# EDITORIAL

Targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with rapidly dividing cells (e.g. with traditional chemotherapy). Targeted cancer therapies may be more effective than current treatments and less harmful to normal cells. The main categories of targeted therapy are small molecules and monoclonal antibodies. Many oncologists believe that targeted therapies are the chemotherapy of the future. As solid tumor cancer continues to be viewed as a chronic condition, methods for long-term treatment, with less side-effects, continue to be investigated. In this special issue current status of molecular targeted therapy for gastrointestinal cancer will be discussed.

## Molecular Targeted Therapy for Colorectal Cancer

Colorectal cancer (CRC) remains the third most common malignancy and the third leading cause of cancer death worldwide. Approximately 25% present with metastases as initial diagnosis and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC. The backbone of first-line palliative chemotherapy consists of a fluoropyrimidine [intravenous **5-fluorouracil** (**5-FU**) or oral fluoropyrimidines **capacitabine** (**CAP**) and **uracil-ftorafur** (**UFT**)] in various combinations and schedules. Combination chemotherapy with **5-FU/LV** (**leucovorin**)/**oxaliplatin** (**FOLFOX**) or **5-FU**/**LV**/**irinotecan** (**FOLFIRI**) provides higher response rates (RR), longer progression-free survival (PFS) and better overal survival (OS) [1]. The exposure to all three cytotoxics (fluoropyrimidines, **oxaliplatin** and **irinotecan**) in various sequences results in the longest survival [2]. The introduction of monoclonal antibodies (mAb) against vascular endothelial growth factor (VEGF) and against the epidermal growth factor receptor (EGFR) into the treatment protocols for advanced CRC has significantly improved the outcomes with median survival now reaching almost 24 months (for review see [3-5]). Adoption of hepatic resection, especially after induction chemotherapy, even in patients with advanced liver metastases has prolonged median survival further up to 29 months [6, 7].

**Bevacizumab** (**BEV, Avastin™**), a recombinant, humanized IgG1 mAb against all isoforms of VEGF-A, increases OS, PFS and RR in first-line treatment in combination with **5-FU**/**LV**/**irinotecan** and in combination with **5-FU/LV** or **CAP** alone. According to a recently presented Greek phase III study **XELIRI** (**CAP**/**irinotecan**)-**BEV** did not show significant differences in efficacy as compared to **FOLFIRI**-**BEV** (median PFS 14.6 mo. vs. 15.8 mo.; median OS 20.0 mo. vs. 26.2 mo.)[1]. However, the toxicity profile was different (less neutropenia and metabolic disorders but more diarrhea and vomiting with **XELIRI**-**BEV**). In combination with **FOLFOX/XELOX BEV** improves PFS in first-line treatment [8] but not OS and RR. However, improvement in PFS, OS and RR has been shown with **FOLFOX**-**BEV** in second-line treatment of metastatic CRC [9] (Table **1**, for meta-analysis see [10]). The addition of **mitomycin** to **CAP** + **BEV** did not show extra benefit [11]. Other long-term observational cohort studies, such as first BEAT [12] and BRITE [13], have now confirmed **BEV** study data. Specific class related side-effects of **BEV** are: hypertension, proteinuria, arterial thrombosis, mucosal bleeding, gastrointestinal perforation and wound healing problems. There are no validated predictive molecular markers available for **BEV** [14]. In medically fit older patients, **BEV** provides similar PFS and OS benefits as in younger patients [15]. Downstaging of isolated liver metastases is another interesting aspect currently investigated in the phase II BOXER study (**CAPOX** + **BEV**) and phase III CELIM 2 study **(FOLFOXIRI** ± **BEV).** In the first study, overall RR was 78% (95% confidence interval 63% to 89%), conversion rate of primary unresectable metastases was 40% (12/30), and primary resection rate was 49% (22/45) [16]. Results of the second study are still pending. Efficacy of **FOLFOXIRI-BEV** combination is also currently investigated by the Italian GONO group in the TRIBE study (Table **1**). One issue that is still debated is length of treatment in the palliative situation. The OPTIMOX1 study has shown that after six cycles of **FOLFOX**, **oxaliplatin** may be safely stopped while continuing **5-FU/LV** for a further 12 cycles after which **oxaliplatin** is reintroduced again, without compromising efficacy [17]. In contrast, complete discontinuation of chemotherapy had a negative impact on duration of disease control and PFS compared with the maintenance therapy strategy as has been shown in the OPTIMOX2 study [18]. Other studies, such as MRC CRO 6B [19], GISCAD [20], and MRC COIN (Adams T., ESMO 2009) showed only a slight reduction of OS while improving quality of life with intermittent treatment. The MARCO trial tried to answer the question whether **BEV** alone can be used as maintenance therapy following induction with **XELOX-BEV**[2]. As a result, **BEV** was not inferior to continuation **XELOX-BEV** (median PFS 10.3 mo. vs. 11.0 mo.; median OS 20.7 mo. vs. 25.3 mo.). The Dutch CAIRO3 study is currently investigating **CAP-BEV** maintenance therapy in comparison to observation following induction with 6 cycles **CAPOX-BEV**. The German AIO group investigates **CAP-BEV** or **BEV** maintenance therapy in comparison to observation following induction with **XELOX/CAPOX/FOLFOX** (AIO Trial KRK 0207). Currently, the label of **BEV** in colorectal cancer prescribes to continue the administration until disease progression (or unacceptable toxicity). Adjuvant treatment is recommended for stage III and "high risk" (lymph nodes sampling < 12; poorly differentiated tumor; vascular or lymphatic or perineural invasion; tumor presentation with obstruction or tumor perforation and pT4 stage) stage II CRC patients. Large prospective adjuvant phase III studies, such as MOSAIC [21, 22], NSABP C-07 [23], X-ACT [24] and NO16968/XELOXA [25] have established

