

combination of CAP and irinotecan (CPT). Based on these data a phase I study of CAP combined with weekly CPT was conducted in patients (pts) with measurable metastatic CRC as first-line chemotherapy.

Methods: CAP (bid) d 1-14 and d 22-35, CPT 30 min. inf. weekly x 6 followed by a one week rest (one cycle). Dose level [DL]: CAP 1000 mg/m² bid and CPT 70 mg/m²; DL2: CAP 1250 mg/m² bid and CPT 70 mg/m²; DL3: CAP 1250 mg/m² bid and CPT 80 mg/m².

Results: 37 patients (pts) were entered on 3 DL and 89 cycles have been administered. Pts characteristics: Male/female 26/11 pts; PS 0 (0-2); median age 60 years (32-71); prior adjuvant CTx or/and RTx 14 pts. In the first 17 pts treated at DL1-3 the MTD has been reached at DL3 with diarrhea and neutropenia being dose-limiting. In order to confirm the recommended dose (RD), this DL2 was extended to 15 pts, demonstrating an incidence of DLTs in 5 (33%) out of 15 pts (diarrhea, neutropenia, one toxic death). Because the incidence of DLTs was considered to be too high, DL1 was extended to a total of 16 pts. DLTs were observed in 3 (19%) out of 16 pts. The main toxicity observed was diarrhea. So far, 13 out of 29 response evaluable pts (DL 1-3) (45%; 95%CI: 26-63%) and 6 out of 13 pts (46%; 95% CI 19-75%) at the RD (DL1) achieved an objective response.

Discussion: DL1 is the recommended dose for further studies. The combination of CAP and CPT is feasible and showed promising efficacy as first-line chemotherapy in advanced colorectal cancer.

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POSTER

Preoperative chemoradiation with raltitrexed ('Tomudex') alone or in combination with oxaliplatin in T3 rectal carcinoma: review of four phase I-II studies

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Aims: Preoperative radiation plus 5-fluorouracil (5-FU) increases the likelihood of sphincter preservation during surgery for rectal cancer. Tumour downstaging following chemoradiation also correlates with improved prognosis. Hence, there is a demand for more potent downstaging drugs to replace 5-FU in chemoradiation. The efficacy of raltitrexed ('Tomudex'), alone or combined with oxaliplatin, in preoperative chemoradiation was studied in patients with T3 rectal carcinoma.

Methods: Since 1998, 62 patients (pts) with stage II-III extraperitoneal rectal carcinoma have been studied in 4 trials. Radiation plus raltitrexed (2 trials): (1) Phase I study to determine the recommended dose (RD) of raltitrexed (2.0, 2.5, 3.0 mg/m²) concurrent to radiation; (2) Phase II study of raltitrexed (3.0 mg/m²/radiation. Radiation plus raltitrexed and oxaliplatin (2 trials): (1) Phase I study to determine the RD of oxaliplatin (65, 85, 110, 130 mg/m²) concurrent to radiation plus raltitrexed (3.0 mg/m²); (2) Phase II study of oxaliplatin (130 mg/m²)/raltitrexed (3.0 mg/m²)/radiation. Pts received 45 Gy pelvic radiation (1.8 Gy/day, 5 days/week) with 5.4 Gy boost on the tumour bed. Raltitrexed, with or without oxaliplatin, was administered on Days 1, 19 and 38.

Results: Radiation plus raltitrexed: in Phase I (n=15) the RD was determined as 3.0 mg/m², and 40% and 66% of pts had downstaging (pT0-1) and sphincter-saving surgery, respectively; only 1 pt had >G2 toxicity (G3 leucopenia, recovery in 3 days). Similar results were observed in Phase II (n=20): 50%, 80% and 15% of pts had downstaging, sphincter-saving surgery and G3 toxicity, respectively. Radiation plus raltitrexed and oxaliplatin: in Phase I (n=18) the RD was determined as oxaliplatin 130 mg/m² combined with raltitrexed 3.0 mg/m² and radiation. Overall, 66% and 72% of pts had downstaging and sphincter-saving surgery, respectively. Two pts had >G2 toxicity (G3 leucopenia and G3 proctitis). The Phase II study (n=9) confirmed these results: 55%, 89% and 11% of pts had downstaging, sphincter-saving surgery and G3 toxicity, respectively.

