001**[*]	Bev + PTX/DTX/ DOX/EPI vs PTX/ DTX/DOX/EPI 25.2 vs 23.8	1.032 0.77–1.38 p = ns[¥]
Renal cell carcinoma										
AVOREN/BO17705 (NCT00738530) Escudier B et al (2007) Lancet; Escudier B et al (2010) JCO [42,50]	Phase 3 blinded randomized controlled	Metastatic clear cell RCC (N = 649)	1L	• Bev + IFNα2a (n = 327) • IFNα2a (n = 322)	• Bev: 10 mg/kg/every 2 wks • IFNα2: 9 MIU/x3/wk	1°: OS 2°: PFS, ORR, SFTY	Bev + IFNα2a vs IFNα2a: 10.2 vs 5.4 *(F/U: ~13mths, 505 events)*	0.63 (0.52–0.75) **p = 0.0001**[*]	Bev + IFNα2a vs IFNα2a: 23.3 vs 21.3 *(F/U to 4.25 yrs]*	0.91 (0.76–1.10) p = 0.3360[¥]
CALGB 90,206 (NCT00072046) Rini BI et al (2008)	Phase 3 blinded randomized controlled	Metastatic clear cell RCC (N = 732)	1L	• Bev + IFNα2a (n = 369) • IFNα2a (n = 363)	• Bev: 10 mg/kg/every 2 wks • IFNα2: 9 MIU/x3/wk	1°: OS 2°: PFS, ORR, SFTY	Bev + IFNα2a vs IFNα2a: 8.5 vs 5.2	0.71 (0.61–0.83) **p = 0.0001**[*]	Bev + IFNα2a vs IFNα2a: 18.3 vs 17.4 *(median F/U 46.2 months]*	0.86 (0.73–1.01) p = 0.069[¥]

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Table 1 (*continued*)

Study name and ID Reference	Study design	Patient population (N)[£]	Treatment line	Treatment arms[§] (n)	Dose and regimen	Endpoints	Median PFS (mths) [#]	HR (95%CI) p-value	Median OS (mths) [#]	HR (95%CI) p-value
JCO Rini BI et al (2010) JCO [51,52]							*(F/U: ~657 events)*			
Glioblastoma[¢]										
AVF3708g (NCT00345163) Friedman HS et al (2009) JCO [56]	Phase 2 open-label randomized	Relapsed (1st/2nd) GBM (N = 167)	2L	• Bev + IRI (n = 115) • Bev (n = 114)	• Bev: 10 mg/kg/ 2 wks • IRI: 340 OR 125 mg/m^2 every 2 wks	• 1°: OR, PFS (at 6mths) • 2°: OS, DOR, SFTY	Bev + IRI vs Bev: 5.6 (4.4–6.2) vs 4.2 (2.9–5.8) *(F/U:* min *6mths for all patients)*	NA	Bev + IRI vs Bev: 8.7 (7.8–10.9) vs 9.2 (8.2–10.7) *(F/U:* min *8mths for all patients)*	NA[¥]
EORTC 26101/MO22968 (NCT01290939) Wick W et al (2017) NEJM [57]	Phase 3, open-label randomized	Relapsed (1st) GBM (N = 437)	2L	• Bev + LO (n = 288) • LO (n = 149)	• Bev: 10 mg/kg/ 2 wks • LO: 90 mg/m^2 every 6 wks	• 1°: OS • 2°: PFS, RR, DOR, SFTY, BCHM	Bev + LO vs LO: 4.2 vs 1.5 *(401 progression events)*	0.49 (0.39–0.61) **p < 0.001**[*]	Bev + LO vs LO: 9.1 (8.1–10.1) vs 8.6 (7.6–10.4) *(329 events)*	0.95 (0.74–1.21) p = 0.65[¥]
AvaGlio/BO21990 (NCT00943826) Chinot OL et al (2014) NEJM [60]	Phase 3 blinded randomized controlled	Newly diagnosed GBM, WHO perform status ≤ 2 (N = 921)	1L	• Bev + RT + TMZ (n = 463) • RT + TMZ (n = 458)	*Initial* • Bev: 10 mg/kg/ 2 wks/6 wks, • RT: 2 Gy/5 days/weekly/6 wks • TMZ: 75 mg/m^2 daily up to 49 days *Maintenance:* • Bev: 10 mg/kg/ 2 wks/ 28 days/6 cycles • TMZ: 150–200 mg/m^2 D1-5 *Monotherapy:* • Bev: 15 mg/kg/ 3 wks to PD	• 1°: PFS/OS • 2°: PFS/OS/ SFTY/QoL	Bev + RT + TMZ vs RT + TMZ: 10.6 vs 6.2 *(median F/U ~ 14mths, 741 events)*	0.64 (0.55–0.74) **p < 0.0001**[*]	Bev + RT + TMZ vs RT + TMZ: 16.8 vs 16.7 *(median F/U ~ 16mths, 741 events)*	0.88 (0.72–1.02) p = 0.10[¥]
RTOG0825 (NCT00884741) Gilbert MR et al. (2014) NEJM [61]	Phase 3 double-blinded randomized placebo-controlled	Newly diagnosed GBM, Karnofsky perform status ≥ 70 (N = 637)	1L	• Bev + RT + TMZ (n = 320) • RT + TMZ (n = 317)	*Initial:* • Bev: 10 mg/kg every 2 wks, up to 24 doses • RT: 2 Gy/5 days/weekly/6 wks • TMZ: 75 mg/m^2 daily up to 49 days *Maintenance:* • TMZ: 150–200 mg/m^2 D1-5/28 days/6–12 cycles	• 1°: OS and PFS (co-primary)	Bev + RT + TMZ vs RT + TMZ: 10.7 vs 7.3 *(median F/U 20.5 mths, 512 events)*	0.79 (0.66–0.94) **p < 0.007**[*]	Bev + RT + TMZ vs RT + TMZ: 15.7 vs 16.1 *(median F/U 20.5 mths, 413 events)*	1.13 (0.93–1.37) p < 0.21[*]
Ovarian, fallopian tube and primary peritoneal cancer										
GOG-0218 NCI-2009–00590 (NCT00262847)	Phase 3 blinded	Advanced (Stage IIIB-IV) OC, FTC or PPC, post	1L	• Bev_6 + PTX + CB: (n = 625)	• Bev_6: 15 mg/kg/ 3 wks/6 cycles	• 1°: PFS • 2°: OS, SFTY, QoL	Bev_6 + PTX + CB vs PTX + CB: 11.2 vs 10.3	0.908 (0.795–1.040) p = 0.16	Bev_6 + PTX + CB vs PTX + CB: 38.7 vs 39.3	1.036 (0.83–1.30) p = 0.76

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Table 1 (*continued*)

