A phase 3 randomized double-blind trial of maintenance with niraparib versus placebo in patients with platinum-sensitive ovarian cancer (ENGOT-OV16/NOVA trial).

Type: Conference Paper
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Conference Name: ASCO

Abstract: Niraparib is a potent, oral poly(ADP-ribose)polymerase (PARP)1/2 inhibitor with efficacy in both germline BRCA mutation (gBRCAmut) ovarian cancer (OvCa) and BRCA negative (nongBRCAmut) high grade serous OvCa (HGSC). Ph I data established a RP2D of 300 mg with anti-OvCa activity and is well-tolerated.

Methods: The ENGOT-OV16/NOVA study is a double-blind, 2:1 randomized, placebo controlled international ph III study of oral niraparib versus placebo in patients (pts) with platinum (plat) sensitive recurrent OvCa. Primary objective is to evaluate efficacy of niraparib as maintenance therapy in pts who have plat sensitive OvCa as assessed by the prolongation of progression free survival (PFS). PFS will be independently evaluated in a cohort of gBRCAmut pts and in pts who have HGSC histology and are nongBRCAmut. Secondary objectives are: (1) bridge the centralized BRCA mutation test method to the candidate companion diagnostic test, if needed; (2) evaluate add'l measures of clinical benefit including pt reported outcomes, PFS2, chemotherapy free interval, overall survival; (3) evaluate the safety/tolerability of niraparib vs placebo; (4) evaluate QTc in a subset of niraparib-treated OvCa pts. A recent food effect sub study in 15 pts demonstrated no effect of a high fat meal on the PK's of a single 300 mg dose of niraparib in OvCa pts. Main study eligibility includes: histologically confirmed
OvCa, fallopian tube or peritoneal cancer, HGSC histology or known gBRCAmut, plat sensitive recurrence, completion of at least 2 previous courses of plat-containing therapy and sensitivity to both via radiographic imaging, normal or CA125 decrease by 90% after last plat, agreement by pt to undergo gBRCA status prior to randomization, availability of FFPE archival tumor, ECOG PS 0-1, normal organ function, and can take PO. The main study is sized to address PFS endpoint w/ an accrual goal of 360 pts. As of 04 February 2014, 37 pts have been enrolled and randomized in the study. The trial will be open at >100 sites in 15 countries in collaboration with ENGOT (NSGO, AGO, NCRI, GEICO, BGOG, GINECO, MaNGO, AGO Austria, MITO). Clinical trial information: NCT01847274.

Proceedings Title Journal of Clinical Oncology
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Tags:
Ovarian Cancer

A randomized, open-label, phase II study assessing the efficacy and the safety of bevacizumab in neoadjuvant therapy in patients with FIGO stage IIIc/IV ovarian, tubal, or peritoneal adenocarcinoma, initially unresectable.

Type Conference Paper
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URL http://meetinglibrary.asco.org/content/130710-144
Volume 32:5s
We hypothesize that improving the response rate of stage IIIC or IV and non-optimally resectable ovarian cancer patients to neoadjuvant chemotherapy would improve the optimal debulking rate at interval debulking surgery (IDS) and ultimately the survival. In the ICON7 and OCEANS trials, addition of bevacizumab to chemotherapy has been shown to improve the response rates. We assume that its administration in the neoadjuvant setting would improve the response rate and consequently will help to achieve optimal debulking rate at IDS.

Methods: This study, named ANTHALYA, is a multicenter, open-label, randomised phase II study, conducted in 15 sites in France. 90 patients with FIGO stage IIIC/IV ovarian, tubal or peritoneal adenocarcinoma, initially unresectable are to be enrolled. At inclusion, patients are randomised (2:1) to receive 4 cycles of neoadjuvant carboplatin and paclitaxel chemotherapy either combined to 3 cycles of bevacizumab in the treatment arm (not given the cycle before surgery) or alone in the control arm. The control arm will be used to assess the complete resection rate in the arm treated without bevacizumab in the neoadjuvant setting.

The primary objective for this study is to evaluate the efficacy of neoadjuvant bevacizumab and chemotherapy measured by the complete resection rate after IDS. Complete resection is defined as the removal of all macroscopic residual tumour at IDS (CC score = 0). The secondary objectives for this study are as follows: (1) to evaluate the safety profile of bevacizumab when added to carboplatin and paclitaxel in the neoadjuvant setting; (2) to assess the efficacy of bevacizumab measured by Objective Response Rate (ORR) for neoadjuvant period and after all courses of treatment, assessed according to RECIST criteria and CA-125 levels; and (3) to evaluate progression-free survival (PFS). Exploratory analysis are conducted to evaluate the biomarkers profile and to explore prognosis and predictive markers. Clinical trial information: NCT01739218.

ANGIOTAX-PLUS trial: A randomized phase II trial assessing the activity of weekly paclitaxel (WP) plus or minus bevacizumab (B) in advanced angiosarcoma (AS).

Type Conference Paper
Author Nicolas Penel
Author Jean-Yves Blay
Author Olivier Mir
Paclitaxel is an active agent in advanced AS. The objective of this study was to explore the activity and safety of adding B to WP in treatment of AS. Methods: We conducted a multicenter randomized (1/1) phase II trial for assessing both regimens. WP: 90 mg/m² d1,8 and 15 in 4-wks cycle for 6 cycles, +/- B 10 mg/kg d1,8 and 15 followed by maintenance therapy 15 mg/kg/3 wks until intolerance/progression. Stratification factors were: superficial vs visceral AS, de novo vs radiation-induced (RI) AS. Primary endpoint was 6-month progression-free rate (RECIST 1.1). Statistical assumptions were: \( P_0=20\%; P_1=40\%, \alpha=10\% \) and \( \beta=20\% \). Results: From 09/2010 to 09/2013, 50 pts (26 in WP and 26 in WP-B arm) have been enrolled in 14 centers. There were 12 men and 38 women (median age 66, 24-82). Most common primaries were: breast (24, 49\%) and skin (6, 12\%). There was 17 (34\%) visceral and 24 (49\%) RI AS. PS was 0 in 24 (50\%) and 1 in 23 (48\%). 16 pts have previously received anthracyclines (32\%); 32 pts (64\%) were chemo-naive. 8/24 (33\%) pts enrolled in WP-B arm have received B as maintenance therapy. Median follow-up was 14.5 months. Both regimens were considered active with a 6-mPFR of 57\% (15/26) in WP arm and 57\% (14/24) in WP+B arm. Median PFS was 6.8 vs 6.9 months. 1-year OS was 55 vs 58\%. 4 pts experienced Gr5-AE: 1 in WP arm (hemorrhage) and 3 in WP-B arm (suicide, intestinal occlusion, general condition deterioration). We had observed arterial hypertension in both arms: WP (1 Gr2) and WP-B (1 Gr2/1 Gr3), hemorrhage in both arms: WP (2 Gr1/1 Gr5) and WP-B (2 Gr1/1 Gr2), thrombosis in both arms: WP (1 Gr1) and WP-B (1 Gr2/1 Gr4) and 1 case of Gr1 proteinuria in WP-B arm. There was no reported wound dehiscence and gastro-intestinal perforation. Hematological toxicity profile was similar in both
arms. Conclusions: WP and WP-B are both active regimens of AS. B did not improve the outcome of AS pts. This study illustrates the importance of randomization in phase II trial. In the present trial, WP provides PFS (6.8 vs 4.0 months) and OS (>12 vs 8 months) significantly higher than previously reported in the AngioTax Study (Penel JCO 2008). Clinical trial information: 2009-017020-59.