[1]Pectasides, D.G.; Xanthakis, I.; Makatoris, T.; Samantas, E.; Varthalitis, I.; Papaxoinis, G.; Papakotoulas, P.; Bournakis, E.; Papandreou, C.; Fountzilas, G. Irinotecan/capecitabine (XELIRI) plus bevacizumab versus irinotecan/fluorouracil/leukovorin (FOLFIRI) plus bevacizumab as first-line treatment in patients with metastatic colorectal cancer : A randomized phase III trial of the Hellenic Cooperative Oncology Group (HeCOG). *J. Clin. Oncol.* **2010**, Vol. *29*, suppl. 4 (ASCO abstract 3541).

[2]Tabernero, J.; Aranda, E.; Gomez, A.; Massuti, B.; Sastre, J.; Abad, A.; Valladares, M.; Rivera, F.; Safont, M.; Diaz-Rubio, E. Phase III study of first-line XELOX plus bevacizumab (BEV) for 6 cycles followed by XELOX plus BEV or single-agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer (mCRC): The MARCO Trial (Spanish Cooperative Group for the Treatment of Digestive Tumors [TTD]). *J. Clin. Oncol.* **2010**, Vol. *29*, suppl. 4 (ASCO abstract 3501).

**FLOX/FOLFOX/XELOX** as standard treatment and **5-FU/LV** or **CAP** when **oxaliplatin** is contraindicated. In contrast, there was no benefit for **CPT-11** (**irinotecan**) based regimens according to the results of CALGB 89803 [26], PETACC-3 [27] and Accord02 [28] studies. Unfortunately, the addition of **BEV** to **mFOLFOX6** does not significantly prolong disease-free survival (DFS) in stages II and III colon cancer, the primary endpoint of the large phase III NSABP C-08 study [29]. In the AVANT study, **BEV** did not prolong DFS or OS when added to either **FOLFOX4** or **XELOX** in patients with stage III colon cancer[3]. Given this lack of improvement in DFS and OS, the use of **BEV** cannot be recommended in the adjuvant treatment of patients with CRC. Results of other studies, such as QUASAR 2 (**CAP** ± **BEV**) and ECOG E5202 (**FOLFOX** ± **BEV**) are still pending.

**Table 1. Development of Bevacizumab (BEV) in CRC Treatment**

| Therapy | Study | Design | Treatment | Reference |
|---|---|---|---|---|
| 1st Line | AVF2192g | Phase II | 5-FU/FA ± BEV | [30] |
| | AVF2107g | Phase III | IFL ± BEV | [31] |
| | BICC-C | Phase III | FOLFIRI/mIFL ± BEV | [32] |
| | NO16966 | Phase III | FOLFOX/XELOX ± BEV | [8] |
| | TREE-1/ TREE-2 | Phase III | mFOLFOX6/bFOL/CapeOx ± BEV | [33] |
| | HeCOG-Study | Phase III | XELIRI + BEV vs. FOLFIRI + BEV | [FN 1] |
| | AGITG MAX | Phase III | CAP ± BEV ± MIT | [11] |
| | TRIBE | Phase III | FOLFOXIRI + BEV vs. FOLFIRI + BEV | Ongoing |
| | CELIM 2 | Phase III | FOLFOXIRI ± BEV (KRAS mut and liver metastases) | Ongoing |
| 2nd Line | E3200 | Phase III | FOLFOX ± BEV | [9] |
| Adjuvant | NSABP C-08 | Phase III | FOLFOX6 ± BEV | [29] |
| | AVANT | Phase III | FOLFOX4/XELOX + BEV vs. FOLFOX4 | [FN 3] |
| | QUASAR 2 | Phase III | CAP ± BEV | Ongoing |
| | ECOG E5202 | Phase III | FOLFOX ± BEV (UICC II, high risk) | Ongoing |

BEV= bevacizumab; CAP = capecitabine; FA = folic acid; MIT = mitomycin.

**Vatalanib** (**PTK787/ZK222584**) is a tyrosine kinase inhibitor (TKI) that blocks the function of VEGFR-1, VEGFR-2, and VEGFR-3, preventing VEGF-mediated angiogenesis to reduce tumor growth and metastasis. Despite encouraging results in phase I/II trials, the results from the phase III study of colorectal oral novel therapy for the inhibition of angiogenesis and retarding of metastases (CONFIRM-1) showed that the addition of **vatalanib** to **FOLFOX-4** did not improve PFS, compared with **FOLFOX-4** alone, as a first-line treatment for metastatic CRC [34]. However, a preplanned meta-analysis from this study and a subsequent study (CONFIRM-2; similar design, but as second-line treatment for metastatic CRC) showed that **vatalanib** specifically benefits patients with high levels of lactate dehydrogenase [35]. These results are in contrast to the clinical benefit observed from **BEV** in patients with the same tumor type. One possible explanation for these negative results is that **vatalanib** has a shorter half-life (4–6 hours) than **BEV**; the once-daily schedule might have been insufficient to inhibit the enzyme for 24 hours.