Study name and ID Reference	Study design	Patient population (N)[£]	Treatment line	Treatment arms[§] (n)	Dose and regimen	Endpoints	Median PFS (mths) [#]	HR (95%CI) p-value	Median OS (mths) [#]	HR (95%CI) p-value
Burger et al (2011) NEJM [66] Tewari et al (2019) [65]	randomized controlled	debulking surgery (N = 1873)		• Bev_{22} + PTX + CB: (n = 623) • PTX + CB (n = 625)	• Bev_{22}: 15 mg/kg/ 3 wks/22 cycles • PTX: 175 mg/m^2 + CB: AUC6 every 3 wks/6 cycles		Bev_{22} + PTX + CB vs PTX + CB: 14.1 vs 10.3 *(F/U: 17.4mths, 1201 events)*	0.717 (0.625–0.824) **p ≤ 0.001**[*]	Bev_{22} + PTX + CB vs PTX + CB: 39.7 vs 39.3 *(F/U: 17.4mths, 444 deaths)*	1.036 (0.73–1.1-5) p = 0.45[¥]
									Bev_{conc} $_{+maint}$ + PTX + CB vs PT + CB: 43.4 vs 41.1 Bev_{conc} PTX + CB vs PTX + CB: 40.8 vs 41.1	0.96 (0.85–1.0-9) p = 0.53 1.06 (0.94–1.2-0) p = 0.34
ICON7 (NCT00483782) Perren et al (2011) NEJM, Oza AM et al (2015) Lancet Onco [67,68]	Phase 3 open label randomized controlled	Advanced (Stage IIIB-IV) or high-risk Stage I/IIA OC, FTC or PPC, post debulking surgery (N = 1528)	1L	• Bev_6 + PTX + CB (n = 719) • Bev_{18} + PTX + CB (n = 470) • PTX + CB (n = 696)	• Bev_6: 7.5 mg/kg/ 3 wks/6 cycles • Bev_{18}: 7.5 mg/kg/ 3 wks/22 cycles • PTX: 175 mg/m^2 + CB: AUC5/6 every 3 wks/6 cycles)	• 1°: PFS • 2°: OS, ORR, DOR, PFI, SFTY, QoL, HEc	Bev_{all}+PTX+CB vs PTX + CB: 19.9 vs 17.5 *(F/U at median 19.4 and 16.3 mths)*	0.93 (0.83–1.05) p = 0.25	Bev_{all} + PTX + CB vs PTX + CB: 58.6 vs 58.0 *(F/U at median 48.8 and 48.6 mths)*	0.99 (0.85–1.14) p = 0.85
							Subgroup analyses high-risk subset[+]: Bev_{all}+PTX+CB vs PTX + CB: 16.0 vs 10.5 *(F/U: at median 15.6 and 10.1 mths)*	*0.73 (0.61–0.88)* ***p = 0.001***[*]	Bev_{all} + PTX + CB vs PTX + CB *39.7 vs 30.2 (F/U at median 38.9 and 29.0 mths)*	*0.78 (0.63–0.97)* ***p = 0.03***[*]
AVF4095g/ OCEANS (NCT00434642) Aghajanian C et al (2012) JCO; Aghajanian C et al (2015) GynOnco [69,70]	Phase 3 blinded randomizedcon-trolled	Recurrent platinum sensitive OC, FTC or PPC (N = 484)	2L	• Bev + CB + GEM (n = 242) • CB + GEM : CB + GEM (n = 242)	• Bev: 15 mg/kg/ every 3 wks • GEM: 1000 mg/m^2 +CB: AUC4) D1 + 8/q3w	• 1°: PFS • 2°: ORR, OS, DOR	Bev + CB + GEM vs CB + GEM: 12.4 vs 8.4 *(F/U: ~24mths, 338 events)*	0.484 (0.388–0.605) **p ≤ 0.0001**[*]	Bev + CB + GEM vs CB + GEM: 33.6 vs 32.9 *(F/U: ~57mths, 353 events)*	0.952 (0.77–1.17) p = 0.6479[¥]
GOG-0213/ML01187 (NCT00565851) Coleman RL et al (2017) Lancet Oncol, Coleman RT et al (2018) ASCO [71,72]	Phase 3 open label randomized controlled	Recurrent platinum sensitive OC, FTC or PPC (N = 674)	2L	• Bev + PTX + CB (n = 377) • PTX + CB (n = 337)	• Bev: 15 mg/kg/ 3 wks/6 cycles • PTX: 175 mg/m^2 + CB: AUC5 every 3 wks/6 cycles	• 1°: OS • 2°: PFS, SFTY, QoL, BMKR	Bev + PTX + CB vs PTX + CB: 13.8 vs 10.4 *(F/U: 49.6mths)*	0.628 (0.534–0.739) **p ≤ 0.0001**[*]	Bev + PTX + CB vs PTX + CB: 42.2 vs 37.3 *(F/U: 49.6mths, 215 deaths)*	0.823 (0.68–1.00) **p = 0.0447-**[*¥]
			2L			• 1°: PFS				

(*continued on next page*)

Table 1 (*continued*)

Study name and ID Reference	Study design	Patient population (N)‡	Treatment line	Treatment arms§ (n)	Dose and regimen	Endpoints	Median PFS (mths) #	HR (95%CI) p-value	Median OS (mths) #	HR (95%CI) p-value
AURELIA MO22224 (NCT00976911) Pujade-Lauraine E et al (2014) JCO [73]	Phase 3 open label randomized controlled	Recurrent platinum resistant OC, FTC or PPC (N = 361)		• Bev + pgDOX + PTX/TCN (n = 377) • pgDOX + PTX/TCN (n = 182)	• Bev: 10 mg/kg/2 wks OR 15 mg/kg/3 wks • pgDOX: 40 mg/m^2/4 wks; • PTX: 1.25 mg/m^2/D1, 8, 15/4 wks; • TCN: 4 mg/m^2/D1, 8, 15/4 wks OR 1.25 mg/m^2/D1, 5/3 wks	• 2°: OS, ORR, SFTY, QoL	Bev + pgDOX + -PTX/TCN vs pgDOX + PTX/TCN: 6.7 vs 3.4 *(F/U: ~13.5mths)*	0.480 (0.38–0.60) **p ≤ 0.001***	Bev + pgDOX + PTX/TCN vs pgDOX + PTX/TCN: 16.6 vs 13.3 *(F/U: ~70% death)*	0.85 (0.85–1.08) p = 0.174¥
Cervical cancer										
GOG-0240 NCI-2009–01084 (NCT00803062) Tewari KS et al (2014) NEJM; Tewari KS et al (2017) Lancet [82,83]	Phase 3 open label randomized controlled	Persistent or Recurrent (stage IVB) CC (N = 452)	1L/2L	• Bev + PTX + CIS (n = 115) • Bev + PTX + TCN (n = 112) • PTX + CIS (n = 114) • PTX + TCN (n = 111)	• Bev: 15 mg/kg/3 wks • CIS: 50 mg/m^2 every 3 wks; • PTX: 135 OR 175 mg/m^2 every 3 wks; • TCN: 0.75 mg/m^2 D1/3 every 3 wks	• 1°: OS, PFS, TR, SFTY • 2°: QoL, BMKR	Bev + PTX + CIS/PTX + TCN $_1$ vs PTX + CIS/PTX + TCN: 8.2 vs 5.9 (F/U: ~20.8mths, 367 events)	0.67 (0.54–0.82) **p = 0.002***	Bev + PTX + CIS/PTX + TCN vs PTX + CIS/PTX + TCN $_1$: 16.8 vs 13.3 *(FA:348 deaths)*	0.77 (0.62–0.95) **p = 0.007-***
							Bev + PTX + CIS vs PTX + CIS: 8.2 vs 5.9†	0.67† (0.54–0.82) **p = 0.002*†**	Bev + PTX + CIS vs PTX + CIS 17.5 vs 14.3	0.68 (0.48–0.97) **p = 0.04***
							Bev + PTX + TCN vs PTX + TCN 7.36 vs 5.29†	NR† p = NR†	Bev + PTX + TCN vs PTX + TCN 16.2 vs 12.7 *(F/U: ~20.8mths, 223 events)*	0.74 (0.53–1.05) p = 0.09¥

Abbreviations: AUC(X): dose calculated to produce an area under the concentration–time curve of (X) mg per milliliter; Bev: Bevacizumab; BMKR: Biomarker assessment; BOR: Best overall response; CP: Capecitabine; CB: Carboplatin; CIS: Cisplatin; CT: Chemotherapy; DOR: Duration of response; DTX: Docetaxel; EGFR: Epidermal growth factor receptor; EPI: Epirubicin; ERL: Erlotinib; GEM: Gemcitabine; FOLFOX: Folinic acid (FOL), fluorouracil (F) and oxaliplatin (OX); FU: fluorouracil; F/U: Follow-up; HEc: Health Economics; FA: Final analysis; FIGO: International Federation of Gynecology and Obstetrics; HER2: human epidermal growth factor receptor 2 (EGFR2/HER2); IFNα2a: Interferon-alfa 2a LV: leucovorin; LO: Lomustine; OX: oxilaplatin; mth(s): month(s); NR: Not reported/recorded; ns: not significant; OR: objective response; ORR: objective response rate; OS: Overall survival; PD: Progressive disease; PFI: Progression-free interval; PFS: Progression-free survival; PTX: Paclitaxel; QoL: Quality of life; RECIST: response evaluation criteria in solid tumors; RR: Response rate; RT: Radiotherapy; TCN: Topotecan; TMZ: temozolomide: TTF: Time to treatment failure; TtR: Time to response; SFTY: Safety/Toxicity; wk(s): week(s); XELOX: capecitabine (XEL/Xeloda) and oxaliplatin (OX); yr(s): year(s) 1L: First-line treatment; 2L: Second-line treatment.