Proceedings Title Journal of Clinical Oncology
Short Title ANGIOTAX-PLUS trial
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Tags:
Soft Tissue

Circulating DNA as a strong multimarker prognostic tool in metastatic colorectal cancer patients.

Type Conference Paper
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Author Denis Pezet
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Abstract The aim of our study was to evaluate the prognostic role of various circulating cell-free DNA (cfDNA) parameters in metastatic colorectal cancer (mCRC) patients. Methods: We used a novel method, termed Intplex, which determines simultaneously from plasma, total cfDNA concentration, cfDNA fragmentation level, KRAS/BRAF mutational status, and cfDNA mutation load (% of mutant cfDNA). These parameters were tested in a mCRC patient cohort (n=98), which enabled validation of plasma DNA as a liquid biopsy to detect KRAS/BRAF mutations using the STARD criteria. Results: Median overall survival (OS) of the patients of the full cohort was 22 months (IC 95% [16.9-28.1]). Data confirmed BRAF mutational status as an excellent factor of poor prognosis (median OS, 22.9 vs. 3.4 months; relative risk (RR)=8.9, (IC95% [3.1-25.4], P<0.001) compared to
KRAS mutational status (RR=1.1, IC 95% [0.7-1.9], P=0.66). OS was statistically different in patient groups with lower total cfDNA concentrations (median=28.1 months) compared with those with higher total cfDNA concentrations (median=17.8 months) than the median (RR=1.94, IC 95% [1.2-3.2], P=0.009). By using the multivariate Cox model, total cfDNA conc. proved statistically to be a strong, independent prognostic factor (P=0.035). Median OS was 31.1 and 11.1 months (P=0.121; RR=1.8, IC 95% [0.9-3.8]) in patients with lower and higher mutation loads than the median (10.3%). This difference was confirmed statistically when considering the mutant cfDNA conc. median (i.e. 3.1 ng/ml, RR=2.4, P=0.015). The fragmentation level did not appear to discriminate patients with regards to survival. CEA level at the conventional threshold conc. (5 ng/ml) was as a moderate prognostic factor (OS, 27.1 vs. 21.8 months; RR=1.24, 95% IC [0.7-2.2], P=0.48). Conclusions: Our study demonstrates for the time in a large cohort of mCRC patients that in addition to providing an advantageous alternative to tumor-tissue analysis for point mutation detection, other cfDNA parameters, such as total conc. and mutation load, are strong prognostic factors. Thus, prospective studies are needed to confirm multi-marker cfDNA analysis as a simple tool to help define the best care management options.

Comparison of ColoPrint risk classification with clinical risk in the prospective PARSC trial.

**Type** Conference Paper

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The 18-gene expression profile, ColoPrint, has been developed and validated for identifying risk of recurrence in patients with early stage colon cancer (CC). In a pooled stage 2 validation study ColoPrint identified 63% of patients as Low Risk with a 3-yr recurrence free survival (RFS) of 93% while High Risk patients had a 3-yr RFS of 82% with a HR of 2.7 (p=0.001). PARSC is a prospective study for the assessment of recurrence risk in stage II CC patients using ColoPrint. ColoPrint classification is compared to NCCN risk classification. Methods: The study enrolled 501 patients with histologically proven stage 2 CC from 31 institutes in Europe, USA, and Asia between October 2008 and September 2013. Synchronous tumors were excluded. ColoPrint results were not disclosed to the physician and patient. Treatment was at the discretion of the physician, adhering to NCCN approved regimens or a recognized alternative. A McNemars test is performed to compare ColoPrint with NCCN risk classification. A p-value ≤ 0.05 indicates the two tests differ significantly. Results: ColoPrint classified 352 (70%) patients as Low Risk and 149 (30%) as High Risk. 97 patients (19%) received adjuvant chemotherapy. In the ColoPrint Low Risk group, 66 (19%) patients received adjuvant chemotherapy and 31 (21%) of ColoPrint High Risk patients received chemotherapy. According to NCCN high risk factors (T4, high grade (exclusive of MSI-H), lymphovascular/perineural invasion, perforation/obstruction, <12 nodes examined, positive margins) 274 (55%) patients were NCCN Low Risk and 227 were NCCN High Risk. 82 (30%) of the NCCN Low Risk patients are ColoPrint High Risk. 160 (70%) of the NCCN High Risk patients are ColoPrint Low Risk. MSI-status was assessed in 96 (18%) patients of which 33 were MSI high and 63 were MSS. All MSI high were classified as ColoPrint Low Risk. Conclusions: The PARSC study is the first prospective study to compare genomic and clinical risk assessment and we observed marked differences between NCCN risk classification and ColoPrint. The clinical validity of these methods will be based on the outcomes at 3 and 5 years. Clinical trial information: NCT00903565.

Tags:
Colorectal Cancer

Comparison of prostate health index and PCA3 values in patients with clinical or biologic suspicion of prostate cancer.
The Prostate Health Index (PHI) and the Prostate CAncer gene 3 (PCA3) have shown to have predictive values for early detection of PCa. The aim of this prospective observational study was to compare the values of the both markers in patients consulting for a suspicion of PCa.