**Cediranib** is a highly potent VEGF signaling inhibitor with activity against all three VEGF receptors. The HORIZON II study compared **FOLFOX/XELOX** + **cediranib** with **FOLFOX/XELOX** + **placebo**[4]. The addition of **cediranib** to **FOLFOX/XELOX** met the co-primary endpoint of PFS prolongation (8.6 mo. vs. 8.2 mo.), but there were no significant differences in OS, RR, duration of response or liver resection rate. The HORIZON III study compared **mFOLFOX6** + **cediranib** with **mFOLFOX6** + **BEV** in patients with previously untreated mCRC[5]. The primary objective was to compare PFS (predefined noninferiority limit upper 95% CI for hazard ratio [HR] <1.2). Secondary endpoints included OS, objective RR, safety and tolerability. There was no statistically significant difference in PFS, OS or RR for **mFOLFOX6** + **cediranib** vs.

[3]De Gramont, A.; van Cutsem, E.; Tabernero, J.; Moore, M.J.; Cunningham, D.; Rivera, F.; Im, S.; Makrutzki, M.; Shang, A.; Hoff, P.M.. AVANT: Results from a randomized, three-arm multinational phase III study to investigate bevacizumab with either XELOX or FOLFOX4 versus FOLFOX4 alone as adjuvant treatment for colon cancer. *J. Clin. Oncol.* **2011**, Vol. *29*, suppl. 4 (GI ASCO abstract 362).

[4]Hoff, P.M.; Hochhaus, A.; Pestalozzi, B.C.; Tebbutt, N.C.; Li, J.; Kim, T.W.; Pike, L.; Fielding, A.; Robertson, J.; Saunders, M.P.; Cediranib + FOLFOX/XELOX versus placebo + FOLFOX/XELOX in patients (pts) with previously untreated metastatic colorectal cancer (MCRC): a randomized, double-blind, phase III study (HORIZON II). *Ann. Oncol.* **2010**; Vol. *21*, Suppl. 8 (ESMO LBA19).

[5]Schmoll, H.; Cunningham, D.; Sobrero, A.; Karapetis, C.; Rougier, P.; Koski, S.L.; Barker, P.; Mookerjee, B.; Robertson, J.; van Cutsem, E. MFOLFOX6 + cediranib vs. mFOLFOX6 + bevacizumab in previously untreated metastatic colorectal cancer (mCRC): a randomized, double-blind, phase II/III study (HORIZON III). *Ann. Oncol.* **2010**; Vol. *21*, Suppl. 8 (ESMO abstract 5800).

**mFOLFOX6 + BEV**; however, the predefined boundary for PFS non-inferiority was not met. The safety profile of **cediranib** was consistent with previous studies, although there was a higher incidence of common adverse events (AEs) with **mFOLFOX6** + **cediranib** than **mFOLFOX6 + BEV**.

**Axitinib** (**AG-013736**, **AG**), an oral selective inhibitor of VEGFR1-3, shows activity in multiple tumor types including those refractory to front-line chemotherapy. A multicenter, open-label, randomized phase II trial compared **AG** and **BEV** in combination with **FOLFOX** or **FOLFIRI** in second-line metastatic CRC[6]. There were no significant differences in PFS or median OS between the **AG** and **BEV** arms with **FOLFOX** or **FOLFIRI**. However, there was a trend towards reduced median OS in the **FOLFIRI** arms with **AG** compared to **BEV**, and a trend towards improved median OS with **AG**+**FOLFOX** vs. **BEV**+**FOLFOX**. There were more treatment discontinuations and a higher incidence of grade ≥ 3 adverse events in the **AG** arms (diarrhea, asthenia, fatigue). A second randomized, open-label, phase II study estimated objective RR, PFS, OS and safety in patients with metastatic CRC treated with **mFOLFOX-6** combined with **AG** or **BEV** or both[7]. Patients receiving prior treatment with antiangiogenic agents were ineligible. All patients received standard mFOLFOX-6 treatment and were randomized to receive either **AG** 5 mg (Arm A), or **BEV** 5 mg/kg (Arm B), or **AG** 5 mg + **BEV** 2 mg/kg (Arm C). The RR was 29%, 49%, and 39% for Arms A, B, and C, respectively. Median PFS was 315 d, 350 d, and 377 d, with 1-year survival of 72%, 79%, and 80% for Arms A, B, and C, respectively. Discontinuations due to adverse events were more common in Arm A (36%), than in Arms B (19%) or C (32%).

**Aflibercept** (VEGF-Trap) is a fully recombinant, decoy fusion protein of the second Ig domain of VEGFR-1 and the third Ig domain of VEGFR-2 fused to the Fc domain of human IgG1. VEGF-Trap binds all isoforms of VEGF-A, placenta growth factor, and VEGF-B with high affinities and prevents them from stimulating angiogenesis. Two phase II clinical trials VELOUR (**FOLFIRI** ± **aflibercept**) and AFFIRM (**FOLFOX6** ± **aflibercept**) are currently under way to determine the clinical benefits of **aflibercept** in patients with metastatic CRC.