Footnotes: Underlined indicates combination targeted therapy.

^Only approved for use in EU.

¢Only approved for use in US.

* and in bold: p-value statistically significant.

‡ Total number of enrolled patients.

§ Number of patients included in primary endpoint analysis for each arm.

At specified analysis timepoint.

¤ Using the on-treatment PFS definition, significant results were evident in both the XELOX (HR, 0.61; 97.5% CI, 0.48 to 0.78; P < 0.0001) and FOLFOX-4 subgroups (HR, 0.65; 97.5% CI, 0.50 to 0.84; P = 0.0002).

¥ Potential confounding influence on overall survival due to cross-over or treatment with subsequent therapies administered after progressive disease in greater than 10% patients.

¶ No NCT number as clinical Trial not registered with clinicaltrials.gov.

+ High-risk of progression subgroup, defined at time of primary progression-free survival analysis (stage IV disease, inoperable stage III disease, or suboptimally debulked [greater than1cm] stage III disesae).

† updated clinical trials.gov data.

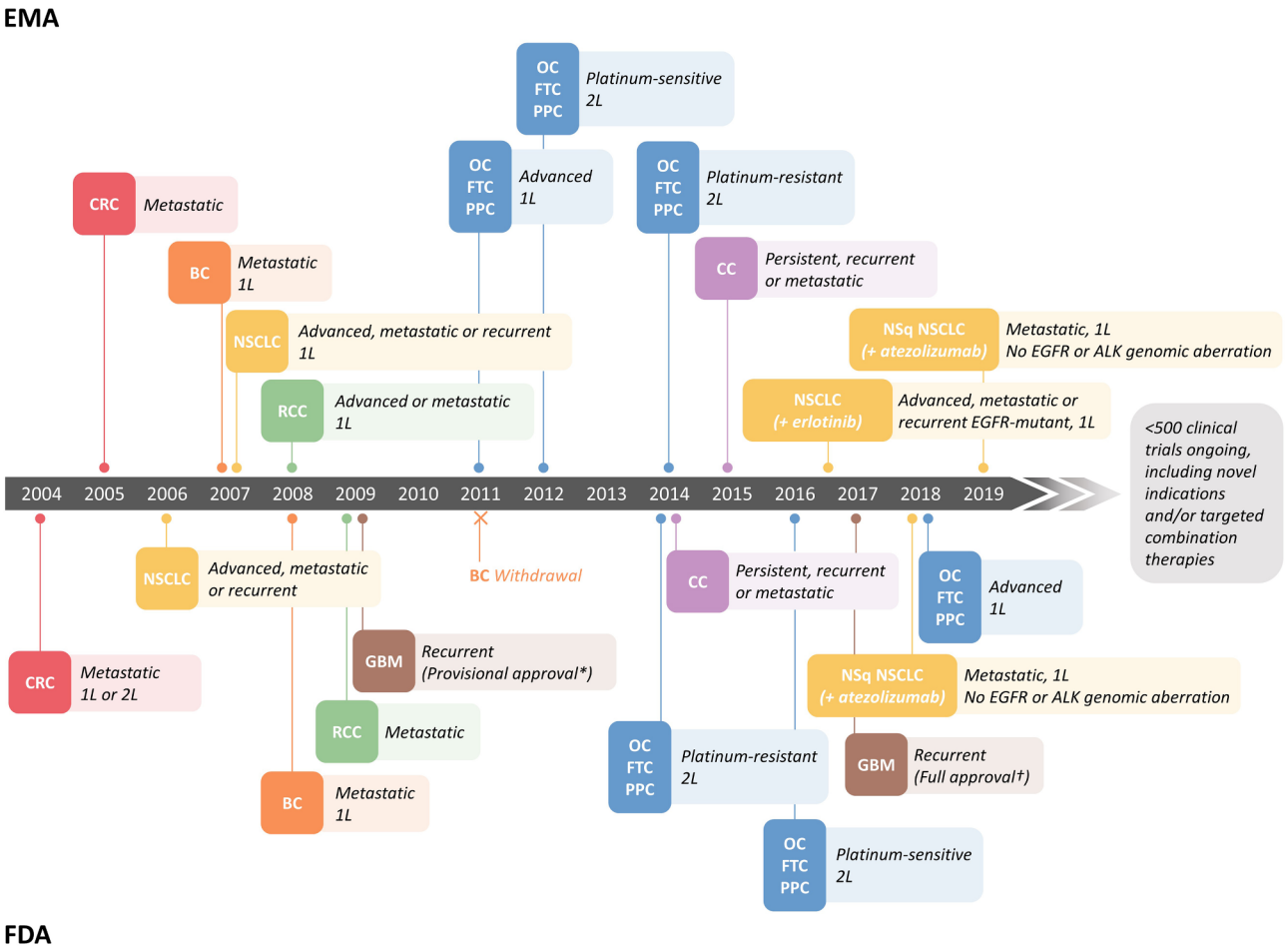

Fig. 1. Timeline of bevacizumab approvals. **Abbreviations**: 1L: First-line treatment; 2L: Second-line treatment; ALK: anaplastic lymphoma kinase; BC: breast cancer; CC: Cervical cancer; CRC: Colorectal cancer; EGFR: Epidermal growth factor receptor; EMA: European Medicines Agency; FDA: (US) Food and Drug Administration; FTC: Fallopian tube cancer; GBM: Glioblastoma; PPC: Primary peritoneal cancer; NSCLC: Non-small-cell lung cancer, Nsq-NSCLC: non-squamous non-small-cell lung cancer; RCC: Renal cell carcinoma. **Footnotes**: * Provisional approval granted under FDA's accelerated approval program based on surrogate endpoint. † Full approval granted, based on totality of evidence of bevacizumab in GBM.

Non-small cell lung cancer

Lung cancer is among the most common cancers in both in men and women, with the majority of patients presenting with advanced disease. Prior to the availability of targeted therapies, median survival for patients with non-squamous advanced NSCLC, the most common form of lung cancer, was only seven to eight months, despite aggressive platinum-based chemotherapy [29]. Bevacizumab was among the first targeted therapies available for this cancer and the first drug to help these patients live longer than one year when added to chemotherapy. Approval in the first-line setting was based on results of the pivotal study E4599 which demonstrated a reduction in the risk of death by 21% (HR: 0.79, p = 0.003) with the addition of bevacizumab to carboplatin plus paclitaxel compared to carboplatin plus paclitaxel alone and an improvement in median OS from 10.3 to 12.3 months [30] (Table 1, Fig. 1). Further clinical studies confirmed progression-free survival (PFS) and overall survival (OS) benefits for bevacizumab in combination with chemotherapy in the first-line setting (AVAiL), as well as in the maintenance setting [31–35].

