patients stopped oxaliplatin due to peripheral neuropathy. There was no toxicity related death.
Conclusion: These data suggest good tolerability and efficacy for second-line CAPOX in non selected (31% ECOG2 and 26% ⩾70 years old) patients with MCRC pretreated with irinotecan based regimen. Our results in clinical practice setting are similar to those published in trials using FOLFOX indicating the promise of this regimen as an effective second-line therapy.

Table 1

Patients' and treatment's characteristics (N = 138)	N° (%)
Median age (years)	65
Range	37–80
Performance Status (ECOG)	
2	43 (31.2)
1	43 (31.2)
0	24 (17.4)
K-RAS gene status: wild type/mutated/unknown	42(30.4)/24(17.4)/72(52.2)
Primary tumour location	
Colon except sigma	79 (57.3)
Sigma	14 (10.1)
Rectum	45 (32.6)
Metastatic disease location	
Liver	113 (81.9)
Nodes	97 (70.3)
Lung	63 (45.7)
Peritoneum	51 (36.4)
Others	12 (8.7)
Number of metastatic sites	
1	29 (21)
>1	109 (79)
Median CEA (ng/ml)	58
Range	0.9–11500
Front-line chemotherapy	
IFL	43 (31.2)
CAPIRI (contraindication of Bevacizumab)	17 (12.3)
CAPIRI + Bevacizumab	78 (56.5)
Chemotherapy dose (cycle repeat every 21 days)	
Capecitabine (mg/m^2/day × 14 days)	
2000	48 (34.8)
1700	60 (43.5)
<1700	30 (21.7)
Oxaliplatin (mg/m^2 day 1)	
130	23 (16.7)
100	94 (68.1)
<100	21 (15.2)
Other chemotherapy lines	
0	54 (39.1)
3	43 (31.2)
>3	41 (29.7)

6104 POSTER

A Phase II Randomized Study of Two Doses of Vorinostat in Combination With 5-FU/LV in Patients With Refractory Colorectal Cancer (CRC)

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Background: Data from a phase I clinical trial confirmed the feasibility of combining vorinostat doses 600- 1700 mg/day x 3 days with standard doses 5-FU/LV in patients (pts) with refractory CRC. Activity was noted at vorinostat dose-levels (DL) of ⩾ 800 mg/day. We conducted a phase II clinical trial to better define the activity of this combination in 5-FU-refractory CRC at the vorinostat DL of 800 and 1400 mg/day (registered on cancer.gov as NCT00942266 and supported by a grant from MERCK).
Methods: Pts with metastatic CRC who failed standard chemotherapy and progressed within 4 weeks from a fluoropyrimidine-based treatment were enrolled. Pts were randomized to receive low dose (LD) 800 mg/day or high dose (HD) 1400 mg/day vorinostat for 3 days. LV 400 mg/m^2 followed by 5-FU 400 mg/m^2 bolus and 2400 mg/m^2 × 46 hrs were administered on days 2−3 of a 14-day cycle. Randomization was stratified by performance status (0−1 vs. 2) and LDH (normal vs. elevated). A 2-stage design was performed: if ⩽ 8/15 pts had disease control at two months, that treatment arm was terminated; if ⩾ 9/15 pts have disease control, a total of 43 pts on that arm were enrolled. 43 pts have an 80% power to detect an improvement in 2-month disease control rate (DCR) by 20% (assuming 50% DCR for 5-FU/LV).
Results: 15 pts (6 male, median-age 62, 7 elevated LDH, 2 ECOG 2) were enrolled at the HD and 43 pts (21 male, median-age 60, 27 elevated LDH, 5 ECOG 2) at the LD levels. Common grade 3/4 toxicities were: grade (G) 3 fatigue in 3 LD pts and 5 HD patients, G3 nausea in 4 LD patients and 2 HD patients, G3 diarrhea in 2 LD and 2 HD patients, G3 hand-foot in 3 LD and 3 HD pts. No differences were noted in the pharmacokinetics cohorts of vorinostat between the LD (10 pts) and HD (10 pts) in terms of C_{max}, C_{ss}, and AUC, suggesting bioavailability saturation at doses ⩾ 800 mg. No G3 QTc was noted on the HD arm in 10 pts with intense EKG monitoring. 8/15 pts had disease control (SD) on the HD arm, which was closed to accrual. 9/15 (1 PR, 8 SD) had disease control on LD, which was expanded. On the LD arm, 1/43 pts had a PR and 22/43 had SD for a 2-month DCR of 53.5%. The median PFS on the LD arm was 2.43 months (KRAS Mt = 2.53 vs. KRAS Wt = 2.04, p = 0.32) and the median OS was 6.74 months (KRAS Mt = 6.74 vs. KRAS Wt = 5.85, p = 0.56). All LD patients deriving disease control ⩾ 6 months were KRAS Mt (4/29) with lung pre-dominant metastases.
Conclusions: The addition of the histone deacetylase inhibitor vorinostat does not enhance 5-FU/LV activity sufficiently to warrant further investigation in unselected 5-FU-refractory CRC patients.

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Phase II Trial of Temsirolimus Alone and in Combination With Irinotecan for KRas Mutant Chemotherapy Resistant Metastatic Colorectal Cancer and the Importance of KRas Mutations in the Plasma

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Background: Metastatic colorectal cancer (mCRC) with *KRAS* mutation represents a major therapeutic challenge. The present study evaluated the safety and efficacy of the mTOR inhibitor temsirolimus alone and in combination with irinotecan in chemotherapy refractory mCRC with *KRAS* mutations. Furthermore, the importance of quantitative measurement of *KRAS* mutations in plasma was investigated.
Methods: The study was planned as two phase II trials in the same study. Patients received a weekly dose of temsirolimus 25 mg IV followed by response evaluation every 6 weeks. Monotherapy was continued until progression, and followed by combination therapy consisting of biweekly irinotecan 180 mg/m^2 IV and temsirolimus. Eligibility criteria included; histopathologically verified chemotherapy resistant mCRC, *KRAS* mutation, adequate PS and organ function. A quantitative PCR method was used to asses the number of *KRAS* mutated alleles in plasma prior to each cycle.
Results: Sixty-four patients were included. There were no grade 4 adverse events, but 30% experienced grade 3 toxicity, primarily infections or laboratory changes. The median number of monotherapy cycles was 3 (range 0−17) and that of combination therapy 3 (0−19). None of the patients achieved an objective response according to RECIST but 38% (24/64) had stable disease on monotherapy and 63% (22/35) on combination therapy. 12 cases of tumour shrinkage were detected. The median time to progression (TTP) was 45 days and 84 days, respectively. The median overall survival was 160 days in the total cohort.
The concordance between *KRAS* status in tumour and plasma (*pKRAS*) was 82%. Patients with high *pKRAS* (>75% quartile) had a 77% risk of early progression on monotherapy compared to 43% in patients with lower levels (p = 0.036). All patients with tumour reduction during treatment had low *pKRAS*. Survival analysis also showed that *pKRAS* was a strong prognostic factor.
Conclusion: Temsirolimus has limited efficacy in metastatic colorectal cancer, but quantitative measurement of *KRAS* in plasma may serve as predictor for outcome and a tool for monitoring patients with *KRAS* mutant colorectal cancer.