Editorial

Oral tyrosine kinase inhibitors targeting VEGF-receptors in patients with metastatic colorectal cancer

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Our understanding of cancer genomics and proteomics associated with normal and malignant cell growth and angiogenesis has increased exponentially in recent years and has resulted in the identification of several critical molecular events that are fundamentally involved in carcinogenesis and tumor progression. Targeting these key ligands, receptors and molecular pathways offers survival benefit in several cancers such as breast cancer, colon cancer and lung cancer.

It is a decade ago since the first targeted drugs proved their efficacy in the treatment of patients with metastatic colorectal cancer (mCRC) (1) and since then Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved a limited number of targeted drugs (cetuximab, panitumumab, bevacizumab, aflibercept, regorafenib) for clinical use in patients with mCRC and a much larger number are in various phases of clinical development.

The anti-epidermal growth factor receptor (EGFR) antibodies—cetuximab and panitumumab—were first successfully implemented in the later line of therapies, and then moved forward into first line therapy. In contrast, the anti-angiogenic antibody bevazicumab was directly introduced in the first line setting and subsequently showed its efficacy in later lines.

In the pivotal BOND study (2), the combination of cetuximab with irinotecan (CetIri) significantly increased response rate (RR) and prolonged progression free survival (PFS) and based on these data CetIri was approved for patients with irinotecan-resistant disease in US and Europe in 2004. Soon after, the benefit of cetuximab and panitumumab as monotherapy was confirmed in patients with chemo-resistant mCRC (1) and as second line in combination with chemotherapy (3,4). Ligand-induced activation of EGFR achieves most of its effect via the RAS-RAF-MAPK pathways, which promote proliferation, invasion, migration and neovascularisation. KRAS mutation in exon 2, found in approximately 40% of mCRC patients, is now an established predictive marker of resistance to anti–EGFR therapy (5,6), but in addition patients with KRAS mutations may even experience inferior outcome if combined with oxaliplatin-containing regimens (7,8). Based on data from a number of phase III studies, cetuximab and panitumumab was subsequently approved in the first line treatment of mCRC patients with KRAS wild-type tumors, in combination with chemotherapy (9,10).

The advantage of anti-EGFR and anti-angiogenic therapy led to hope for additional progress, and it was obvious to test if multi-blockade with a combination of anti-angiogenic and anti-EGFR therapy could further improve survival.

This "add-on principle" was supported by promising data from preclinical models suggesting that increased angiogenic potential may be involved in the resistance to anti-EGFR antibodies (7). Clinical data supported the hypothesis of an increased efficacy of combined therapy as a randomized phase II study (8) comparing the combination of irinotecan, cetuximab and bevazicumab to cetuximab and bevazicumab in patients with pre-treated mCRC showed a higher RR and longer PFS compared to historical data on cetuximab and irinotecan in the BOND study (2,8).

However, despite the above-mentioned promising results on double-blockade in preclinical models and from early clinical data, two large phase III studies—

the CAIRO2 and the PACCE studies—failed to confirm this and both trials actually showed that addition of bevazicumab to an anti-EGFR antibody and chemotherapy in chemo-naïve patients was associated with an inferior outcome compared to an anti-EGFR antibody and chemotherapy (11,12).

Another way of achieving multi-blockade is by the use of oral multi-targeted receptor tyrosine kinase (TKI) inhibitors including sunitinib, sorafenib, regorafenib, valatinib, axatinib, cediranib, and brivanib (13-22).

Sunitinib is an inhibitor of several TKI receptors including platelet-derived growth factor receptors (PDGF-R), the vascular endothelial growth factors receptors (VEGFRs), c-KIT, RET and FLT3. Saltz *et al*. published a phase II trial with sunitinib as mono-therapy in 82 patients with chemo-resistent mCRC (23). One patient achieved a partial response. Median PFS in the prior bevacizumab and bevacizumab-naıve cohorts was 2.2 and 2.5 months, respectively, whereas median overall survival (OS) was 7.1 and 10.2 months, respectively. The authors concluded that sunitinib did not demonstrate a meaningful single-agent activity, but the mechanisms of action, the relative mild safety profile and easy administration warranted further study in combination with standard chemotherapy regimens for mCRC.

In a phase I study, the maximum tolerated dose (MTD) of sunitinib combined with FOLFIRI for untreated mCRC was 37.5 mg/day when administered 4 weeks on and 2 weeks off (24). The predominant dose limiting toxicity (DLT) was neutropenia. The authors concluded that the combination had acceptable tolerability and showed preliminary antitumor activity and based on these promising data a large phase III study comparing FOLFIRI plus placebo or FOLFIRI and sunitinib was initiated—without a phase II study—to confirm the activity of sunitinib in mCRC. The primary aim was to prolong PFS from 8.0 months to 10.8 months (35% improvement), which would require 568 events (16).

Two interim analyses were planned at 25% and 60% of the 568 PFS events, and the stopping boundary for futility at the second interim analysis was a hazard ratio (HR) of ≥0.88. A final analysis was planned after inclusion of 720 patients.

Enrolment began in July 2007. At the second interim analysis in June 2009, after enrolment was complete and 367 PFS events had occurred, the HR for PFS was 1.095 in favour of the placebo arm. There were also increased toxic events (including neutropenia and diarrhoea and numerically a larger number of toxic deaths) in patients receiving sunitinib plus FOLFIRI.