In about 10–20% of patients with metastatic NSCLC, targetable driver mutations are present, most frequently aberrations in the EGFR gene. Patients with EGFR-mutated tumors are usually treated with EGFR tyrosine kinase inhibitor (TKI) monotherapy; however, although multiple lines of TKI therapy are now available, resistance eventually occurs in almost all patients. Results of the pivotal study JO25567 showed that the addition of bevacizumab to the EGFR TKI erlotinib reduced the risk of disease progression by 46% (HR: 0.54, p = 0.015) compared to erlotinib alone [36] (Table 1). Based on these results, the combination therapy of bevacizumab and erlotinib was recently approved for treatment of NSCLC with EGFR-activating mutations (Fig. 1). These results were further confirmed by two phase 3 studies (NEJ026 and Artemis) [37,38]. Besides EGFR TKIs, further targeted therapies have become available in the past decade for patients with NSCLC, targeting other molecular aberrations such as anaplastic lymphoma kinase (ALK), BRAF, neurotrophic tropomyosin receptor kinase (NTRK) and ROS1 [39,40]. Furthermore, the advent of cancer immunotherapy has profoundly transformed the treatment landscape of NSCLC, with immune checkpoint inhibitors achieving durable responses in subsets of patients [39,40]. Recently, the combination of the immune checkpoint inhibitor atezolizumab and bevacizumab was approved in non-squamous NSCLC, based on the pivotal study IMpower150, which demonstrated a reduction in the risk of progression by 38% (HR 0.62, p < 0.001) with the addition of atezolizumab to bevacizumab and chemotherapy compared to bevacizumab and chemotherapy alone; this benefit was observed regardless of EGFR and ALK status [41].

Even though the treatment landscape for NSCLC has substantially evolved, bevacizumab likely remains an important part of the treatment landscape in the future, including as a partner in combinations with other targeted therapies such as erlotinib and atezolizumab [39,40].

Metastatic breast cancer

Breast cancer is the most common cancer in women, with a particularly dire prognosis for women with advanced and metastatic breast cancer. Median survival remains at only around three years, despite a range of available treatment options, including chemotherapeutic agents, as well as endocrine agents and trastuzumab for estrogen-receptor-positive and HER2-positive breast cancers, respectively [42]. In particular, the treatment of patients with triple-negative breast cancer (TNBC) is a clinical challenge due to the lack of targeted therapies, and for this subset of patients bevacizumab offered the first targeted treatment option. The pivotal study ECOG 2100 in HER2-negative mBC demonstrated a reduction in the risk of disease progression by 40% (HR: 0.60, $p < 0.001$) with the addition of bevacizumab to paclitaxel compared to paclitaxel alone [43] (Table 1), resulting in the approval of bevacizumab for first-line treatment of mBC (Fig. 1). Subsequent studies with bevacizumab in the first-line and second-line setting confirmed significant improvements in median PFS; however, as for many commonly used chemotherapy regimens in mBC, a clear OS benefit could not be demonstrated [37–46]. While bevacizumab's approval in the mBC indication was reversed by the US Food and Drug Administration (FDA) approximately two years following its initial approval due to reassessment of its risk/benefit balance, this assessment has been controversial and bevacizumab remains approved for mBC in the EU, as well as many other countries. Moreover, based on results from the RIBBON-1 study [46], the indication was extended to include first-line treatment of mBC in combination with capecitabine in patients where other chemotherapy options including taxanes or anthracyclines are not considered appropriate.

Despite divergent regulatory assessments, bevacizumab continues to be recommended in selected patients with mBC [42,47]. In recent years, a range of novel targeted therapies have become available for the treatment of mBC, including EGFR/HER2 pathway inhibitors other than trastuzumab, CDK4/6 inhibitors, poly ADP ribose polymerase (PARP)-inhibitors for breast cancer (BRCA) gene-mutated advanced breast cancer, and immune checkpoint inhibitors for first-line treatment of metastatic TNBC.

Renal cell carcinoma

Roughly one third of patients of patients with RCC present with advanced or metastatic disease, which is associated with very low 5-year survival rates. Prior to the availability of other targeted therapies, the standard of care treatment for these patients was surgery combined with interferon alfa 2b and median survival was only approximately seven months [48]. Bevacizumab was the first antiangiogenic treatment to show clinical efficacy in advanced RCC. The pivotal study AVOREN demonstrated a reduction in the risk of disease progression (secondary endpoint) by 37% (HR: 0.63, $p = 0.0001$) with the addition of bevacizumab to interferon alfa 2b compared to interferon alfa 2b alone [49,50] (Table 1), which, however, did not translate into an OS benefit (primary endpoint). Based on these results, bevacizumab was approved for treatment of RCC in the first-line setting in combination with interferon alfa 2b (Fig. 1). The results from the pivotal study were confirmed in the subsequent CALGB 902065 study [51,52].

Angiogenesis is a prominent characteristic of RCC and many anti-angiogenic agents have since been approved in RCC, including the VEGFR1-3 inhibitor tivozanib, the multi-kinase inhibitors sorafenib, sunitinib, pazopanib, axitinib, cabozantinib and lenvatinib, as well as the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus that additionally target oncogenic signaling [53,54]. Anti-angiogenic therapy remains a standard treatment approach in RCC, with bevacizumab as an important treatment option among other available angiogenesis inhibitors. Recently, cancer immunotherapy was added to the arsenal for treatment of RCC [15], with the combination of the PD-1 inhibitor nivolumab and the anti-CTLA-4 antibody ipilimumab for first-line treatment for poor- and intermediate-risk advanced RCC [53,54]. Furthermore, a combination therapy targeting both immune checkpoints and angiogenesis, the PD-L1 inhibitor avelumab and multi-kinase inhibitor axitinib has been approved by the FDA and the European Medicine Agency (EMA), and promising results from the IMmotion151 study investigating the combination of bevacizumab and atezolizumab further support this novel treatment approach.

Glioblastoma

GBM is a rare but devastating cancer, with a median survival of 15 months despite aggressive treatment with radio- and chemotherapy [55]. Chemotherapeutic treatment options are limited to agents crossing the blood–brain barrier, which are associated with potential adverse reactions. In this difficult-to-treat disease, bevacizumab has shown unprecendented response rates. The pivotal study AVF3708g in relapsed or progressing GBM demonstrated PFS benefits compared to historic controls in recurrent GBM, with a median PFS of 4.2 months and 5.6 months with bevacizumab as a single agent and in combination with irinotecan, respectively [56] (Table 1). Based on these results, bevacizumab was approved for treatment of relapsed or progressing GBM in the US and other countries, but not in the EU (Fig. 1). Subsequently, the phase 3 study EORTC 26101 confirmed the PFS benefit, demonstrating a reduction in the risk of disease progression (secondary endpoint) by 51% (HR: 0.49, $p < 0.0001$) with the addition of bevacizumab to lomustine compared to lomustine alone [57]. However, the observed PFS benefits did not translate into an OS benefit in these pivotal studies. Nevertheless, epidemiologic data provide indirect evidence that the availability of bevacizumab positively impacts OS in this patient population, as cancer registry data show an increase in median survival, the timing of which coincides with the approval of bevacizumab in this indication [58,59].

In first-line treatment of GBM, the pivotal study AvaGlio/BO21990 demonstrated a reduction in the risk of disease progression (co-primary endpoint) by 36% (HR: 0.64, $p < 0.0001$) with the addition of bevacizumab to radiotherapy and temozolomide compared to radiotherapy and temozolomide alone, though this did not translate into an OS benefit (co-primary endpoint), similar results were obtained in the RTOG0825 study [60,61]. Notably, bevacizumab was the first pharmacologic treatment for patients with GBM demonstrating clear-cut evidence of a longer maintenance of quality of life and performance status [60]. Furthermore, treatment with bevacizumab was associated with reduced glucocorticoid requirements, which are used to treat brain edema in patients with GBM but have potentially serious side effects, causing notable morbidity. In the bevacizumab treatment group, a higher proportion of patients who were receiving glucocorticoids at baseline were able to discontinue glucocorticoids compared to radiotherapy and temozolomide alone (66.3 vs 47.1%), and the time to initiation of glucocorticoids was longer in patients who were not receiving glucocorticoids at baseline (12.3 months vs 3.7 months) (Table 1).