Methods:

Samples of 573 consecutive patients presenting a suspicion of PCa were included in a biobank between 2010 and 2012. Total PSA (tPSA), Free PSA (fPSA) and -2proPSA (Beckman Coulter) were performed on serum to calculate the PHI ([-2proPSA/fPSA] X [tPSA]^1/2). Urine samples were collected after digital rectal examination (DRE) by an urologist in order to calculate the PCA3 score ([PCA3 mRNA]/[PSA mRNA] X 1,000). Prostate biopsies were performed for 235 men according usual clinical practice. Correlation between PSA, PHI, PCA3 score and clinico-pathological factors were studied with the Kruskall–Wallis tests. ROC–derived area under the curve (AUC) was used to quantify the predictive accuracy of the tests predicting pathologic findings in biopsies specimens. Results: PCA3 score was only correlated with age (Spearman’s rho = 0.21; p=0.001) and PHI was only correlated with tPSA (Spearman’s rho = 0.35; p<0.0001). PHI and PCA3 were slightly correlated (Spearman’s rho = 0.16; p=0.01). Comparing biomarkers values in patients with positive (P+; n=60, 25.5%) and negative biopsy (P-; n=175, 74.5%), PHI and PCA 3 were statistically different according to patients status. Conclusions: In this large series of patients consulting for a suspicion of PCa, tPSA is hardly more effective than a coin toss to predict PCa. PHI, an independent biological marker, presented a higher predictive value for positive biopsy prediction than PCA3, a marker slightly correlated with age.
Comparison of three longitudinal analysis models for the health-related quality of life in oncology: A simulation study.

Type: Conference Paper
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URL: http://meetinglibrary.asco.org/content/131501-144
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Conference Name: ASCO
Abstract: Most clinical trials now integrate Health-related Quality of Life (HRQoL) as one of the major endpoints to investigate the clinical benefit of new therapeutic strategies for the patient and the health system. However, longitudinal analysis of HRQoL remains complex and unstandardized. Moreover, it is necessary to propose accessible statistical methods and meaningful results for the clinician. The objective was to compare three strategies of longitudinal analyses for HRQoL data in oncology clinical trials through a simulation study. Methods: The methods proposed were the score and mixed model (SM), the longitudinal partial credit model (LPCM) and survival analysis approach based on the time to HRQoL score deterioration (TTD). Simulations compared the methods regarding the type I error and statistical power of the test of an interaction effect between treatment arm and time. Longitudinal HRQoL data were performed using a LPCM considering that the latent trait (HRQoL) follows a multivariate normal distribution with a first-order autoregressive covariance matrix. Several scenarios of simulations were explored based on the EORTC HRQoL questionnaires and varying the number of patients (100, 200 or 300), items (1, 2 or 4) and response category per item (4 or 7). Five or 10 measurement times were considered with a low to high correlation between each measure. The impact of informative missing data on these methods was also studied to reflect most of clinical trials. Results: With complete data, type I error rate were closed to the expected value (5%) for all methods and SM method was the most powerful method. The power of the TTD is low for uni-item dimension because only four possible values exist for the score. When the number of items increases, the power of TTD method increases while the power of LPCM and SM remains stable. For 10 measurement times, the LPCM is less efficient. With informative missing data, the results for SM and LPCM are similar whereas the power of TTD method increases. Conclusions: To conclude, SM method is as efficient as LPCM. Moreover, the TTD approach, which began to be used...
Conditional probability of survival (CPS) in ovarian cancer (OC) long-term survivors: Prognostic factors.

**Type** Conference Paper  
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**URL** http://meetinglibrary.asco.org/content/127424-144  
**Volume** 32  
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**Date** May 2014  
**Accessed** 28/5/2014 16:55:50  
**Library Catalog** ASCO Meeting Library  
**Conference Name** ASCO  
**Abstract** In high grade OC, most deaths occur in the first 36-50 months after diagnosis. Beyond the median survival time, mortality decreases down to a plateau observed from 5-6 years. This long-term survivor population represents around 20% of the patients initially treated. Methods: This retrospective study aimed to estimate the CPS and to identify prognostic factors among long-term survivors. From patients (pts) with advanced OC treated at the ICM from 1995 to 2012, we collected the cancer histology, surgical staging (FIGO), BRCA status, delivered chemotherapy and outcome. Overall survival (OS), progression-free survival (PFS), and CPS were calculated. To estimate 95% confidence intervals (CIs) we used a variation of the "Greenwood’s formula," usual for unconditional survival. Prognostic factors were evaluated using the Cox proportional hazards model. Results: Among the 359 pts identified (med age 59 years [17-89]), 80% and 20% were stage III and IV, respectively. Histology was of serous type in 71% of pts, not specified in 17% and of other subtypes in 12%. Surgery was performed first in 91% of pts including 67% of debulking, and 33% of exploratory surgery. Out of the 208 pts operated at diagnosis, 39% had no macroscopic residual disease left, and 32% and 29% had 0-1-cm and >1-cm lesions left, respectively. The pts received a median of 7 cycles (1-10) of first-line chemotherapy. Median OS was 44 mths (95% CI [39.6-51.6]), and median PFS was 18 mths (95% CI [16.8-20.4]). Survivors at 1 y post-diagnosis had a CPS of 26% at 8 y (95% CI [18.8%-32.5%]). The CPS extensively in HRQoL data analysis, could be optimal for phase III clinical trials with a multi-item scale.
increased up to 49% (95% CI [37.0%-61.0%]) and 61% (95% CI [47.6%-75.2%]) when assessed at 4 and 5 y, respectively. The usual prognostic factors at diagnosis (PS, serous histology, no residual disease, sensitivity to chemotherapy, progression free interval) were not found as well when assessed at 4 y survival; PFI > 18 m was the only prognostic factor (RR 0.29 (IC95% [0.16-0.54]). BRCA status was available for 24 pts; among the 12 mutated pts, 9 were long-term survivor pts. Conclusions: These results showed that intrinsic biological factors, related to sensitivity to chemotherapy, significantly influence the prognostic of OC, and shall be a challenge for the next years.