Another important molecular target for metastatic CRC treatment is the epidermal growth factor receptor (EGFR). Constitutive activation of the EGFR/RAS/PI3K cell-signaling pathway that may occur through molecular aberrations in core pathway components plays a role in many solid tumors, including CRC. The results from the CRYSTAL (combination with **FOLFIRI**) [36] and OPUS (combination with **FOLFOX**) [37] studies (Table **2**) indicate that the benefit from the addition of **cetuximab (CET)**, a mouse-human chimeric monoclonal antibody, to first-line chemotherapy is restricted to mCRC patients with wild-type KRAS gene (~60% of all CRC patients), with the best outcomes observed among those with unmutated forms of both the KRAS and BRAF genes. However, that has not been confirmed in the preliminary data from the MRC COIN trial[8]. Therefore, the role of BRAF mutations (~5-10%), mutually exclusive with KRAS mutations, in predicting resistance to anti-EGFR mAbs is not yet consolidated. It appears that BRAF mutations may play a strong negative prognostic role and only a slight role in resistance to anti-EGFR Abs [38]. There might be also a negative interaction between **CET** and **CAP** according to the MRC COIN study (Table **2**). In addition, it has been shown that **CET** improves OS of chemorefractory patients compared with best supportive care (Table **2**) [39]. However, the combination of **CET** with **irinotecan** is more active than **CET** monotherapy in chemorefractory patients. In addition, recent results of the above mentioned MRC COIN study and the recently presented NORDIC VII study[9] show that a combination of **CET** with **oxaliplatin** may not be favorable, which was not confirmed in the German AIO KRK 0104 study [40] (Table **2**). In addition, the optimal duration of anti-EGFR therapy has not been tested, currently the label of these agents prescribes to continue administration until disease progression (or unacceptable toxicity). Regarding the contribution of **CET** in the treatment of isolated liver metastases in combination with **FOLFOX** or **FOLFIRI** confirmed RR reached 70% in KRAS wild-type tumors in the CELIM study allowing R0 resections in 34% of all patients [41]. CELIM 2 is going to investigate **CET** plus **FOLFOXIRI** vs**. CET** + **FOLFOX** in the same setting (Table **2**). As it is the case for **BEV** a role of **CET** in the adjuvant treatment of CRC has not been established so far. The two ongoing randomized trials PETACC-8 and NCCTG N0147 are currently investigating this issue in CRC patients (Table **2**). Preliminary data of NCCTG N0147 for KRAS mut and wt patients presented at ASCO 2010 showed that the addition of **CET** to **mFOLFOX6** resulted in impaired DFS and a trend toward impaired OS in resected stage III CRC patients[10,11]. The study originally included also two **irinotecan** arms, which were discontinued.

**Panitumumab (PAN),** a fully human anti-EGFR monoclonal antibody, has been shown to be more active in KRAS wild-type patients [42]. Thus, those patients with KRAS mutation must not be selected for anti-EGFR therapy. **PAN** monotherapy improves PFS compared to best supportive care in chemorefractory metastatic KRAS wild-type CRC [39]. However, this **PAN**

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[6]Bendell, J.C.; Tournigand, C.; Bednarczyk, M.; Swieboda-Sadlej, A.; Chung, I.; Barone, C.; Tarazi, J.C.; Rosbrook, B.; Ricart, A.D.; Sobrero, A.F. Axitinib or bevacizumab (bev) plus FOLFOX or FOLFIRI as second-line therapy in patients (pts) with metastatic colorectal cancer (mCRC). *J. Clin. Oncol.* **2011**, Vol. *29*, suppl. 4 (GI ASCO abstract 478).

[7]Infante, J.R.; Cohn, A.L.; Reid, T.R.; Edenfield, W.J.; Cescon, T.; Hamm, J.T.; Tarazi, J.C.; Kim, S.; Rosbrook, B.; zartwright, T.H. A randomized phase II study comparing mFOLFOX-6 combined with axitinib or bevacizumab or both in patients with metastatic colorectal cancer (mCRC). *J. Clin. Oncol.* **2011**, Vol. *29*, suppl. 4 (GI ASCO abstract 485).

[8]Maughan T., Adams R.A., Smith C.G., *et al*. Addition of cetuximab to oxaliplatin-based combination chemotherapy in patients with KRAS wild-type advanced colorectal cancer: a randomized superiority trial (MRC COIN). *Eur. J. Cancer* **2009**, Vol. *7* (suppl), (ESMO LBA6).

[9]Tveit, K.; Guren, T.; Glimelius, B.; Pfeiffer, P.; Sorbye, H.; Pyrhonen, S.; Kure, E.; Ikdahl, T.; Skovlund, E.; Christoffersen, T. Randomized phase III study of 5-fluorouracil/folinate/oxaliplatin given continuously or intermittently with or without cetuximab, as first-line treatment of metastatic colorectal cancer: the NORDIC VII study (NCT00145314), by the nordic colorectal cancer biomodulation group. *Ann. Oncol*. **2010**, Vol. *21* (suppl. 8), (ESMO LBA20).

[10]Goldberg, R.M., Sargent, D.J.; Thibodeau, S.N.; Mahoney, M.R.; Shields, A.F.; Chan, E.; Gill, S.; Kahlenberg, M.S.; Nair, S.; Alberts, S.R. Adjuvant mFOLFOX6 plus or minus cetuximab (Cmab) in patients (pts) with KRAS mutant (m) resected stage III colon cancer (cc): NCCTG Intergroup Phase III Trial N0147. *J. Clin. Oncol*. **2010**, Vol. *29*, suppl. 4 (ASCO abstract 3508).