Based on known biomarkers of GBM, therapies targeting EGFR, platelet-derived growth factor receptor (PDGFR) or other molecular alterations, as well as immune checkpoint inhibitors have been investigated in clinical trials, in combination with bevacizumab or sequentially, albeit with limited success [62]. Bevacizumab remains the only approved anti-angiogenic agent and targeted therapy in GBM and continues to be among the preferred recommended regimens [63] in countries in which it is approved for this indication. Efforts to further optimize treatment approaches are ongoing [64].

Ovarian, fallopian tube and primary peritoneal cancer

OC, FTC and PPC are insidious and patients frequently present with advanced disease. Although most patients achieve remission after initial treatment, the rate of recurrence is high and most patients

Table 2
Overall patient exposure to bevacizumab in clinical trial and post-marketing setting.

Indication	Patient exposure in manufacturer-sponsored clinical trials[‡]	Estimated patient exposure in post-marketing setting[§]
Gastrointestinal cancer/ CRC	12 319	2 024 159
Breast cancer	10 242	325 154
Lung cancer/NSCLC	8 316	630 173
Renal cancer	1 305	43 247
Glioblastoma multiforme	1 083	97 728
Female reproductive tract cancer and cervical cancer/OC, FTC, PPC + CC	1 907	326 062
Other cancer	2 024	29 237
Total	**37 196**	**3 500 59**

Abbreviations: CC: Cervical cancer; CRC: Colorectal cancer; FTC: Fallopian tube cancer; NSCLC: Non-small cell lung cancer; OC: Ovarian cancer; PPC; Primary peritoneal cancer.
Footnotes:
[‡] Completed, current and ongoing as per February 2019 [19].
[§] As per February 2019 [19].

eventually relapse. Prior to the availability of targeted therapies, the treatment approach remained largely unchanged for over 40 years and was limited to surgical debulking and platinum-based chemotherapy. Bevacizumab was the first targeted therapy approved for treatment of advanced OC, FTC and PP and represented a much-needed new therapeutic option that could delay tumor progression compared with chemotherapy alone. Approval in the front-line setting was based on the results from the pivotal study GOG-0218, which showed a significant increase in median PFS from 10.3 months to 14.1 months with the addition of bevacizumab [65,66] (Table 1; Fig. 1). Although in GOG-0218 there was no significant difference in OS between treatment arms in the overall population, in the subgroup of patients with stage IV disease, bevacizumab used concurrently to chemotherapy followed by maintenance treatment demonstrated an improvement in OS compared to chemotherapy alone (median OS 42.8 months vs 32.6 months, HR 0.75) [65]. The efficacy of bevacizumab in the front-line setting was confirmed in ICON7, and further key phase 3 clinical trials in the platinum-sensitive (OCEANS and GOG-0213) and platinum-resistant (AURELIA) setting led to its approval in the recurrent setting [67–73] (Table 1, Fig. 1).

Five years later, bevacizumab remains an important standard of care and the only approved anti-angiogenic agent for treatment of OC, FTC and PPC [74–76]. Recently, new therapeutic options have demonstrated significant benefit and in particular the advent of PARP inhibitors, which target tumors with BRCA mutations or other deficiencies in homologous recombination DNA repair, has significantly changed the treatment landscape [74–76]. Several phase 3 trials are currently investigating bevacizumab in combination with PARP inhibitors (PAOLA-1) and immune checkpoint inhibitors (IMagyn050, ATALANTE, AGLO OVAR 2.29, NRG-GY009) [77–79]. First results from the PAOLA-1 study in front-line OC indicate a PFS benefit with the combination of bevacizumab and the PARP inhibitor olaparib in the maintenance setting [80].

Cervical cancer

Patients with recurrent CC have a median survival of 12 to 24 months. Until a few years ago, no targeted therapies for CC were available, and treatment options were limited to chemotherapy, with only short-lived responses [81]. Bevacizumab represented the first significant progress in many years in the treatment of persistent or recurrent CC, filling a high unmet medical need and setting the global standard for this patient population. The pivotal study GOG-0240 demonstrated a reduction in the risk of death by 23% (HR: 0.77, p = 0.007) and a reduction in the risk of disease progression by 33% (HR: 0.67, p = 0.002) with the addition of bevacizumab to paclitaxel and cisplatin or paclitaxel and topotecan compared to paclitaxel and cisplatin or paclitaxel and topotecan alone, [82,83] (Table 1), resulting in the approval of bevacizumab (Fig. 1).

Bevacizumab remains the only approved anti-angiogenic therapy in CC, and continues to be recommended by the guidelines as the standard of care [84–86]. Recently, the immune checkpoint inhibitor pembrolizumab has been approved for use in recurrent and metastatic CC expressing the programmed cell death protein 1 (PD-1) [87,88]. The combination of bevacizumab with the immune checkpoint inhibitor atezolizumab and chemotherapy is currently being evaluated in the phase 3 study BEATcc.

Safety profile across indications

Bevacizumab's safety profile is mainly based on its use in combination with the respective standard chemotherapy regimens in a range of advanced malignancies. Based on its pharmacokinetic (PK) profile and mode of action, no clinically significant interactions are expected or were observed between bevacizumab and chemotherapies or vice versa [89,90]. More recently, studies of combination therapies with bevacizumab and other monoclonal antibodies such as atezolizumab have shown that the safety profile of the combination treatment was consistent with the safety profiles of the individual treatments, and no new safety signals were identified [41].

The most frequent adverse events in patients treated with bevacizumab include hypertension, fatigue or asthenia, diarrhea and abdominal pain [89,90] (Table 3). Bevacizumab is associated with a dose-dependent increased incidence of hypertension, which requires monitoring of blood pressure during treatment and can, in most cases, be successfully managed with standard antihypertensive treatment. Furthermore, bevacizumab is associated with the development of proteinuria, with the highest incidence in renal cancer, the severity of which may range from asymptomatic to nephrotic syndrome; therefore, monitoring is recommended.

The most frequent serious adverse events include gastrointestinal (GI) perforations, hemorrhage and arterial thromboembolism [89,90] (Table 3). The highest incidence of potentially serious GI perforations was observed in patients with CC, where all affected patients had a history of prior pelvic radiation exposure. Further risk factors for GI perforation include colorectal cancer and other inflammatory GI disorders, anti-inflammatory medications and abdominal surgery or other procedures. Serious tumor-associated hemorrhage events were observed in specific indications, such as pulmonary hemorrhage/hemoptysis in NSCLC, or more rarely GI-bleeding in mCRC patients and

Table 3
Important adverse events associated with bevacizumab.

