Conclusions: Patients in the Italian cohort of CONSIGN appeared similar to those in the overall cohort, except that a higher proportion of patients in the Italian cohort had a baseline ECOG PS of 0 (76% vs 47% in the overall cohort). The AE profile in the Italian cohort was consistent with that of the overall cohort, and median PFS in the Italian cohort (2.9 months) was similar to that in the overall cohort (2.7 months).

Treatment-emergent AE	Percentage of patients	
	Italian cohort (N = 683)	All patients (N = 2864)
Grade ⩾3	74	80
Drug-related	55	57
Fatigue	16	18
Hypertension	14	17
HFSR	10	14
Diarrhea	5	6
Hypophosphatemia	10	7
Serious	23	44
Drug-related	4	9
Leading to discontinuation	19	25
Drug-related	6	9

Conflict of interest: *Ownership: Siena: Ignyta. Moscovici: Bayer. Advisory Board: Ciardiello: Roche, Merck Serono, Bayer, Sanofi, Astellas, Amgen, Lilly. Falcone: Amgen, Bayer, Roche, Merck-Serono, Sanofi, Lilly. Cascinu: Bayer, Roche, Sanofi. Sobrero: Roche, Bayer, Merck, Sanofi, Celgene, Amgen. Barone: Novartis, Merck, Amgen, Roche, Bayer. Siena: Roche, Bayer, Amgen, Sanofi, Ignyta. Di Bartolomeo: Lilly S.p.a. Corporate-sponsored Research: Falcone: Roche, Merck-Serono, Sanofi. Siena: Bayer. Van Cutsem: Bayer. Other Substantive Relationships: Siena: patents (Amgen). Moscovici: Bayer employee. Boni, Barone, Luppi, Maiello, Zagonel, Carteni, Di Costanzo, Santoro, Russo, Zaniboni: Nothing to disclose.*

2144 POSTER

High levels of D-dimer correlated with disease status and poor prognosis of inoperable metastatic colorectal cancer patients treated with bevacizumab

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Background: To assess the levels of D-dimer baseline levels in inoperable metastatic colorectal cancer (mCRC) patients treated with bevacizumab and its relationship with prognosis.
Materials and Methods: From June 1, 2011 to December 31, 2013, a total of 121 patients with mCRC received beacizumab combined with chemotherapy and 74 of them were included in the present study. A nonparametric statistical test was performed to analyze the relationship between plasma D-dimer levels and clinical pathological factors. The Cox proportional model was used to analyze the effects of D-dimer on progression-free survival (PFS) time and overall survival (OS).
Results: Of the 74 cases, 40 were men and 34 women (aged 31−74 years), with a median age of 55.5 years. The median of PFS and OS were 6.3 and 17.8 months respectively. High levels of baseline plasma D-dimer were correlated with high scoring of Eastern Cooperative Oncology Group-Performance Status (P = 0.001), IV phase of disease at the first visit (P = 0.001), unremoval primary focal (P = 0.006), the number of metastatic organs ⩾2 (P = 0.034), abdominal cavity effusion (P = 0.004) and no history of adjuvant chemotherapy (P = 0.003). It was found by single factor analysis that plasma baseline D-dimer levels ⩾1.9 μg/mL were closely related with a short PFS (hazard ratio [HR] 2.14, 95% confidence interval [CI] 1.04–4.40, P = 0.038) and OS (HR 5.22, 95% CI 2.05–13.28, P = 0.001). After adjustment for other factors, plasma baseline D-dimer levels ⩾1.9 μg/mL were still closely correlated with a short OS (HR 3.52, 95% CI 1.28–9.67, P = 0.015).
Conclusion: High levels of plasma baseline D-dimer correlated with high tumor load, advanced disease status and poor prognosis of inoperable mCRC patients treated with bevacizumab. However, clinical research on a much larger cohort of patients will be required to verify these findings.
No conflict of interest.

2145 POSTER

Masitinib plus FOLFIRI for second-line treatment of metastatic colorectal cancer: 2-year follow-up of phase 2, open label trial