**Expression of angiopoietin (Ang) pathway markers and their relationship to progression-free survival (PFS) in TRINOV A-1.**

**Type** Conference Paper  
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**URL** [http://meetinglibrary.asco.org/content/128113-144](http://meetinglibrary.asco.org/content/128113-144)  
**Volume** 32:5s  
**Pages** abstract #5542  
**Date** May 2014  
**Accessed** 28/5/2014 18:03:45
Trebananib, an investigational recombinant peptide Fc-fusion protein, targets Ang1 and 2. In TRINOV A-1, a randomized phase 3 study, trebananib plus paclitaxel (P) compared with placebo plus P significantly improved PFS (primary endpoint) in recurrent ovarian cancer. Biomarker evaluation was an exploratory endpoint. Methods: Women (≥ 18 years, GOG ≤ 1) with recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer received trebananib 15 mg/kg IV QW or placebo IV QW plus P 80 mg/m² IV QW (3 wks on/1 wk off). Serum samples were collected pre-infusion at wk 1 to evaluate baseline levels of Ang1, Ang2, and soluble Tie2 (sTie2). Analytes were quantified using enzyme-linked immunosorbent assays (ELISA; R&D Systems). Analyses of PFS as a function of biomarker expression addressing prognostic and predictive testing included: 1) subpopulation treatment effect pattern plots (STEPP) for Ang1, Ang2, sTie2, Ang1/Ang2, and Ang2/Ang1 (prognostic test); 2) evaluation of Ang1, Ang2, sTie2, Ang1/Ang2, and Ang2/Ang1 as continuous variables (prognostic test); and 3) median thresholds to dichotomize Ang1, Ang2, and sTie2 levels (prognostic and predictive tests). Results: Serum samples were available for 834 of 919 enrolled women. Per STEPP, no threshold in biomarker expression was associated with PFS. Using continuous models, there was no linear association with PFS (Ang1, p = 0.55; Ang2, p = 0.47; sTie2, p = 0.63; Ang1/Ang2, p = 0.17; Ang2/Ang1, p = 0.66). Using median thresholds, low Ang1 (median, 23.30 ng/mL) or Ang2 (median, 2.86 ng/mL) levels were associated with improved PFS (p = 0.044 and 0.009, respectively) when not corrected for multiple testing. Those relationships were not consistent at the extreme Ang1 or Ang2 values. There was no evidence of an interaction of either Ang1 or Ang2 by treatment arm (p = 0.10 and 0.68, respectively). sTie2 (median, 27.8 ng/mL) was not predictive or prognostic of PFS. Conclusions: In TRINOV A-1, no consistent predictive or prognostic relationships between baseline levels of Ang1, Ang2, or sTie2 were observed. Clinical trial information: NCT01204749.
Thirteen hundred prostate cancer patients have been treated with Intensity modulated radiotherapy (IMRT) since 2001. We present the final results of the pilot study concerning the first 373 patients with a median follow-up of 72.7 months (range 0 to 130). Methods: All patients received the entire treatment course to a prescribed total dose of 80 Gy. No pelvic irradiation was applied. Androgen ablation therapy was delivered for 6 months and 2 to 3 years in intermediate and high-risk patients, respectively (n=142, 38%). Prostate-specific antigen (PSA) failure was defined as nadir + 2. Toxicity was assessed according to the National Cancer Institute (NCI)/Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Multivariate analysis using the Cox model was performed to assess factors that may impact on PSA relapse. Logistic regression was used to correlate clinical and physical parameters with grade 2 or higher gastro-intestinal and genitourinary toxicities. Results: Median age was 69 (range 40 to 81). One hundred thirty nine (37.3%), 167 (44.8%), and 67 (18%) patients were classified as low (group 1), intermediate (group 2), and high-risk (group 3) patients, respectively. The 5 year biochemical relapse-free survival (5y-biochemical recurrence-free survival [bRFS]) was 85.7% (95% CI, 0.81-0.89). For the three prognostic groups, 5y-bRFS was 91% (95% CI, 0.85-0.95), 82% (95% CI, 0.75-0.87), and 80% (95% CI, 0.67-0.88) for groups 1, 2, and 3, respectively. Multivariate analysis showed that the absence of hormonotherapy in the group 2 and the number of positive biopsies impact on PSA relapse (p=0.04, HR 1.8 and p=0.01, HR 2.13, respectively). The incidence of late grade 2 or higher rectal and urinary toxicities were 10.5% and 12.7%, respectively. The dose received by 50% (D50) of the rectum was the only factor significantly correlated with late grade 2 or higher rectal toxicities (p = 0.04). Similarly, the dose received by 50% (D50) of the bladder was the only factor significantly correlated with late grade 2 or higher bladder side-effects (p = 0.02). Conclusions: IMRT to 80 Gy can provide good to excellent carcinologic results and low late toxicity rates in all prostate cancer subgroups. Hormonotherapy combined to high dose IMRT seems to be a serious option to consider in intermediate-risk patients. Clinical trial information: ICM 2001-13.
Impact of neoadjuvant chemotherapy cycles prior to interval surgery in patients with advanced epithelial ovarian cancer.

Type  Conference Paper
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Author  Michel Fabbro
Author  Philippe Rouanet
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Date  May 2014
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Library Catalog  ASCO Meeting Library
Conference Name  ASCO
Abstract  Complete surgery with no macroscopic residual disease at primary or interval debulking surgery (IDS) is the principal goal of the surgical management of advanced epithelial ovarian cancer (EOC). In the case of neoadjuvant chemotherapy (NAC), IDS is generally recommended after 3 to 4 cycles, but few studies have specifically analyzed this point. The aim of this work was to evaluate the impact on survival of the number of NAC cycles before IDS in a large cohort of EOC patients. Methods: Data from patients with advanced EOC (stages IIIC-IV), operated between 1995 and 2010 were consecutively recorded in a prospective database and evaluated retrospectively. Patients treated with NAC/IDS (group B) were analyzed according to the number of NAC cycles (≤ 4 = group B1; > 4 = group B2) and compared with patients receiving primary surgery (group A). Patients with complete resection were specifically analyzed in both groups. Results: Clinical data of 367 patients with advanced EOC were analyzed. 219 received upfront surgery (group A) and 148 had IDS after NAC (group B). The average follow-up was 82 months. In group B, 38 patients (26%) received more than 4 NAC cycles before IDS (group B2). Patients in group B2 presented more frequently stage IV disease (p=0.015). The rate of complete cytoreduction was higher in group B2 (67%) compared to groups B1 (62%) and A (44%) (p=0.002). Patients in group B2 had worse survival compared to patients in group B1 (p=0.04). Patients with complete surgery at the end of IDS and who had received more than 4 cycles of NAC had poor survival (p<0.001) with a relative risk of death after multivariate analysis of 3 (95% CI : 1.7-5.5) with an independent impact from stage and performance status. Conclusions: Patients with advanced EOC receiving complete IDS after more than 4 cycles of NAC have poor prognosis. Despite worse prognostic factors observed in this group of patients, our study reinforces the concept of early and complete removal of all macroscopic tumors in the therapeutic sequence of EOC. These results call into question the interest of a delayed debulking in advanced cases thought to be unresectable after 3 to 4 cycles of NAC.

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Date Added  28/5/2014 17:34:29
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Impact of preoperative treatments on the immune microenvironment of colorectal liver metastases.