Adverse event	Incidence all grades[‡]
Bleeding/Hemorrhage	39.1% (2524/6449) *Up to 44.2% (354/801) in NSCLC*
Pulmonary hemorrhage	2.1% (134/6449) *Up to 8.9% (71/801) in NSCLC*
Proteinuria	10.5% (729/6950) *Up to 20.2% (68/337) in RC*
Arterial thromboembolic events (ATE)	2.5% (173/6950) *Up to 3.8% (24/624) in GBM*
Hypertension	27.1% (1881/6950) *Up to 36.4% (227/624) in GBM*
Congestive heart failure (CHF)	1.2% (78/6449) *Up to 3.3% (46/1399) in BC*
Wound healing complications	3.2% (204/6449) *Up to 5.4% (34/624) in GBM*
GI perforations	1.9% (121/6449) Up to 9.2% (20/218) in CC
Posterior Reversible Encephalopathy Syndrome (PRES)	0.2% (11/6449)
Neutropenia	43.1% (2777/6449) *Up to 71.1% (1584/2208) in OC*
Venous thromboembolic events (VTE)	6.7%% (469/6950). *Up to 11.7% (159/1363) in CRC*
Fistulae (Non-GI)	1.0% (64/6449) *Up to 3.7% (8/218) in CC*
Thrombotic microangiopathy	< 0.1% (2/6449)
Pulmonary hypertension	0.1% (5/6449)
Ovarian failure	None in clinical trials Sporadic cases reported
Hypersensitivity and infusion reactions	27.6% (1720/6449) *Up to 35.5% (784/2208) in OC*
Gallbladder perforation	< 0.1% (1/6449) in OC
Peripheral sensory neuropathy	25.4% (1638/6449) *Up to 61.5% (134/218) in CC*
Non-CHF/ATE cardiac disorders	2.7% (174/6449) *Up to 3.8% (85/2208) in OC*
Osteonecrosis of the jaw (ONJ)	0.1% (4/6449). *Up to 0.2% (3/1399) in BC*
Necrotizing fasciitis	0% in clinical trials 87 reported in ARISg and MedDRA safety databases
Off-label intravitreal use	17,332 cases reported in safety databases up to 31 December 2014: ● *SAEs*: 23.3% (5595/17332) ● *Drug-related systemic AEs:* 27.8% (4812/17332) ● *Anterior eye AEs*: 8.9% (1537/17332) ● *Posterior eye AEs*: 39.0% (6759/17332)
Infection (use with temozolomide and radiotherapy in GBM)	44.9% (2896/6449) *Up to 52.7% (329/624) in GBM*
Thrombocytopenia	26.8% (1726/6449) *Up to 50.1% (1106/2208) in OC*

Abbreviations: AE: Adverse event; ATE: arterial thromboembolic event; BC: Breast cancer; CC: Cervical cancer; CHF: Congestive heart failure; CRC: Colorectal cancer; GBM: Glioblastoma; GI: Gastrointestinal; NA: Not applicable; NSCLC: Non-small cell lung cancer; OC: Ovarian cancer; RC: Renal cancer; SAEs: Serious adverse event.
Footnotes:
[‡] All incidence values based upon calculated incidence from Bevacizumab / Avastin® PSUR/PBRER [19].

central nervous system (CNS) bleeding in patients with CNS metastases. An increased incidence of arterial thromboembolism was observed across indications, and included cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and other arterial thromboembolic reactions; risk factors include a history of arterial thromboembolism, diabetes or more than 65 years of age. Of note, patients with a history of lower than grade 4 thromobembolism, as well as patients on stable anticoagulant treatment were typically not excluded in clinical trials. In a safety study in front-line treatment of OC, where treatment with bevacizumab was continued until disease progression (median treatment duration 15.5 months), the first occurrence for most AEs of special interest was during early cycles of treatment, when bevacizumab was given concomitant to chemotherapy; however, in some patients proteinuria and hypertension appeared only after more prolonged bevacizumab exposure [91].

Importantly, the use of bevacizumab is contraindicated during pregnancy, due to the essential role of VEGF-signaling in embryofetal development and angiogenesis, as evidenced in non-clinical studies by reproductive toxicity and malformations, and reported cases of fetal abnormalities in the post-marketing setting [89,90]. Accordingly, bevacizumab must not be given to pregnant women, and the use of effective contraception during treatment, as well as up to six months after treatment, is recommended [89]. Furthermore, wound healing complications are related to bevacizumab's mode of action, and therefore treatment initiation should be appropriately timed in relation to major surgeries.

Overall, bevacizumab is well-tolerated in a diverse range of tumor types and in combination with a range of chemotherapy regimens. Based on extensive clinical and post-marketing experience, its safety profile is well-characterized and adverse events are manageable in the vast majority of cases.

Lessons learnt and future outlook

An broadly applicable strategy for treatment of solid tumors

In the 15 years since its first approval, bevacizumab has changed the treatment paradigm for a range of solid tumor indications by offering novel treatment options as the first or one of the first available targeted therapies. Although, in the meantime, a host of targeted therapies have become available, initiating the era of personalized medicine, bevacizumab still remains part of the standard of care in many indications. As a hallmark of cancer, targeting of angiogenesis had been proposed as a universal approach for the treatment of solid tumors. Despite its well-established efficacy, the precise modes of action of bevacizumab remain incompletely understood, and their individual contribution to its overall effect may be tumor-type specific [7]. For example, in NSCLC, the initially predominant mode of action during induction treatment may be vascular normalization to improve the delivery of cytotoxic chemotherapeutic agents, while in the subsequent maintenance treatment phase, bevacizumab's mode of action depends more on anti-angiogenic effects. In OC, where bevacizumab has demonstrated superior efficacy in a maintenance setting, the predominant mode of action of VEGF inhibition may be more dependent on its anti-angiogenic properties by preventing new vessel formation and reduction of microvascular permeability. In GBM, where bevacizumab has been shown to improve quality of life by decreasing the requirement for glucocorticosteroids, the anti-permeability mode of action of VEGF inhibition may be key. Since the initial characterization of the role of VEGF in angiogenesis, additional roles of VEGF in the complex tumor microenvironment were identified, which could be harnessed to further increase the efficacy of bevacizumab as a cancer therapy. Based on deeper understanding of the angiogenesis-independent roles of VEGF in tumor development, such as its immune-modulatory roles, promising approaches for combination treatments with potentially synergistic efficacy are currently being investigated.

Across indications, bevacizumab has provided statistically significant and clinically meaningful PFS benefits as well as improvements in other efficacy measures, such as increased response rates, improved quality of life and reduced tumor size [16]. Statistically significant OS benefits were not observed in all studies; however, interpretation of OS is complex, since a relatively long post-progression period and lack of control for subsequent therapy are likely to obscure a potential benefit. In most studies with bevacizumab the primary endpoint was median PFS, which is generally considered a sensitive measure of drug activity and an appropriate endpoint for evaluating the treatment effect of

Table 4
Overview of key ongoing or completed phase III studies of combination treatment with bevacizumab and targeted therapies.

Combination treatment partner (INN)	Type of drug	Molecular targets	Indication and study ID
Immune checkpoint inhibitors			
Atezolizumab	mAb	PD-L1	• CC: NCT03556839/BEATcc • HCC: NCT04102098/IMbrave050, NCT03434379/IMbrave150 • mCRC: NCT02997228/COMMIT • **NSCLC***: NCT02366143/Impower150 • Ns-NSCLC: NCT03991403 • OC/FTC/PPC: NCT02891824/ATALANTE, NCT03038100/IMagyn050, NCT03353831/AGO OVAR.2.29, NCT02839707/NRG-GY009 • PM: NCT03762018/BEAT-meso • RCC: NCT024420821/IMmotion151
Durvalumab	mAb	PD-L1	• HCC: NCT03847428/EMERALD-2, NCT03778957/EMERALD-1
PARP inhibitors			
Olaparib	Small molecule	PARP	• OC/FTC/PPC: NCT02477644/PAOLA-1
Immune checkpoint inhibitor and PARP inhibitor			
Niraparib and TSR042	Small molecule and mAb	PARP and PD-1	• OC/FTC/PPC: NCT03806049/ENGOT-OV42-NSGO/AVANOVA-Triplet
Other targeted therapies			
Erlotinib	Small molecule	EGFR	• mCRC: NCT00598156, NCT00265824/DREAM, NCT00598156/ACT1, NCT01229813/ACT2 • **NSCLC**§: NEJ026, NCT02759614/JO25567/Artemis, NCT02633189/BEVERLY, NCT00257608/ATLAS, NCT00130728/BeTa
Cetuximab	mAb	EGFR	• mCRC: NCT01878422/ITCa • NSCLC: NCT00946712/S0819
Trastuzumab	mAb	HER2	• mBC: NCT00391092/AVEREL
Letrozole	Small molecule	Aromatase	• Adv. BC: NCT00545077/GEICAM2006-11, NCT00601900/GALGB 40,503/Alliance
Temsirolimus	Small molecule	mTor	• Adv RCC: NCT00631371/INTORACT
Vorinostat	Small molecule	HDAC	• GBM: NCT01236560