[11]Alberts, S.R.; Sargent, D.J.; Smyrk, T.C.; Shields, A.F.; Chan, E.; Goldberg, R.M.; Gill, S.; Kahlenberg, M.S.; Thibodeau, S.N.; Nair, S. Adjuvant mFOLFOX6 with or without cetuximab (Cmab) in KRAS wild-type patients (pts) with resected stage III colon cancer (cc): Results from NCCTG Intergroup Phase III Trial N0147. *J. Clin. Oncol.* **2010**, Vol. *29*, suppl. 4 (ASCO abstract CRA3507).

trial did not show a survival difference due to the cross-over design of the trial. In the PRIME study, **PAN** improved mPFS (9.6 mo. vs. 8.0 mo., p = 0.02) but not mOS (23.9 mo. vs. 19.7 mo., p = 0.072) in the KRAS wild-type stratum when combined with first-line **FOLFOX4** in comparison to **FOLFOX4** alone [43]. The results were similar when combined with second-line **FOLFIRI** in the KRAS wild-type population (mPFS 5.9 mo. vs. 3.9 mo., p = 0.004; mOS 14.5 mo. vs. 12.5 mo., p = 0.12) [44] (Table **3**). Due to these results the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion on the combination of **PAN** with other anti-cancer medicines both as first-line and as second-line treatment on March 17, 2011.

**Table 2. Development of Cetuximab (CET) in CRC**

| Therapy | Study | Design | Treatment | Reference |
|---|---|---|---|---|
| 1st Line | CRYSTAL | Phase III | FOLFIRI ± CET | [36] |
| | OPUS | Phase II | FOLFOX ± CET | [37] |
| | NORDIC VII | Phase III | FLOX ± CET | [FN 9] |
| | CELIM | Phase II | FOLFIRI/FOLFOX ± CET | [41] |
| | MRC COIN | Phase III | OxFp ± CET | [FN 8] |
| | AIO KRK 0104 | Phase II | CAPIRI + CET vs. CAPOX + CET | [40] |
| | CELIM 2 | Phase III (KRAS wt) | FOLFOX/FOLFOXIRI + CET | Ongoing |
| 2nd Line | BOND | Phase III | Irinotecan ± CET | [45] |
| | EPIC | Phase III | Irinotecan ± CET | [46] |
| ≥3rd Line | NCIC CO.17 | Phase III | CET vs. BSC | [47] |
| Adjuvant | PETACC 8 | Phase III | FOLFOX ± CET | Ongoing |
| | NCCTG N0147 | Phase III | FOLFOX ± CET | Ongoing |

BSC= best supportive care; CET = cetuximab; OxFp = oxaliplatin plus fluoropyrimidine.

**Table 3. Development of Panitumumab (PAN) in CRC**

| Therapy | Study | Design | Treatment | Reference |
|---|---|---|---|---|
| 1st Line | PRIME | Phase III | FOLFOX ± PAN | [43] |
| | | Phase II | FOLFIRI ± PAN | Köhne *et al.* GI ASCO 2010 |
| 2nd Line | | Phase III | FOLFIRI ± PAN | [44] |
| 3rd Line | | Phase III | PAN vs. BSC | [48] |

BSC= best supportive care; PAN = panitumumab.

After successful introduction of **BEV** and **CET**/**PAN** into the armamentarium of new drugs in the situation of metastatic CRC it was obvious to investigate a combination of both targeted therapies since the VEGF and EGFR pathways seem to be linked in solid tumors. In a phase II study of patients with metastatic CRC (the BOND-2 study) the combination of **BEV** and **CET** with or without **irinotecan** produced a partial response in 20% of patients and a median TTP of 4.9 months [49]. The first phase III trial to evaluate the combination of mAbs against EGFR and VEGF was the Panitumumab in Advanced Colorectal Cancer Evaluation (PACCE) trial [50]. Patients were treated with **FOLFOX** or **FOLFIRI** (physicians' choice) plus **BEV** and then randomly assigned to groups that were or were not given concurrent **PAN**. The combination therapy with **PAN** was not found to be more effective than the control arm with no differences reported in RR, PFS, or OS. The recently reported phase III trial CAIRO-2 presented similar results for the combination of **CAP**, **oxaliplatin**, and **BEV**, with or without **CET** [51]. In addition, **IMC-A12**, a human monoclonal antibody that blocks insulin-like growth factor receptor-1 (IGF-1R), alone or in combination with **CET** was insufficient to warrant additional study in patients with colorectal cancer refractory to EGFR inhibitors [52].

In summary, the biologic agents **BEV**, **CET**, and **PAN** have improved patient outcomes and survival and have been incorporated into routine clinical practice establishing a new standard of care for metastatic CRC, however a combination of **CET/PAN** + **BEV** is not recommended (Fig. **1**). Wild-type KRAS is a prerequisite for EGFR-targeted therapy, the role of BRAF still needs to be defined. Other potentially useful biomarkers of resistance to EGFR-targeted therapy in the process of clinical validation include PTEN loss and PI3KCA mutations, nuclear factor-kappa beta (NF-κβ) pathway activity, and expression of alternative EGFR ligands. Functional genomics elucidation of drug resistance pathways using RNA interference (RNAi) techniques may provide novel therapeutic approaches in disease resistant to EGFR pathway targeting and accelerate predictive biomarker development [53].