An adaptive CD8+/CD45+ immune response is considered as a favorable prognostic factor in primary colorectal cancer (CRC). FoxP3+ regulatory T lymphocytes (Ly) inhibit this response. Such data are lacking in CRC liver metastases (LM), notably after preoperative treatments. We aim to analyze this subject.

Methods: 105 CRC LM were selected as follows: chemotherapy alone (CT, n=29), CT + anti-VEGF (bevacizumab) (n=27), CT + anti-EGFR (cetuximab) (n=20), surgery alone (control group, n=29). LM were treated in first-line. Histologic response was assessed according to the Tumor Regression Grade (major response: MR, partial response: PR, no response: NR). Immune microenvironment was evaluated as follows: intratumoral (IT), peritumoral (PT), classified as minor or major and assessed by immunohistochemistry to characterize: i) T Ly: CD8+ (cytotoxic), CD45+ (memory), Tbet+ (T helper 1), FoxP3+ (regulators) ii) macrophages: CD68+, CD163+. Results: A major immune infiltrate was more frequently associated with LM showing MR vs PR vs NR, with the following markers and locations: CD8+ (IT; p = 0.003), CD45+ (IT; p = 0.011), Tbet+ (PT; p = 0.015), CD68 (IT; p = 0.050), CD163 (PT, IT; p = 0.002, p = 0.023). Conversely, a major FoxP3+ IT infiltrate was more frequently associated with LM displaying NR vs PR vs MR (p = 0.033). Moreover, a major immune infiltrate was more frequently associated with treated LM than with untreated LM as follows: CD8+ (IT; p = 0.012), Tbet+ (PT, IT; p = 0.015 p=...
Low skeletal muscle density as predictive for febrile neutropenia in patients treated by doxorubicin/trabectedin/pegfilgrastim combination as a first-line treatment of advanced or metastatic leiomyosarcoma (LMS) (LMS02 study).

Proceedings Title  Journal of Clinical Oncology
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Tags:
Colorectal Cancer

Type  Conference Paper
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Abstract  Studies have shown that skeletal muscle mass (SMM) and skeletal muscle densities (SMD) are associated to chemotherapy toxicity. In 110 patients treated with a combination of doxorubicine (doxo) and trabectedin (trab), neutropenia and febrile neutropenia are still observed despite the use of granulocyte colony stimulating factor (G-CSF) (ASCO 2013; abstract 10505). Our aim was to analyze whether SMM or SMD are predictive of febrile neutropenia. Methods: SMM and
SMD were assessed with computed tomography (CT) imaging before treatment by measuring cross-sectional areas of the tissues for SMM and the mean muscle Hounsfield Units (HU) for SMD. SMD assessed by this method reflects fatty muscle infiltration with lower mean HU reflecting lower density, and more fatty infiltration. Toxicity profile was collected for all cycles. Therefore severe toxicity is defined as any grade 3 or 4 toxicity. The cut-off level which predicts the occurrence of toxicity most accurately was deduced from the receiver operating characteristic curve (for SMD the value is: 37.1 HU). Pts received doxo 60 mg/m2 followed by trab 1.1 mg/m2 IV in 3-h at day 1, and pegfilgrastim 6 mg on day 2 every 21 days for a maximum of 6 cycles. Results: 55 pts were included (46 females and 9 males), with median age of 58 years, 27 pts with uterine LMS and 28 with soft tissue LMS were analyzed. Only 2 pts had an ECOG PS score >1. Pts received a total of 285 cycles with a median of 6 cycles per pt. Pts with a low density (SMD <37.1) had a higher probability of febrile neutropenia (8/19; 42%) than pts with a SMD > 37.1 (6/36; 17%) (p=0.05). No association between toxicity and SMM was found. Conclusions: Despite the use of GCSF, febrile neutropenia is observed in pts treated with doxo + trab. In this pilot study including a few pts, muscle density has been found to be associated with a high probability of febrile neutropenia. These interesting results need to be confirmed. They might highlight the concept of “frailty” i.e. a group of non-oncologic parameters associated with a higher susceptibility to events.

Multivariate prospective pharmacogenetic analysis in patients with resectable metastatic colorectal cancer (mCRC) receiving FOLFOX chemotherapy.

**Proceedings Title**  
Journal of Clinical Oncology

**Date Added** 28/5/2014 18:09:27

**Modified** 28/5/2014 18:18:43

**Tags:** Palliative Care, Supportive Care, Symptom Management
To prospectively test the predictive value of gene polymorphisms related to fluorouracil (FU) and oxaliplatin (Oxa) pharmacodynamics in mCRC patients receiving FOLFOX regimens. Methods: 205 mCRC patients out of 284 included in the MIROX trial (GERCOR group) were enrolled (67 women, 138 men; mean age 60). All received a FOLFOX regimen (FOLFOX4 for 104 patients, FOLFOX7 for 101 patients). Maximum toxicity (NCI-CTCAE) for each toxic pattern along with best response (RECIST criteria) were recorded. Polymorphisms of genes relevant for FU, thymidylate synthase (TYMS, 5’UTR repeats and 3’UTR deletion), dihydropyrimidine dehydrogenase (DPYD, IVS14+1 G>A), 5-10methylenetetrahydrofolate reductase (MTHFR, 677C>T and 1298A>C), and for Oxa, glutathione S-transferase pi (GSTP1, 105Ile>Val), xeroderma pigmentosum (ERCC2, 751Lys>Gln), were determined (blood). Results: 62% of patients presented at least a grade 3-4 (G3-4) toxicity (29.8% neutropenia, 22% digestive toxicity (nausea/vomiting/diarrhea/mucositis)). Global toxicity, hematotoxicity and vomiting were significantly more frequent in women. Patients homozygous for the deficient MTHFR 1298C allele (favouring elevated methylenetetrahydrofolate concentrations) had a significantly higher risk of developing G3-4 neutropenia as compared to others (OR 3.1, 95%CI 1.1-8.6, adjusted on gender), and tended to present a greater risk of digestive toxicity (OR 2.4, 95%CI 0.9-7.0). Patients with ERCC2 751Lys/Gln or Gln/Gln genotype had a greater global toxicity as compared to others (OR 2.30, 95%CI 1.25-4.24, adjusted on gender), and a greater digestive toxicity (OR 2.35, 95%CI 1.1-5.1, adjusted on gender). Among the 3 patients with DPYD mutation (heterozygous) only 2 developed G3-4 toxicity. Response (51.8% CR+PR) was significantly lower in MTHFR 677TT patients relative to others (OR 0.16, 95%CI 0.05-0.52). ERCC2 751Lys/Gln+Gln/Gln genotype tended to be associated with longer DFS relative to Lys/Lys (RR 0.74, 95%CI 0.51-1.07). Conclusions: Present data confirm previous findings showing that toxicity and response to FOLFOX therapy may be driven by MTHFR germinal polymorphisms. Clinical trial information: NCT00268398.
Nomograms to predict prognosis in pseudomyxoma peritonei: A Peritoneal Surface Oncology Group International (PSOGI) multicenter study.