Abbreviations: Adv: Advanced, ALK: anaplastic lymphoma kinase; BC: Breast cancer; mCRC: Colorectal cancer; CYP19: Aromatase; EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; FTC: Fallopian tube cancer; HER2: Human epidermal growth factor growth factor receptor–2 (EGFR-2/ERBB2/neu); GBM: Glioblastoma; HCC: Hepatocellular carcinoma; HmAb: monoclonal antibody; mTOR: mammalian target of rapamycin; OC: Ovarian cancer; PANC: Pancreatic cancer; PARP: Poly (ADP-ribose) polymerase; PD–L1: Programmed death–ligand 1; PD–1: Programmed cell death protein 1; PM = Pleural Mesothelioma; PPC: Primary peritoneal cancer; VEGF–A: Vascular endothelial growth factor–A.
Source: Clinicaltrials.gov, accessed 28 Nov 2019.
Footnotes:
* Indication for combination treatment approved in the EU and US.
§ Indication for combination treatment approved in the EU.

cancer therapies [92–94].

While clinical benefits of VEGF-inhibition with bevacizumab have been demonstrated in a wide range of solid tumor indications, in some other solid tumors, including pancreatic cancer, gastric cancer and prostate cancer, bevacizumab showed no significant treatment effect. Potential reasons for the unresponsiveness to anti-angiogenic treatment include dense tumor stroma preventing sufficient perfusion of the tumor, redundancy of angiogenic factors resulting in treatment resistance and interference of other signaling pathways with angiogenic signaling [5,95–98].

Identification of biomarkers for patient selection and monitoring

Unlike most other targeted therapies, bevacizumab is used in general patient populations not pre-selected by a biomarker. Despite intense efforts, no predictive biomarker has been identified that would enable a more personalized use of bevacizumab [99,100]. Plasma levels of VEGF-A (pVEGFA) were investigated as a potential predictive biomarker for the clinical efficacy of bevacizumab in 14 pivotal randomized trials in 7 indications and in a study of samples from five clinical trials, with inconsistent or inconclusive results [101–104]. Further, a prospective evaluation of pVEGF in mBC (MERiDiAN) did not support baseline pVEGF-A as a predictive biomarker for bevacizumab efficacy [105,106]. Other potential biomarkers of resistance to anti-angiogenic treatment which have been investigated in a range of indications include VEGF-D, angiopoietin 2 (Ang2), hepatocyte growth factor (HGF), placental growth factor (PlGF), stromal cell-derived factor 1 (SDF-1), microvascular density (MVD), interleukin (IL) 6 and IL-8 [100,102,107–113]. Attempts to identify a VEGF-dependent, predictive vasculature gene signature did not provide positive results [114]. In GBM, radiomic imaging, computer tomography (CT) perfusion, and delayed-contrast/perfusion magnetic resonance imaging (MRI) are investigated as non-invasive techniques/biomarkers of response to treatment with bevacizumab [115]. In patients with isocitrate dehydrogenase (IDH) wild-type GBM, a “proneural” gene expression signature was identified as a molecular subgroup with better responses to bevacizumab in which a significant OS benefit compared to placebo was observed [116]. Thus, while some promising biomarkers have been investigated, a validated, predictive biomarker for response to bevacizumab remains elusive. As the biology of angiogenesis and its role in

tumor development varies between indications, suitable biomarkers may likely be tumor type-specific.

Addressing resistance to angiogenesis inhibition with bevacizumab

As for other targeted therapies, particularly those inducing a cytostatic rather than cytotoxic response, the development of treatment resistance limits efficacy in the longer-term setting [4]. Both molecular changes within the tumor cells themselves as well as tumor-induced changes of the microenvironment contribute to resistance to anti-angiogenic therapy [117,118]. Angiogenesis may be re-activated by up-regulation of VEGF-A itself, alternative members of the VEGF family or alternative pro-angiogenic pathways, such as PlGF, SDF-1/CXC-chemokine receptor (CXCR)-4 and CXCR7, HGF/Met [117,118]. Besides angiogenesis, tumor cells may adopt alternative modes of tumor vascularization, including co-option of existing vasculature, vasculogenic mimicry of cancer cells, vasculogenesis from cancer stem cell differentiation, the splitting of one vessel into multiple vessels (vessel intussusception) and vasculogenesis based on bone-marrow derived precursors of endothelial cells [118]. While the potential mechanisms of resistance to angiogenesis inhibition have become increasingly well-understood, there is so far limited success in translation of this knowledge to clinical strategies for overcoming resistance to treatment with bevacizumab. Clinical studies have investigated the concomitant use of a VEGFR inhibitor with bevacizumab, or targeting of angiogenic signaling molecules, including angiogtensin-2 (Ang-2), fibroblast growth factor (FGF), HGF activation of c-Met, delta-like ligand 4 (Dll4)-induced Notch signaling, hedgehog (HH) signaling or inhibition of Zeste homolog 2 (EZH2), an intracellular mediator of angiogenic signaling [119–122]. Combinations of bevacizumab with MET, Ang-2 and HH inhibitors are or have been under investigation in clinical trials (Table 4). Importantly, phase III studies in ovarian, colorectal and breast cancer have shown significant efficacy benefits with bevacizumab following re-treatment after disease progression in patients who had previously received a bevacizumab-containing regimens [123,124,22]. In the ML18147 study, both PFS and OS were significantly improved when bevacizumab was added to chemotherapy in bevacizumab-experienced patients with mCRC (5.7 months vs 4.1 months; HR: 0.68 [95% CI 0.59–0.79]; $p < 0.0001$ and 11.2 months vs 9.8 months; HR: 0.81 [95% CI 0.69–0.94]; $p < 0.0062$) [22]. In the TANIA study, PFS was significantly improved when bevacizumab was added to second-line chemotherapy in bevacizumab-experienced patients with HER2-negative locally recurrent or metastatic breast cancer (6.3 monthsvs 4.2 months, HR: 0.75 [95% CI 0.61–0.93], $p = 0.0068$) [123], though there were no significant differences in third-line PFS or OS [125]. Similarly, in the Mito-16b/Mango-OV2b study, PFS was significantly improved when bevacizumab was added to chemotherapy in bevacizumab-experienced patients with recurrent OC (8.8 months vs 11.8 months; HR: 0.51 [95% CI 0.41–0.64]; $p < 0.001$), though this did not translate into a significant OS benefit [124]. These data indicate that progression of disease in patients treated with a bevacizumab-containing regimen does not necessarily indicate irreversible resistance to bevacizumab.

Combination with immune checkpoint inhibitors

Besides its key role in angiogenesis, VEGF was shown to have an angiogenesis-independent role in immune modulation, contributing to the suppression of adaptive immunity at several steps of the cancer immunity cycle [118,126]. Specifically, tumor-secreted VEGF inhibits the differentiation of hematopoietic stem cells to dendritic cells and the functional maturation of dendritic cells to antigen-presenting cells, inhibiting early steps of the cancer immunity cycle and promoting immune evasion of tumors. VEGF also interferes with later steps of the cancer immunity cycle by down-regulation of adhesion molecules on endothelial cells required for the rolling of leukocytes as well as their adhesion and transmigration, inhibiting tumor infiltration by T cells. Additional mechanisms of VEGF-mediated suppression of the adaptive immune system include the induction of apoptosis in T cells by activation of expression of FAS ligand on endothelial cells, and the expansion of immune-suppressive myeloid-derived suppressor cells [7]. Due to the intimate relationship between angiogenesis and immunosuppression, there is a scientific rationale to investigate whether the addition of immune checkpoint inhibitors to bevacizumab could lead to synergism and more durable clinical benefit.