As mentioned, two interim analyses were planned. The authors do not disclose the result of the first interim analysis, and they do not explain why 48 supplementary patients were included. Shortening of the time to approval of new drugs is crucial, however it is important that interim analyses can terminate a trial before inclusion of the planned number of patients—especially if a phase III study is built directly upon a phase I study.

As shown in *Table 1*, sunitinib is not the only oral multi-TKI inhibitor that has failed to improve OS in mCRC patients. So far the only randomized phase III study in which an oral multi-TKI inhibitor has prolonged PFS and OS is the CORRECT trial (21), in which regorafenib monotherapy prolonged PFS from 1.7 to 1.9 months (HR, 0.49) and OS from 5.0 to 6.4 months (HR, 0.77).

One of the most important advances in recent years in the treatment of patients with mCRC is the translational studies discovering the impact of the KRAS mutational status on efficacy of anti-EGFR therapy as described above. Recently, retrospective analyses of prospective randomized studies have demonstrated that additional mutations in KRAS and NRAS predict a lack of efficacy to anti-EGFR therapy. Therefore the European label for panitumumab (10) and cetuximab (25) was recently modified to require testing for KRAS and NRAS mutations and in addition a meta-analysis suggests that mutation in BRAF and PIK3CA and a non-functional PTEN also predict resistance to anti-EGFR therapies (26). Some of the multi-TKI inhibitors have improved PFS; however without translation into improvements in OS (17,19,22) and thus may have efficacy in subgroups of patients.

It is therefore very important that clinical studies—also in late lines of therapy—are combined with translational studies in order to improve our knowledge of the biology of mCRC and the identification of new predictive markers. However, it is important that these marker studies do not solely focus on the targeted agents but as well aim to identify predictive markers for the "classic cytostatics" in order to further improve outcome for patients with mCRC.

Table 1 Randomized studies evaluating TKIs targeting VEGFR in mCRC

Randomized studies	Author, year	Regimen	Phase	No.	RR (%)	Median PFS (months)	Median OS (months)
First line therapy	Tabernero *et al.*, *CCR* 2013, RESPECT	FOLFOX + Pl	II	101	59	8.7	18.1
		FOLFOX + Sor		97	44	9.1	17.6
	Hecht *et al.*, *JCO* 2011, CONFIRM 1	FOLFOX + Pl	III	583	-	7.6	20.5
		FOLFOX + Val		585	-	7.7	21.4
	Infante *et al.*, *Cancer* 2013	FOLFOX + Ax	II	42	29	11.0	18.1
		FOLFOX + Bev		43	49	15.9	21.6
		FOLFOX + Ax + Bev		41	39	12.5	19.7
	Carrato *et al.*, *JCO* 2013	FOLFIRI + Pl	III	382	34	8.4	19.8
		FOLFIRI + Sun		386	32	7.8	20.3
	Hoff *et al.*, *JCO* 2012, HORIZON II	FOLFOX/XelOx + Pl	III	358	50	8.3	18.9
		FOLFOX/XelOx + Ced 20		502	51	8.6*	19.7
		FOLFOX/XelOx + Ced		216	Terminated, 20 mg sufficient		
	Schmoll *et al.*, *JCO* 2012, HORIZON III	FOLFOX + Bev	III	713	47	10.3	21.3
		FOLFOX + Ced 20		709	46	9.9	22.8
Second line therapy	Cutsem *et al.*, *JCO* 2011, CONFIRM 2	FOLFOX + Pl	III	429	-	4.2	11.9
		FOLFOX + Val		426	-	5.6*	13.1
	Cunningham *et al.*, *BJC* 2013, HORIZON I	FOLFOX + Bev	II	66	27	7.8	19.6
		FOLFOX + Ced 20		71	18	5.8	14.3
		FOLFOX + Ced 30		73	20	7.2	16.8
Third line therapy	Grothey *et al.*, *Lancet* 2013, CORRECT	BSC	III	255	0	1.7	5.0
		Rego		505	1	1.9*	6.4*
	Siu *et al.*, *JCO* 2013, C0.20	Cet + Pl (KRASwt)	III	374	7	3.4	8.1
		Cet + Briv (KRASwt)		376	14*	5.0*	8.8

*, Significant difference; Pl, placebo; Val, valatinib, oral TKI that targets VEGFR1-3; Sor, sorafenib, oral TKI, against VEGFR, PDGFR, KIT; Ax, axatinib, oral TKI that targets VEGFR1-3; Sun, sunitinib, oral TKI against VEGFR, PDGFR, KIT; Ced, cediranib, oral TKI that targets VEGFR1-3; Briv, brivanib, oral TKI that targets VEGFR and FGFR; Rego, regorafenib, oral TKI that targets VEGFR, PDGFR and FGFR; Cet, cetuximab; Bev, bevacizumab; BSC, best supportive care; TKI, tyrosine kinase; VEGFR, vascular endothelial growth factors receptor; mCRC, metastatic colorectal cancer; RR, response rate; PFS, progression free survival; OS, overall survival; *CCR*, *Clinical Cancer Research*; *JCO*, *Journal of Clinical Oncology*; *BJC*, *British Journal of Cancer*.

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