Type Conference Paper
Author Shigeki Kusamura
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Author Marcello Deraco
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Abstract We built nomograms for predicting overall (OS) and progression-free survivals (PFS) in patients with pseudomyxoma peritonei (PMP) treated with cytoreductive surgery (CRS)+/-intraperitoneal chemotherapy (IPCT). Methods: Data from 1,715 PMP patients in 31 centers from 1993 to 2012 constituted the developing set. The covariates were previous systemic chemotherapy (sCT), histologic subtype (Ronnett’s criteria), peritoneal cancer index (PCI), completeness of cytoreduction (CC), IPCT (Hyperthermic intraperitoneal chemotherapy [HIPEC], early postoperative chemotherapy [EPIC], or both), lymph node status (LN), G3-5 morbidity (NCI CTCAE v3), and surgical proficiency. Centers with >100 procedures for PMP were considered proficient. Continuous variables were transformed using restricted cubic splines. We handled missing data using multiple imputation with chained equations (MICE) approach. We fitted a Cox model in each of the different completed developing datasets generated by MICE. Pooled estimates of regression coefficients, variances, and models’ discriminations
(bootstrap corrected Harrell C indexes) were obtained using Rubin’s rule. The nomograms were externally validated on 733 PMP patients from two high-volume referral centers in USA (validating set). Results: In the developing set the median follow-up was 39 months. Five-year OS and PFS rates were 74.1% (95%CI: 71.3-76.8) and 52.3% (95%CI: 49.4-55.2), respectively. The means of adjusted Harrell C indexes for OS and PFS were 0.80 and 0.74 in the developing set and 0.74 and 0.72 in the validating set. In the developing set significant predictors of OS were sCT, PCI, CC, IPCT, histological subtype, LN, and G3-5 morbidity while those of PFS were surgical proficiency, sCT, histological subtype, PCI, CC, and IPCT. Conclusions: These nomograms may allow predicting OS and PFS providing individualized outcome prognostication. They would support therapeutic decision-making and stratification of future clinical trials.

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**Short Title** Nomograms to predict prognosis in pseudomyxoma peritonei  
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**Tags:**  
Other GI Cancer

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**PENELOPE/AGO-OVAR 2.20: A double-blind placebo (PLA)-controlled randomized phase III ENGOT trial evaluating chemotherapy (CT) with or without pertuzumab (P) for platinum-resistant ovarian cancer.**

**Type**  Conference Paper  
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**Author**  Jose Maria Del Campo  
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**Author**  Felix Hilpert  
**Author**  Angiolo Gadducci  
**Author**  Petronella Ottevanger  
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**Author**  Ignace Vergote  
**Author**  Isabel Bover  
**Author**  Michel Fabbro  
**Author**  Frederik Marmé  
**Author**  Yolanda Garcia  
**Author**  Frédéric Selle  
**Author**  Martina Gropp-Meier  
**Author**  Beatriz Pardo  
**Author**  Ulrich Freudensprung  
**Author**  Ru-Amir Walker  
**Author**  Antonio Gonzalez-Martin  
**URL**  http://meetinglibrary.asco.org/content/130339-144  
**Volume** 32:5s
Adding P to gemcitabine (GEM) for platinum-resistant ovarian cancer improved progression-free survival (PFS) in a subset of patients (pts) with low tumor HER3 mRNA expression [Makhija 2010]. PENELOPE (NCT01684878) comprises a safety run-in (Part 1, complete) and PLA-controlled randomized assessment of CT ± P (Part 2, below). Methods: Eligible pts have: measurable/non-measurable recurrent platinum-resistant epithelial ovarian, primary peritoneal or fallopian tube cancer (progression during or within 6 mo of completing ≥4 platinum cycles); centrally tested low HER3 mRNA expression (concentration ratio ≤2.81 by qRT-PCR on cobas z480); and have received ≤2 prior lines of CT. The primary Part 2 objective is to determine if PFS (assessed by independent review committee; IRC) is superior with P + CT vs PLA + CT. The key secondary endpoint is overall survival (OS). Both endpoints are part of a closed testing procedure. Additional endpoints include investigator-assessed PFS, objective response rate (RECIST v1.1), safety (NCI CTCAE v4.0), quality of life (including EORTC QLQ-C30 and QLQ-OV28) and pharmacokinetic parameters. Translational studies aiming to scrutinize and validate the preselection concept by correlating markers of signal pathway activation with efficacy have been implemented. Additional exploratory analyses will include gene expression profiling. Investigators select CT (topotecan, paclitaxel or GEM) before 1:1 randomization to P or PLA. Treatment is continued until progression or unacceptable toxicity. Stratification factors are: selected CT; prior anti-angiogenic therapy; and platinum-free interval (<3 vs 3–6 mo). The planned Part 2 enrollment is 154 pts. Recruitment to each CT cohort is capped at 1/3 of the total sample size. Primary PFS analysis will be done after 109 IRC-assessed PFS events, providing 95% power to detect a PFS hazard ratio (HR) of 0.50 (median PFS 1.4→2.8 mo) with 2-sided log-rank at α=0.05. Final OS analysis is planned after 129 deaths in Part 2, providing 80% power to detect an OS HR of 0.61 (median OS 8.4→13.8 mo); 2-sided log-rank at α=0.05. By 27 Jan 2014, 62 pts were randomized. Clinical trial information: NCT01684878.

Perioperative chemotherapy with FOLFOX in resectable gastroesophageal adenocarcinoma: Preliminary results of an AGEO multicentric retrospective study.