Conclusion: The high rates of tumour response and sphincter-sparing surgery plus low levels of toxicity suggest that raltitrexed is effective with an acceptable toxicity profile, both alone and combined with oxaliplatin, when given concurrently to pelvic radiation preoperatively.

'Tomudex' is a trade mark of the AstraZeneca group of companies

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POSTER

Weekly combination of oxaliplatin (OX) and irinotecan (IRI) in 5-FU resistant colorectal cancer (CRC)

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Purpose: OX and IRI are active agents in CRC. The combination of both drugs could enhance the efficacy of a salvage regimen in patients (pts) in whom progression (PD) occurs while they receive a 5-FU based chemotherapy (CT): 5-FU resistant 2nd-line population (FRP). In a recently published trial with OX-IRI only 14/36 pts were FRP and 31/36 received G-CSF to ameliorate risk of neutropenic fever (J Clin Oncol 17:902).

Methods: We performed a prospective multicenter phase II trial with OX 60 mg/sqm/1h and IRI 80 mg/sqm/1h both on days 1, 8, 15 q 28d, without any use of G-CSF. Instead individual dose optimisation (IDO) was performed in case of toxicity (TOX) by dose modification and omitting scheduled days according to predefined guidelines.

Results: 68 pts received 1 to 9 cycles and are evaluable for TOX: In 27 pts CT was stopped due to objective or subjective TOX before PD occurred and 9 pts had to be admitted to the hospital mainly due to diarrhea. CTC ° II/IV TOX by pts: Diarrhea 26/3, Neutropenia 6/1, no case of neutropenic fever and no toxic death occurred. CTC ° II/III TOX by pts: Nausea 19/1, Emesis 15/1, Asthenia 16/3, Alopecia 8/0, Neurotoxic 9/5. In 25/225 and 65/225 cycles of CT scheduled day 8 resp. day 15 was omitted due to persisting diarrhea. IRI was increased to 100 mg/sqm in 5 pts (no TOX cycle 1) and reduced to 60 mg/sqm in 20 pts and to 50 mg/sqm in 5 pts in forthcoming cycles due to diarrhea or neutropenia. EFFICACY: FRP = 49 pts with median TTP 5 months, median survival from start of 2nd-line 16 months. Response was evaluable in 44 FRP cases: Best response: 5 CR, 10 PR, 15 confirmed NC, 5 not confirmed NC, 9 PD: ORR 34%. In 3rd-line and pts pretreated with OX or IRI activity was poor.

Conclusion: Weekly OX-IRI shows a remarkable activity in 5-FU resistant CRC compared to IRI alone or OX combined with 5-FU but despite IDO the objective and subjective TOX of the reported schedule is substantial and a starting dose of 60 mg/sqm of both drugs should be tested to define a safer protocol. Neutropenia, Nausea and alopecia seem to be less pronounced than in other published OX-IRI combinations.

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POSTER

Integrated analysis of overall survival from two multicenter randomized trials of 5-fluorouracil (5-FU) and leucovorin (LV) with or without trimetrexate (TMTX) in patients with advanced colorectal cancer (ACC)

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Purpose: TMTX is a biomodulator of 5-FU cytotoxicity, especially in combination with LV. Favorable results are seen in Phase II studies of TMTX/5-FU/LV in ACC. Two Phase III, multicenter, randomized trials, one in the United States (TMTX-0034) and one in Europe (TMTX-0509), are designed to compare the efficacy and safety of TMTX/5-FU/LV with 5-FU/LV in first-line treatment of ACC. Survival data from these two studies will be integrated to increase statistical power to detect clinically relevant survival differences between the two treatment arms.

Methods: TMTX-0034 is a double-blind, placebo-controlled trial in 384 patients with ACC, and TMTX-0509 is an open-label trial in 385 patients with ACC. Both studies are similar in design, have identical objectives, include patient populations with similar baseline demographics, and are conducted in parallel. In TMTX-0034, patients receive TMTX 110 mg/m² (Arm I) or placebo (Arm II) as 60-minute infusions followed 24 hours later by LV 200 mg/m² as a 60-minute infusion, 5-FU 500 mg/m² as a bolus infusion, and LV 15 mg orally q6 hours for 7 doses starting 6 hours after 5-FU. The same schedule was used in TMTX-0509, but without the placebo control and with 5-FU at 600 mg/m² in the control arm. In both studies, each cycle of treatment consists of 6 weeks chemotherapy followed by 2 weeks