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Background: Masitinib (MAS) is a selective inhibitor of c-Kit and mast cell function. Increased mast cell activity in the tumor microenvironment is linked to poor prognosis and a protumoral immune response in colorectal cancer (CRC). In vitro, MAS acts as a chemosensitizer of 5-fluorouracil and irinotecan in CRC cell lines. This open label phase 1b/2 trial evaluated MAS in combination with chemotherapies for second-line treatment of metastatic CRC. Updated survival and safety data after a median follow-up of 2 years are reported for the cohort receiving MAS + FOLFIRI.
Methods: Patients with nonresectable, metastatic CRC after progression to first-line treatment received MAS + FOLFIRI until progression, refusal or unacceptable toxicity. Patients previously treated with irinotecan were excluded. Phase 1 evaluated safety of the combination with Dose Limiting Toxicity (DLT) determining subsequent dose and recruitment. DLT was defined as grade 3 non hematological adverse event (AE) or any grade 4 AE related to MAS. The phase 2 study evaluated efficacy.
Results: Eighteen patients (50% with mutated KRAS) from 6 centers in France were treated with MAS + FOLFIRI. No DLT was reported for the phase 1 stage (3 patients) at 9 mg/kg/day. Overall, 6/18 patients (33%) reported grade 3−4 AE and 4/18 patients (22%) experienced serious AE. No treatment related deaths were reported. After a median follow-up of 24.3 months, median OS was 17.6 months (95% CI [6.8; 21]) and median PFS was 5.6 months (95% CI [1.8; 9.2]). Objective response rate was 28%, including 1 patient with a confirmed complete response. For the final 3 patients MAS dose was reduced from 9 to 6 mg/kg/day based on new mechanistic understanding and to minimize risk of toxicity. Efficacy was still evident in these patients as evidenced by PFS of 9.2, 6.2 and 5.6 months with no grade 3−4 AE reported in this cohort.
Conclusions: The safety profile of MAS + FOLFIRI was acceptable. Efficacy findings seem to compare favorably against historic benchmarks (see table below) with the comparatively high objective response rate and notable confirmed complete response in one patient. MAS may therefore offer patients a new active compound for mCRC. A confirmatory phase 3 trial evaluating FOLFIRI +/− MAS at 6 mg/kg/day as second-line for mCRC is ongoing with OS as a primary efficacy criterion. A second objective of this ongoing phase 3 study will be to identify those subgroups that best respond to MAS.

	MAS + FOLFIRI	FOLFIRI wt KRAS*	FOLFIRI mutant KRAS*
OS (months)	17.6	12.5	11.1
PFS (months)	5.6	3.9	4.9
Objective Response Rate	28%	10%	14%
Complete	6%	0%	0%
Partial	22%	10%	14%

wt = wild-type.
*Peeters et al. (2010) J Clin Oncol 28: 4706.

Conflict of interest: *Ownership: Patrice Dubreuil (AB Science). Colin Mansfield (AB Science). Alain Moussy (AB Science). Olivier Hermine (AB Science). Board of Directors: Alain Moussy (AB Science). Corporate-sponsored Research: Research Funding Source: AB Science.*

2146 POSTER

Association between proton-pump inhibitors (PPI) and metronomic capecitabine (MCAP) as salvage treatment for patients with advanced gastro-intestinal tumours: A randomized phase II study

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Background: Several researches have shown that acidification of tumor microenvironment is the basis for tumor invasiveness, ability to metastasize

and cytotoxic agents resistance; therefore proton pump inhibitors (PPI) could significantly increase the chemosensitivity. In our retrospective work we have investigated the role of capecitabine (mCAP) at metronomic dosage of 1500 mg/die as salvage chemotherapy in patients with metastatic colorectal cancer, showing a moderately activity and well tolerability. In this prospective study we evaluated safety and activity of mCAP in the advanced gastro-intestinal patients and the putative chemosensitizing activity of a specific PPI (Rabeprazole) in association to this therapy.

Materials and Methods: This is a single centre, open label, randomized phase II study to determine safety and activity of Rabeprazole (1.5 mg/kg bis in die for 3 days a week) combined with mCAP (1500 mg/die, continuously) compared to mCAP alone. Inclusion criteria considered pre-treated patients with advanced gastrointestinal tumors, performance status (ECOG) $\leqslant$2, life expectancy >3 months, adequate organ (liver, kidney, heart and bone marrow) function.

This trial is registered at EU Clinical Trials Register, no. 2013-001096-20.

Results: 41 patients have been recruited (median of previous chemotherapy regiments 2), well balanced in the two treatment arms by sex and age. All patients were evaluable for response at 12 weeks. 6 (29%) patients treated with mCAP and 4 (20%) patients treated with mCAP+PPI had a clinical benefit. The PFS was 15 weeks in both treatment arms; the median OS was 26 and 29 weeks in mCAP and mCAP+PPI arm respectively. No grade 4 toxicity occurred (table).

Conclusions: We believe mCAP is a therapeutic hope for patients who cannot resort to more standard treatments. Pharmacokinetic analysis for evaluating whether the administration of high-dose PPI favors the absorption, the distribution and the effects of mCAP are underway but our preliminary data shown adverse events and activity in the two populations are similar.

	mCAP n (%) 21 (51)	mCAP-PPI n (%) 20 (49)
Sex		
Female	9 (43)	7 (35)
Male	12 (57)	13 (65)
Median age (range)	68 (45−84)	68 (56−85)
ECOG PS		
0	7 (33)	9 (45)
$\geqslant$1	14 (67)	11 (55)
Localization		
Upper GI-cancer	2 (10)	1 (5)
Lower GI-cancer	19 (90)	19 (95)
Haematological toxicity G3	2 (11)	0
Non-haematological toxicity G3	4 (22)	3 (15)
Response rate		
CR	0	0
PR	0	1 (5)
SD	6 (29)	3 (15)
PD	13 (62)	16 (80)
Not available	2 (9)	
Median PFS (weeks)	15	15
Median OS (weeks)	24	29

No conflict of interest.