The promise of a combined anti-angiogenic and immunotherapy approach is exemplified by the recent approval of bevacizumab in combination with atezolizumab and chemotherapy, based on the results of the IMpower150 trial in metastatic non-squamous (NSq)-NSCLC, demonstrating PFS and OS benefits of the combination treatment, without new safety signals compared to the individual treatments [41]. Interestingly, the benefits of the combination treatment were seen in the overall population regardless of programmed death-ligand 1 (PD-L1) expression status, and were further enhanced in patients with a high effector T cell gene signature, indicative of active adaptive immune responses.

This potential synergy is further supported by results of a phase I clinical study (NCT02715531) investigating the combination of bevacizumab and atezolizumab for treatment of solid tumors. In patients with hepatocellular carcinoma (HCC), this study demonstrated significant improvement in the primary endpoint median PFS compared to atezolizumab alone (5.6 vs 3.4 months, HR 0.55, $P = 0.0108$) [127], while there had been no or limited responses with the individual therapies. This combination has been granted FDA granted breakthrough designation and is further investigated in the ongoing phase III study IMbrave150. First results demonstrate significant benefits for the co-primary endpoints PFS and OS (6.8 vs 4.2 months, HR 0.59, $P < 0.0001$ and not reached vs 13.2 months, HR 0.58, $P = 0.0006$) for the combination of bevacizumab with atezolizumab compared to sorafenib, with an ORR of 27% vs 12% ($P < 0.0001$) [128]. Results were consistent across clinical subgroups and the safety profile of the individual treatments, with no new safety signals identified with the combination treatment. Promising results have also been obtained in the IMmotion151 study with the combination of bevacizumab and atezolizumab compared to sunitinib in PD-L1-positive RCC [129]. The combination of bevacizumab with immune checkpoint inhibitors is also under investigation for further indications in several ongoing phase III clinical trials, for example OC in both front-line (IMagyn050) and recurrent platinum-sensitive (ATALANTE) or platinum-resistant (AGO OVAR.2.29, NRG-GY009) settings and in front-line cervical cancer (BEATcc) [7,15] (Table 4).

Combination with PARP inhibitors

Pruning of tumor vasculature in response to anti-angiogenic therapy results in hypoxia, causing a mutagenic environment and down-regulation of the homologous recombination DNA repair pathway [130]. Targeting the base excision DNA repair pathway, PARP inhibitors induce synthetic lethality in tumor cells with homologous recombination deficiencies [131]. Thus, combining bevacizumab with PARP inhibitors is proposed to sensitize cancer cells to the cytotoxic effects of PARP inhibitors, while mitigating consequences of VEGF-inhibition-related hypoxia. PARP-inhibitors are approved for treatment of BRCA-mutated cancers and BRCA-like cancers, such as OC and BC, and are being investigated in many additional cancer indications. Accordingly, the combination of bevacizumab with PARP inhibitors was investigated in phase 3 clinical trials, including PAOLA-1, which evaluated olaparib plus bevacizumab in front-line OC maintenance treatment. In PAOLA-1, patients with newly diagnosed OC, FTC and PPC, regardless of BRCA mutation status, who have achieved a complete or partial response to platinum-based chemotherapy in combination with bevacizumab, were randomized to either olaparib plus

bevacizumab or placebo plus bevacizumab [80]. Results have demonstrated superiority of the combination of olaparib plus bevacizumab compared to bevacizumab alone in the primary endpoint (median PFS 22.1 vs 16.6 months, HR = 0.59, p < 0.001), with a safety profile consistent with those associated with the individual treatments. Prespecified subgroup analyses showed that the observed benefit was driven by the subgroup of patients with BRCA mutant (median PFS 22.1 vs 16.6 months, HR = 0.31 [95% CI 0.20–0.47]) and homologous recombination deficiency (HRD)-positive tumors (median PFS 37.2 vs 21.7 months, HR = 0.33 [95% CI 0.25–0.45]), including HRD-positive tumors without BRCA mutation (median PFS 22.1 vs 16.6 months, HR 0.43; 95% CI, 0.28–0.66). In contrast, there was little benefit in the subgroups of patients with BRCA mutation-negative tumors (median PFS 18.9 vs 16.0 months, HR 0.71 [95% CI, 0.58–0.88]) and tumors with negative or unknown HRD status (median PFS 22.1 vs 16.6 months, HR 0.92; [95% CI, 0.72–1.17]).

Conclusions

The angoigenesis inhibitor bevacizumab was the first or among the first available targeted therapies for a range of solid tumors. By improving overall and/or progression-free survival in patients with no or only limited treatment options besides chemotherapy, bevacizumab has changed the treatment paradigm and became a standard of care in the treatment of advanced cancers. Other currently available anti-angiogenic agents have neither shown such consistent efficacy across indications, nor have a comparably well-established clinical efficacy and safety profile, based on extensive clinical and post-market experience.

Rather than directly targeting cancer cells, bevacizumab targets the tumor microenvironment, characterized by complex interactions between cancer cells, normal cells and the extracellular matrix. Due to this complexity, the effects of VEGF-inhibition are likely tumor-type and microenvironment-specific. Furthermore, recent research has shown that VEGF has additional angiogenesis-independent roles in the complex tumor microenvironment, including the modulation of cancer immunity. To date, clinically validated, reliable biomarkers for treatment response and resistance to bevacizumab remain elusive, precluding a more personalized use of bevacizumab. While the understanding of mechanisms of resistance to anti-angiogenetic treatment has advanced, effective clinical approaches to overcome resistance to treatment with bevacizumab are not yet available.

Since the initial approval of bevacizumab, a number of targeted cancer therapies have become available, transforming the treatment landscape in many solid tumor indications and creating opportunities for novel combination treatment approaches. Indeed, the combination of bevacizumab with immune checkpoint inhibitors has recently been approved in NSq-NSCLC, and further results showing clinical benefits with this combination have been obtained in clinical studies in patients with RCC and HCC and with PARP inhibitors in patients with OC. These promising results indicate that bevacizumab may enhance these novel targeted therapies, as has been shown when bevacizumab is combined with chemotherapy.

Considering the vast and established evidence on the efficacy of bevacizumab in combination with chemotherapy and increasing evidence on further improved treatment outcomes when combined with other new treatments such as cancer immunotherapy or PARP inhibitors, bevacizumab is expected to remain a key agent in the treatment of cancer patients.

Declaration of Competing Interest

Dr. Garcia is employee of F. Hoffmann-La Roche Ltd. Dr. Hurwitz reports grants and personal fees from F. Hoffmann-La Roche Ltd./Genentech, Inc., outside the submitted work; and is employee of Genentech, Inc. Dr. Sandler is employee of Genentech, Inc.; in addition, Dr. Sandler has a patent related to a Taxol, Carboplatin, Tecentriq® and Avastin® regimen. Dr. Miles reports honoraria from F. Hoffmann-La Roche Ltd./Genentech, Inc. and acted in a consulting/advisory role for F. Hoffmann-La Roche Ltd./Genentech, Inc. outside the submitted work. Dr. Coleman reports grants from the NIH, the Gateway Foundation and the V Foundation; and grants from AstraZeneca, Merck, Clovis, Genmab, F. Hoffmann-La Roche Ltd./Genentech, Inc. and Janssen; and personal fees from AstraZeneca, Tesaro, Medivation, Clovis, Gamamab, Genmab Roche/Genentech, Janssen, Agenus, Regeneron and OncoQuest outside the submitted work. Dr. Deurloo is employee of F. Hoffmann-La Roche Ltd. Dr. Chinot reports honoraria and non-financial research support from F. Hoffmann-La Roche Ltd., and acted in a consulting/advisory role for F. Hoffmann-La Roche Ltd., outside the submitted work; in addition, Dr. Chinot has a patent related to a plasmatic biomarker of bevacizumab efficacy (Europe 12305565.9) issued to the Aix-Marseille University.

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