Type  Conference Paper
Author  Florence Mary
Perioperative 5-fluorouracile (5-FU) associated with cisplatin chemotherapy improved overall and recurrence free survival, the R0 resection rate, in resectable gastro-oesophageal junction and gastric adenocarcinoma. The aim of this study is to evaluate the feasibility, R0 resection rate, survival and tolerance of the 5-FU with oxaliplatin perioperative chemotherapy. Methods: We enrolled all the resectable gastric or gastro-oesophageal adenocarcinoma who had at least 3 cycles of pre-operative folfox based regimen (simplified folfox 6; or folfox 6: oxaliplatin 100 mg/m2, 400 mg/m2, 5-fluorouracile bolus, and 2400 mg/ m2, 5-fluorouracile during 2 days). The following data were collected: age, weight, height, karnofsky index, toxicity, dose, surgery R0, histology, post-operative radiotherapy, recurrence and death. Overall and disease free survival was calculated with the Kaplan-Meyer method. Results: We enrolled 106 patients in 11 centers. There were 72 men, the median age was 66 years. Gastro-oesophageal junction represented 28.3%. The median number of chemotherapy cycle was 4 before surgery and 2.5 after. In univariate analysis the karnofsky index at inclusion was the only factor associated with the realization of 8 cycles chemotherapy. A grade 3-4 toxicity occurred in 13.8%. The R0 rate was achieved in 98 patients. The median overall and disease free survival was 41 and 28 month. The ACE rate was in univariate analysis a predictive factor for overall and disease free survival. The other predictive factor for overall survival was: Karnofsky index and the number of post surgery chemotherapy cycle. Conclusions: The oxaliplatine perioperative regimen is an alternative instead of cisplatin based regimen for the gastric and gastro-oesophageal junction resectable adenocarcinoma with a good tolerance and efficacy. A 12 cycle treatment is rarely achievable, 8 cycles seems to be more feasible.
Phase II trial of oxaliplatin and 5-FU in patients (pts) with platinum-resistant recurrent (PRR) ovarian carcinoma (OVCA)

**Abstract**

Background: Based on clinical data and the partially non-cross-resistance of oxaliplatin with other platinum compounds, this phase II trial evaluated the safety and efficacy of a modified FOLFOX6 regimen in pts with PRR OVCA with a platinum-free interval of less than 6 months after any previous platinum-containing line of therapy. Methods: From 10/2008 till 08/2013, a total of 43 eligible pts with measurable (RECIST) and/or evaluable (CA125) disease were included in this study and received a median number of 8 courses (range: 1-14) of a modified FOLFOX6 regimen consisting in oxaliplatin 85 mg/m² d1, L-leucovorin 200 mg/m² d1 followed by a continuous iv infusion of 5-FU 2600 mg/m²/48hrs every 2 weeks until disease progression or unacceptable toxicity. Pt characteristics: median age 57 years (range: 37-81), median PS 1 (0-2), serous histological subtype 60%, median number of previous lines 3 (1-12), prior exposure to carboplatin 100%, paclitaxel 98%, pegylated liposomal doxorubicin 63%, gemcitabine 23%, topotecan 23%, cyclophosphamide 14%, bevacizumab 9%. Results: Antitumor activity was seen in 35 cases with measurable disease: 1 CR + 15 PR, for an objective response rate of 46% (95%CI: 29-63%) and a median duration of response of 7.0 months (95%CI: 5.5-8.4 months); 13 SD (37%); 6 PD (17%). A clinical benefit rate (CR + PR + SD > 6 months) was observed in 21/43 (49%) pts (95% CI: 34-64%). Overall, the median time to progression was 5.8 months (95%CI: 4.9-6.5). Most side effects were moderate (G1&2): anemia in 88%, thrombocytopenia 67%, leucopenia 56%, neurological 81%, fatigue 72%, liver 51%, mucositis 41%, diarrhea 30%, renal 18%, hand-foot syndrome 9% of the pts. G3 toxicities included febrile neutropenia in 9%, neurological 9%, diarrhea 7%, mucosal 2% and liver toxicity 2% of the pts, leading to dose reductions in 13 pts (30%). Two hypersensitivity reactions to
oxaliplatin also occurred. Conclusions: In this heavily pretreated patient population with PRR OVCA, this modified FOLFOX6 regimen exhibited a promising activity with an expected, but acceptable safety profile and might deserve further exploration, maybe in combination with biological or targeted agents.

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Attachments

- Kerger et al. - 2014 - Phase II trial of oxaliplatin and 5-FU in patients.pdf

Prediction of recurrence with the Oncotype DX recurrence score in node-positive, HR-positive, breast cancer patients treated with adjuvant chemotherapy: Results from PACS01 trial.

Type  Conference Paper
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Author  Thomas Filleron
Author  Bernard Asselain
Author  Frederick L. Baehner
Author  Pierre Fumoleau
Author  Magali Lacroix-Triki
Author  Steven M. Butler
Author  Farid Jamshidian
Author  Diana B. Cherbavaz
Author  Steven Shak
Author  Lise Roca
Author  Christine Sagan
Author  J. Lemonnier
Author  Anne-Laure Martin
Author  Henri Hubert Roche
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Pages  abstract #11052
Date  May 2014
Library Catalog  ASCO Meeting Library
Conference Name  ASCO
Abstract  The Recurrence Score (RS) predicts outcome in node- and node+, ER+ pts treated with endocrine therapy and predicts chemotherapy benefit. We studied the prognostic impact of RS in node+, HR+ pts treated with adjuvant chemotherapy plus endocrine therapy in PACS01 Methods: PACS01 compared FECX6 with FECX3+ docetaxel X3(FEC-D) in 1999 pts. After a protocol amendment, HR-positive pts received 5 yrs of tam after chemo. The current study includes 530
pts from the PACS01 parent trial who were central IHC HR+ with sufficient tissue for OncotypeDX. The primary objective was to estimate the association between RS and distant recurrence free interval (DRFI). Secondary endpoints included disease free survival (DFS) and overall survival (OS). Median follow-up time was 7.7 yrs Results: Of the 530 pts, 209 (39.4%) had low RS; 159 (30.0%) intermediate RS; and 162 (30.6%) high RS. 74.2% were treated with tam. In the primary analysis, RS was a significant predictor of DRFI (HR= 4.1 for a 50 point difference, P<0.001), DFS (HR=3.3, P<0.001) and OS (HR=5.0, P<0.001). In multivariate analyses, RS provided independent prognostic information beyond clinicopathologic factors including treatment, age, tumor size & grade, number of + nodes, surgery type and Ki-67 status (P<0.001). RS was a significant predictor of DRFI, DFS, and OS in both treatment arms (P<0.001). There was no statistically significant interaction between RS and treatment arm in predicting distant recurrence (P=0.79). Conclusions: The 21-gene RS maintains significant prognostic impact in HR+, node+ pts who have received FEC or FEC-D adjuvant chemotherapy. These findings emphasize the need to target pts with high residual risk for recurrence with additional therapies to overcome unfavorable biology, potential endocrine and/or chemotherapy resistance.