2147 POSTER

Pathological response as a prognostic factor for disease free survival on colorectal cancer with liver limited disease

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Background: Patients with metastatic colorectal cancer, sincronic, with disease free survival <1 year or non-resectable liver limited disease at diagnostic benefit from neoadjuvant chemotherapy (nCT). This study analyzes the pathological responses (pR) in colorrectal liver metastasis (CRLM) depending on the nCT received (alone or with antiVEGF/antiEGFR antibodies) and its impact on disease free survival (DFS).

Methods: Single center study, evaluating pR by tumor regression grade (TRG) according to Rubbia criteria (1−2 good response; 3 to 5 bad response), in patients with resected CRLM after neoadjuvant treatment, between January/2006 to April/2015. A blinded to treatment specialized pathologist, reviewed retrospectively all samples obtained. Tumor radiological response (rR) was evaluated using response evaluation criteria (RECIST 1.1v). The difference among variables was calculated by chi-square (χ^2) test and DFS was estimated using Kaplan–Meier method.

Results: Forty-six patients (p.) were included; 97% had good performance status (ECOG 0−1); 58% men; 32p with primary colon cancer and 14p. with rectal one; a media of 2.41 liver metastasis (1−7 SD 1.68) with greatest one of 4.2cm size media (1−13cm SD 2.68) at diagnostic. They received an average of 5.2 (1−18 SD 3.86) neoadjuvant cycles, with 72.2% patients fulfilling the planned treatment, 14 patients received CT, 21 CT plus Bevacizumab, and 11 CT plus antiEGFR schedule. Radiological responses was achieved in 78.8% of them (RECIST), and 43,9% good pR (TRG 1−2). There was no relation between pR and rR (χ^2 p = 0.36). Patients treated with Bevacizumab reached the best pR (52% vs 28% χ^2 p = 0.09), and the difference was even greater between antiVEGF and antiEGFR treatments (58% vs 18% χ^2 p = 0.06). No significant difference was seen in DFS relationed to nCT, but those treated with Bevacizumab (41.3 vs 36.9 months p = 0.07) and patients who obtained pR showed a statistical trend over improving DFS (69.7 vs 21.1m p = 0.08).

Conclusion: Patients treated with bevacizumab reached the best pathological response in liver metastasis. No significant difference in DFS was seen between different neoadjuvant treatments received, but pathological response seems to be a good prognostic factor in patients with colorectal cancer liver limited disease.

No conflict of interest.

2148 POSTER

Locally advanced colon cancer and the use of neo-adjuvant chemotherapy in the Netherlands

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Background: Neo-adjuvant chemotherapy is already widely established as accurate treatment protocol to achieve downsizing and downstaging of the primary tumor in gastric, oesophageal and rectal cancer. Recent studies demonstrate that there might be a place for neo-adjuvant chemotherapy in locally advanced colon tumors as well. This nationwide study aims to review the frequency of neo-adjuvant chemotherapy for stage II and III colon cancer in the Netherlands, and to assess its safety and feasibility.

Methods: The Dutch Cancer Registry was used to extract all patients who were diagnosed between 2008 and 2012 with stage II and III colon cancer. Patients who received neo-adjuvant chemotherapy prior to surgical resection were identified and compared to a control group of patients with locally advanced tumors (defined as clinical or pathological T-stage 4). Demographic data and surgical as well as oncological outcomes were compared. To assess downsizing of the tumor, clinical T-stage before receiving chemotherapy was compared to pathological T-stage in the resection specimen. Overall survival was calculated using Kaplan Meier curves.

Results: Out of 25,852 patients who were diagnosed with stage II or III colon cancer, 92 patients (0.36%) received neo-adjuvant systemic therapy. The control group consisted of 5887 patients. Patients in the neo-adjuvant group were significantly younger compared to the control group, median age 62 years (range 29−80) versus 71 (range 11−98), p < 0.001. Clinical T-stages prior to systemic therapy were T2 in one patient (1%), T3 in six patients (6.5%) and T4 in 63 patients (68.5%), (unknown in 22 patients). Thirty-one of the 63 T4 tumors (68.5%) showed downsizing after neo-adjuvant therapy: 25 were staged ypT3 after therapy, three regressed into ypT2 and three showed a complete response to ypT0. No significant difference in major complications such as anastomotic leakage and abscess formation was demonstrated between the two groups. Patients in the neo-adjuvant group were less likely to undergo emergency surgery (2.2 vs 12.5%). In 87% of patients (n = 73) R0 resection were achieved, five patients had R1 resections (6%) and six patients had R2 resections (7%). This is comparable to the control group. The 30-day mortality was zero versus four percent in the neo-adjuvant group compared to the control group, p = 0.03. Two-year survival was 83% in the neo-adjuvant group versus 70% in patients who did not receive neo-adjuvant therapy.

Conclusion: In the Netherlands, neoadjuvant chemotherapy is currently only administered in a small selection of patients with locally advanced colon cancer. This treatment seems to be safe and feasible with good short- and long term results. As downsizing was noted in a significant number of T4 tumors, this treatment strategy should especially be considered in patients with locally advanced colon cancer.

No conflict of interest.