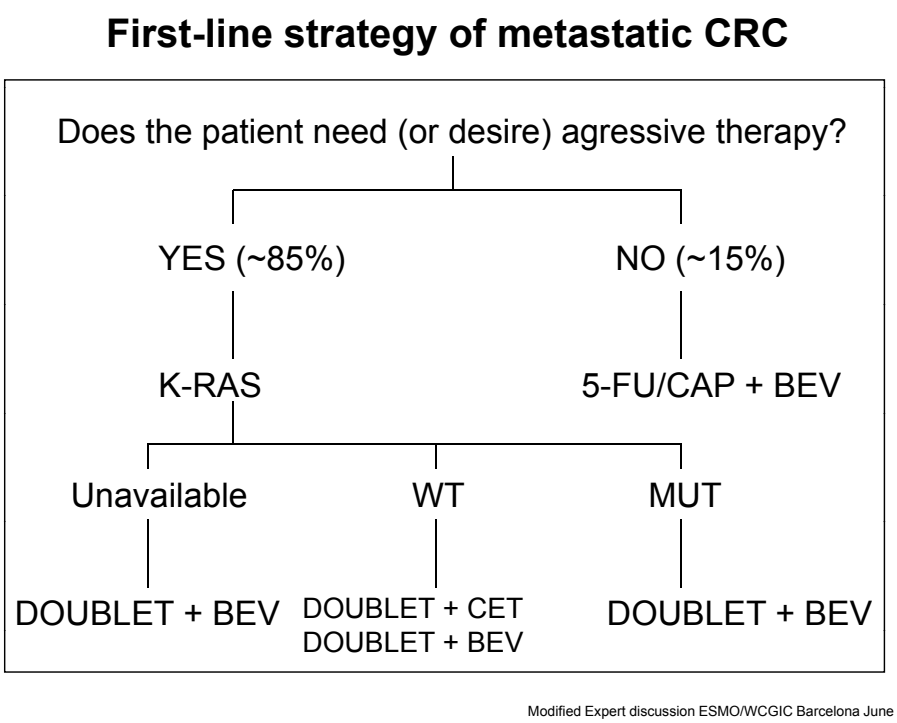


**Fig. (1).** First-line strategy of metastatic CRC.

**Molecular Targeted Therapy for Neuroendocrine Gatropancreatic Tumors (GEP-NET)**

Neuroendocrine gastropancreatic tumors (GEP-NET) represent relatively rare and heterogeneous malignancies with their origin in neuroendocrine cells of the embryological gut, most commonly with the primary lesion located in the gastric mucosa, the small and large intestine, the rectum or the pancreas. They are the most common group among neuroendocrine tumors (NETs). In most cases they are advanced at diagnosis and slow-growing, therefore conditioning a better prognosis compared with non-neuroendocrine carcinomas from the same sites. Surgery is the primary treatment for localized tumors and might be curative providing 5-year survival rates of 80-100% in resectable cases. The majority of patients present with metastatic disease. Even with metastatic disease, surgery plays an important role by reducing tumor masses. Radiofrequency ablation and embolization/chemoembolization of liver metastases are important as additional cytoreductive procedures. Cytotoxic treatment has been of limited value for the treatment of low-proliferating GEP-NET tumors, such as typical midgut carcinoids (RR ~10-15%), but has been standard of care for malignant endocrine pancreatic tumors (RR ~30-55%). Biological treatment, such as somatostatin analogues (SSA) and **α-interferons** has proved effective in the control of associated clinical symptoms related to hormon production and release [54]. The PROMID study is the first placebo-controlled, double-blind, prospective, randomized study on the effect of **octreotide LAR** in the control of tumor growth in patients with metastatic well-differentiated neuroendocrine midgut tumors [55]. The hypothesis was that **octreotide LAR** may prolong time to tumor progression and survival. Median TTP in the **octreotide LAR** and placebo groups was 14.3 and 6 months, respectively (hazard ratio [HR] = 0.34; 95% CI, 0.20 to 0.59; p = 0.000072). After 6 months of treatment, stable disease was observed in 66.7% of patients in the **octreotide LAR** group and 37.2% of patients in the placebo group. Functionally active and inactive tumors responded similarly. The most favorable effect was observed in patients with low hepatic tumor load and resected primary tumor. The HR for overall survival was 0.81 (95% CI, 0.30 to 2.18), which was not confirmatory because of the low number of observed deaths. A combination of SSA and **α-interferons** has been effective in patients with resistance to either drug. Peptide receptor radionuclide therapy (PRRT) is an option in patients who present with high-grade uptake on somatostatin receptor scintigraphy [56]. In addition, new SSA, covering a higher number of SSTR subtypes, were developed, including **pasireotide** (**SOM230**), which controls 25% of carcinoid syndromes resistant to full dose **octreotide LAR**. Chimeric analogs, which bind SSTR2/SSTR5 and dopamine-2 receptor subtype (D2), are in preclinical phase of development. Among the numerous molecular targeted agents investigated in GEP-NETs, mTOR inhibitors and VEGF/VEGFR/PDGFR inhibitors are in most advanced clinical phase of investigation. In a phase II study, efficacy of **RAD001** (**everolimus**), an oral inhibitor of mTOR, and **octreotide LAR** combination in advanced low- to intermediate-grade neuroendocrine tumors has been shown [57]. In another phase II study (RADIANT-1), daily **everolimus** with or without concomitant **octreotide LAR**, demonstrated antitumor activity as measured by objective RR and PFS (16.7 vs. 9.7 months) and was well tolerated in patients with advanced pancreatic NETs after failure of prior systemic chemotherapy [58]. Resently, in a large phase III randomized controlled trial (RADIANT-2), **everolimus** + **octreotide LAR** provided a 5.1 months clinically meaningful increase in median PFS compared to placebo + **octreotide LAR** in patients with progressing well or moderately differentiated advanced NET and a history of carcinoid