**Proceedings Title** Journal of Clinical Oncology  
**Short Title** Prediction of recurrence with the Oncotype DX recurrence score in node-positive, HR-positive, breast cancer patients treated with adjuvant chemotherapy  
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Retrospective analysis of CA19-9 decrease in patients with metastatic pancreatic carcinoma (MPC) treated with FOLFIRINOX or gemcitabine (gem) in a randomized phase III study (ACCORD11/PRODIGE4).

**Type** Conference Paper  
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**Author** Sophie Gourgou  
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**Author** Unicancer GI  
**URL** http://meetinglibrary.asco.org/content/125568-144  
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**Date** May 2014
RECIST criteria remain the reference for tumor response evaluation. Carbohydrate antigen 19-9 (CA19-9) is known to be a sensitive and specific serum marker in pancreatic cancer. Its determination could be helpful to assess early therapeutic efficacy (MPACT trial, ASCO 2013, abstract 4058). Our retrospective analysis aims to evaluate CA19-9 decrease in patients included in the randomized phase III study ACCORD11/PRODIGE4 comparing FOLFIRINOX and gem in MPC. Methods: 342 patients were treated in the ACCORD11/PRODIGE4 study. CA19-9 levels were available at inclusion for all patients and 283 had abnormal values. CA19-9 measures were performed at 8 weeks ± 2 for 160 patients (gem arm, 75 patients and FOLFIRINOX arm, 85 patients). In this retrospective study, best CA19-9 decrease, or 8-week CA19-9 decrease ≥ 20% were analysed. According to these CA19-9 rates, efficacy parameters, progression free survival (PFS) and overall survival (OS) were estimated. Results: FOLFIRINOX superiority compared with gem is confirmed in this population subgroup with a better PFS (6.7 vs 3.9 months; HR 0.52, IC95%: 0.36-0.73, p<0.001) and OS (12.0 vs 7.6 months; HR 0.55; IC95%; 0.38-0.79, p=0.001). 8-week CA19.9 decrease ≥20% was correlated with a better OS [10.3 vs 7.8 months; HR 0.57, (IC95%; 0.40-0.81); p=0.002] and PFS [6.1 vs 3.0 months, HR=0.58 (IC95%; 0.42-0.81), p=0.001]. A higher proportion of patients in the FOLFIRINOX arm had an 8-week CA19-9 and a best CA 19-9 decreases ≥20%. Median OS, PFS and ORR for those patients were improved (Table). Conclusions: CA19-9 response was increased in patients treated with FOLFIRINOX regimen and correlated with OS, PFS and ORR. CA19-9 could be considered as a potential early surrogate marker and therefore help to evaluate the efficacy of FOLFIRINOX and gem regimen.

Trastuzumab duration effects within patient prognostic subgroups in the PHARE trial.

Type Conference Paper
Author Xavier B. Pivot
Author Thomas Denis Bachelot
Author Marc Debled
Author Jean-Yves Pierga
Author Pierre Kerbrat
Author Marc Espie
Author Pierre Fumoleau
Author David Khayat
Abstract

At 42.5 months of median follow-up, PHARE failed to show that 6 was non-inferior to 12 month of adjuvant trastuzumab. From the results of PHARE questions remain regarding whether the magnitude of benefit derived from 1 year is sufficient to justify its systematic use for different patient subgroups. Methods: Treatment effects were evaluated according to various tumour characteristics, and multivariate Cox proportional hazards regression models were performed on metastatic disease free survival (M-DFS) in the 12 month control arm. A prognostic score was defined providing the identification of patient categories with similar risks. The 6 months arm was used as a validation set in order to test for heterogeneity. Results: A total of 261 M-DFS events were observed and 4 prognostic groups were defined: very low, low, intermediate and high risks. In the 12 month arm, the corresponding 3-year M-DFS rates were 98.3%, 95.8%, 90.4% and 78.4% in the 4 prognostic groups, respectively. In the 6 month arm, the 3-year M-DFS rates were 98.3%, 94.2%, 85.7%, and 74.8% in the 4 prognostic groups, respectively. Conclusions: In the very low risk and low risk groups, the potential absolute benefit of standard duration of trastuzumab was small enough to indicate that optimal standard treatment might be clinically questionable. On the other hand, the 3-year metastasis occurrence rates strongly support the need for a search of a more efficient treatment in the intermediate and high risk groups. Clinical trial information: NCT00381901.

Proceedings Title
Journal of Clinical Oncology

Type
Conference Paper

Author
Hélène Senellart
Emmanuelle Samalin
Antoine Adenis

UCGI 25: A multicentric randomized phase II trial evaluating dual targeting of the epidermal growth factor (EGFR) using the combination of cetuximab and afatinib versus cetuximab alone in patients (pts) with chemotherapy refractory wtRAS metastatic colorectal cancer (mCRC).

Type
Conference Paper

Author
Hélène Senellart
Emmanuelle Samalin
Antoine Adenis
A previous study assessing erlotinib-cetuximab combo in chemo-refractory wt KRAS mCRC (Weickhardt AJ, et al J Clin Oncol 2011;30:1505-12) has shown encouraging data (ORR=41%, PFS=5.6 months). Afatinib is an Erb-B family blocker that irreversibly blocks signaling from all relevant Erb-B family homo and heterodimers. Methods: We conduct a randomized phase II study to determine the benefit of afatinib plus cetuximab versus cetuximab alone in patients with wtRAS metastatic CRC after oxaliplatin and irinotecan failure. Key eligibility criteria: pts with mCRC expressing wt KRAS/NRAS status; ECOG status 0 or 1; no disease progression with previous anti-EGFR targeted therapy; failure with a prior regimen containing irinotecan or oxaliplatin for metastatic disease; pts must have previously received a thymidylate inhibitor at any point for treatment of CRC; pts are randomized 2:1 to receive oral afatinib (40 mg/qd) in combo with i.v. cetuximab (500mg/m2 q 2 weeks) or cetuximab alone (500mg/m2 q2 weeks). Dose adjustments are permitted according to the occurrence of drug related Adverse Events (AE). Pts receive treatment until PD or unacceptable AE. Pts randomized in the cetuximab arm have the opportunity to crossover to the combo arm after disease progression. The primary endpoint is the 6-month PFS rate. Secondary endpoints include ORR, median PFS, OS, safety and tolerability. Target enrolment is 75 pts. Completion of pt recruitment and data analyses are awaited. This study is promoted by UNICANCER GI. Clinical trial information: NCT01919879.