symptoms[12]. In a second large phase III clinical trial (RADIANT-3), **everolimus** significantly prolonged PFS compared to placebo in patients with advanced pancreatic NET [59]. Treatment resulted in a clinically meaningful 2.4-fold prolongation in median PFS. Eighteen months PFS estimates indicated that a sizable portion of patients experienced prolonged benefit. **Everolimus** had an acceptable safety profile consistent with the known safety profile of **everolimus** in cancer patients. These results represent important progress for the treatment of patients with advanced pancreatic NET. This has also been the case for **sunitinib (SU11248, Sutent™)**, an inhibitor of VEGFRs, platelet-derived growth factor receptors (PDGFRs), KIT and related kinases, which produced significant RR, PFS (11.4 mo. vs. 5.5 mo.; p = 0.0001), and OS benefit versus placebo in advanced progressing well-differentiated pancreatic NETs [60]. SSA use was allowed at study entry and during the study, which resulted in a nonstatistically significant improvement in PFS (HR 0.777, P=0.31) vs. no on-study SSA use. Other biologicals, that have been tested in (smaller) phase II studies are: **bevacizumab** (**BEV**), **MK-0646**, a mAb that blocks the insulin-like growth factor receptor (IGF-1R), **pazopanib**, a potent and selective multi-targeted receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-a/β, and c-kit**, sorafenib**, a small-molecule inhibitor of the VEGFR-2 and PDGFR-β tyrosine kinase domains, and **gefitinib**, an EGFR-inhibitor (Table **4**).

**Table 4. Molecular targeted therapy of GEP-NETs**

| Therapy | Study | Design | Treatment | Reference |
|---|---|---|---|---|
| 1st Line | PROMID | Phase III | OCTREOTIDE LAR vs. BSC | [55] |
| | | Phase II | OCTREOTIDE LAR + EVEROLIMUS | [57] |
| | RADIANT-2 | Phase III | OCTREOTIDE LAR + EVEROLIMUS | Pavel *et al*.; ESMO 2010 |
| | RADIANT-3 | Phase III | EVEROLIMUS vs. BSC | [59] |
| | | Phase II | MK-0464 | Reidy *et al.* ASCO 2010 |
| | | Phase II | EVEROLIMUS + BEV | Yao *et al.* ASCO 2010 |
| | | Phase II | CAPOX + BEV | Kunz *et al*. ASCO 2010 |
| 1st/2nd Line | | Phase III | SUNITINIB vs. BSC | [60] |
| | | Phase II | OCTREOTIDE LAR + PAZOPANIB (GW786034) | Phan *et al*. ASCO 2010 |
| | | Phase II | GEFITINIB | Hobday *et al.* ACSO 2006 |
| 2nd Line | | Phase II | SORAFENIB | Hobday *et al.* ACSO 2007 |
| | RADIANT-1 | Phase II | EVEROLIMUS + OCTREOTIDE LAR | [58] |

BEV = Bevacizumab; BSC= best supportive care.

## Molecular Targeted Therapy for Pancreatic Cancer

Pancreatic cancer is one of the most highly fatal cancers, with > 95% of those affected dying of their disease. Radical surgery is the treatment of choice for patients with early stage of disease. Postoperatively, six cycles of **5-fluorouracil** (**5-FU**) or **gemcitabine** may be suggested on the basis of three randomized trials [61-63]. In all other cases, the aim of treatment is palliation of distressing symptoms related to this type of cancer. While treatment with **gemcitabine** may be a reasonable choice, the use of a combination treatment including other cytotoxic agents, is not supported by an advantage in survival appart from **gemcitabine** plus **CAP** and **FOLFIRINOX** (**5-FU** plus **irinotecan** plus **oxaliplatin**). However, for both combinations there is only one positive trial and **FOLFIRINOX** shows significant toxicity. Therefore, the search for additional molecular targeted therapy is important as discussed by Porzner *et al*. in this issue. Unfortunately, so far only a combination of **gemcitabine** and **erlotinib**, an EGFR-inhibitor, has been approved by the FDA and EMEA on the basis of a randomized trial from the NCI of Canada [64]. However, the very modest survival gain (about two weeks, or a total of 6.37 months for overall survival) and the high economic costs question the role of this combination in metastatic pancreatic cancer. In addition, there is no standard chemotherapy for patients who have progressed in first-line treatment. The CONKO-003 study has shown a benefit for a **5-FU/oxaliplatin** combination which might be considered as standard [65]. Up to now, there is no role for a second line molecular targeted therapy.

## Molecular Targeted Therapy for Gastric Cancer

The overall incidence of gastric cancer is declining, however there has been a relative increase in the incidence of tumors of the esophago-gastric junction (OGJ) and gastric cardia. The peak incidence is in the seventh decade, and the disease is

[12]Pavel, M.; Hainsworth, J.D.; Baudin, E.; Peeters, M.; Hoersch, D.; Anthony, L.; Hoosen, S.; Peter, J.St.; Jehl, V.; Yao, J.C. A randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus + octreotide LAR vs. placebo + octreotide LAR in patients with advanced neuroendocrine tumors (NET) (RADIANT-2). *Ann. Oncol*. **2010**; Vol. *21*, Suppl. 8 (ESMO abstract LBA 8).

approximately twice as common in men as women. Surgical resection is the only modality that is potentially curative. Two randomized trials (UK MRC and FFCD) supported preoperative and postoperative chemotherapy [66, 67]. A North American Intergroup randomized trial demonstrated that postoperative chemoradiotherapy resulted in about 15% improvement in 5-year overall survival [68]. Although this treatment approach is considered to be standard in the USA, it has not gained wide acceptance in Europe because of concerns about toxicity and quality of surgery used. In Japan, oral fluoropyrimidine **S-1** has become standard as adjuvant therapy according to a large randomized trial [69]. Patients with inoperable, locally advanced gastric cancer should be treated with palliative chemotherapy and may be reassessed for surgery if a favourable response is achieved. Neo-adjuvant chemoradiation may be feasable for locally advanced OGJ tumors [70]. Patients with metastatic disease should be considered for palliative chemotherapy, which improves survival compared with best supportive care alone. Combination regimens incorporating a platinum derivative and a fluoropyrimidine are generally used. According to a meta-analysis best survival results are achieved with three-drug regimens containing a platinum derivative, a fluoropyrimidine, and an anthracycline [71]. Four large randomized prospective studies have established the role of **docetaxel**, **CAP**, and **oxaliplatin** in the palliative treatment [72-75]. As discussed by Moehler *et al.* in this issue the addition of **trastuzumab** to **cisplatin** plus fluoropyrimidine chemotherapy in patients with HER2-positive gastric cancer is the first approved molecular targeted treatment option which has clinically and statistically improved response rate, median progression-free survival, and median overall survival [76]. A median survival of 13.8 months was reached with this combination, which suggests a gain of 2.6 months in comparison to EOX (**epirubicin**, **oxaliplatin**, **CAP**), the most efficient chemotherapy regimen according to Cunningham *et al*. [73].

## Molecular Targeted Therapy for Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) are rare tumors, with an estimated incidence of 1.5/100,000/year. Multidisciplinary treatment planning is needed involving pathologists, radiologists, surgeons and medical oncologists, which is available in reference centers for sarcomas and GISTs. Standard treatment for localized GISTs is complete surgical resection. In locally advanced inoperable patients and metastatic patients treatment options had been limited for a long time. As discussed by Reichardt *et al*. in this issue multi-thyrosine kinase inhibitor **imatinib** has revolutionized the treatment of GISTs. It became the standard for the palliative treatment of GISTs [77], adjuvant treatment for those patients with a substantial risk of relapse [78] and for cytoreduction prior to surgery [79, 80]. However, molecular analysis detected a subgroup of patients with exon 9 KIT mutations which need a higher dose of **imatinib** to show efficient response [81]. In addition, mechanisms of **imatinib**-resistance were identified, requiring dose escalation [82] or second line treatment with multi-thyrosine kinase inhibitor **sunitinib** [83]. Currently, several other molecular targeted inhibitors, such as **nilotinib** or **everolimus**, are tested in clinical trials. Finally, it is generally accepted that treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumor progression in virtually all cases even when lesions have been previously surgically excised [84]. This causes a tremendous financial burden to our health care systems.

## Molecular Targeted Therapy for Hepatobiliary Cancer

Hepatocelluar carcinoma (HCC) is the fifth most common cancer in men and eight most common cancer in women worldwide, resulting in at least 500,000 deaths per year. It accounts for 90% of all liver cancers. The treatment of every patient with HCC should always be discussed and planned by a multidisciplinary team. The treatment plan should be based on the presence or absence of liver cirrhosis, extent of disease, growth pattern of tumor, hepatic functional reserve and patient`s performance status. The applicable treatment possibilities include surgical (liver resection, transplantation), ablative (transarterial chemoembolization (TACE), radiofrequency ablation, yttrium-90 microsphere radioembolization (SIRT)) and medical modalities. Until recently there has been no standard medical therapy for advanced HCC. As discussed by Wiedmann *et al*. in this issue the positive results of a phase III study called the Sorafenib Hepatocarcinoma Assessment Randomized Protocol (SHARP) led to first time approval of molecular targeted therapy in this tumor type as standard treatment [85]. As a result of this study, combinations of **sorafenib** with TACE/SIRT and **sorafenib** with chemotherapy are currently investigated as well as **sorafanib** in an adjuvant setting. Other thyrosine kinase inhibitors such as **BEV**, **brivanib**, **linifanib**, or **erlotinib** have to prove their efficacy in currently ongoing studies.

Biliary cancer as a rare tumor of the gastrointestinal tract is subdivided into gallbladder cancer, intra- and extrahepatic cholangiocarcinoma. Although complete surgical resection is the only curative approach, this can be accomplished in a minority of patients, since most of them present with advanced disease. In addition, those patients who have undergone complete surgical resection experience a high tumor recurrence rate. Non-resectable biliary tract cancer is associated with a poor prognosis due to wide resistance to chemotherapeutic agents and radiotherapy. In addition, there is a lack of prospectively randomized phase III trials testing modern chemotherapy regimens. The only exception is a recent UK trial (ABC-02) which detected a significantly increased median TTP of 8.5 months and median OS of 11.7 month with a combination of **gemcitabine** and **cisplatin** [86]. It is therefore essential to search for new therapeutical approaches. After several years of preclinical research, the first clinical study data are now available for this tumor entity. Inhibitors of the EGFR family, such as **erlotinib**, **CET**, and **lapatinib** were recently investigated. Furthermore, **bortezomib**, an inbibitor of the proteasome, **imatinib**, **BEV**, and **sorafenib**, were studied, as well. Although early evidence of antitumor activity was seen, the results are still preliminary and require further investigations (for review see [87]).

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