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Édito

R&D UNICANCER Confirme son dynamisme dans un contexte toujours plus complexe

Christian Cailliot, Directeur de la recherche et du développement.

La recherche dans le cancer se complexifie. Cette complexité croissante à mener des recherches en cancérologie provient tout à la fois de l'explosion des connaissances scientifiques, des cibles potentielles et de la diversité des approches thérapeutiques : immunothérapie, médecine de précision, théranostique, pharmaco-génomique, génomique. Ainsi, aucune structure ne peut prétendre pouvoir avancer seul.

Pour ces raisons, le maître mot de 2016 a été «coopérations» avec tous les acteurs de la cancérologie, nationaux ou transfrontaliers, publics comme privés. Ceci s'est traduit par une forte croissance de l'activité tant en termes de nombre d'essais cliniques que de patients inclus dans ces essais.

Ce mouvement continue naturellement d'être poursuivi afin de renforcer la place de R&D UNICANCER en tant qu'acteur incontournable de la recherche académique en cancérologie.

L'explosion des approches thérapeutiques mais aussi les évolutions réglementaires et légales au niveau national et européen sont autant de challenges à relever. C'est pourquoi R&D UNICANCER se structure afin de répondre à tous les acteurs de la recherche et du soin qui nous font confiance en nous délégant la promotion de leurs essais.

Confirmant le mouvement déjà initié, les perspectives pour 2017 sont incarnées par la création de nouveaux groupes thématiques tels qu'un groupe de recherche en immunothérapie afin de mobiliser les acteurs clefs, et une fois encore étendre notre réseau de collaborations nationales et internationales et développer des projets ambitieux de recherche dans la lutte contre le cancer.

UNICANCER R&D Confirms its dynamic momentum in an increasingly complex environment

Christian Cailliot, Research and Development Director.

Cancer research is becoming an increasingly complex field, underpinned by the explosion in scientific knowledge and potential targets as well as the diversity of therapeutic approaches: immunotherapy, precision medicine, theranostics, pharmacogenomics, genomics. Consequently, no research organisations can expect to make progress alone.

Hence the keyword for 2016 was «cooperation», with all oncology stakeholders, be they national or international, public or private. This led to strong growth in our activities, in terms of both the number of clinical trials and the amount of patients enrolled in these trials.

And the momentum is continuing, the aim being to reinforce UNICANCER R&D's role as a key player in the academic cancer research landscape.

The dramatic increase in therapeutic approaches and evolving regulations and legislation on both a national and European level pose real challenges. To reflect this and to meet the needs of the research and clinical players who have demonstrated their confidence by choosing us to sponsor their trials, UNICANCER R&D is continuing to fine-tune its organisation.

Building on this momentum, 2017 will be marked by the creation of new themed groups, including an immunotherapy research group, in order to rally the support of key stakeholders, further expand our network of national and international collaborations and develop ambitious cancer research projects.

Épidémio-Stratégie Médico-Économique

UNICANCER ESMÉ

Scientific articles

Paclitaxel plus bevacizumab or paclitaxel as first-line treatment for HER2-negative metastatic breast cancer. (S Delaloge, Ann Oncol. 2016 Sep;27(9):1725-32. doi: 10.1093/annonc/mdw260. Epub 2016 Jul 19).

BACKGROUND

Bevacizumab combined with paclitaxel as first-line chemotherapy for patients with HER2-negative metastatic breast cancer (MBC) has led to mixed results in randomized trials, with an improvement in progression-free survival (PFS) but no statistically significant overall survival (OS) benefit. Real-life data could help in assessing the value of this combination.

PATIENTS AND METHODS

This study aimed to describe the outcome following first-line paclitaxel with or without bevacizumab in the French Epidemiological Strategy and Medical Economics (ESME) database of MBC patients, established in 2014 by Unicancer. The primary and secondary end points were OS and PFS, respectively.

RESULTS

From 2008 to 2013, 14 014 MBC patient files were identified, including 10 605 patients with a HER2-negative status. Of these, 3426 received paclitaxel and bevacizumab (2127) or paclitaxel (1299) as first-line chemotherapy. OS adjusted for major prognostic factors was significantly longer in the paclitaxel and bevacizumab group compared with paclitaxel [hazard ratio (HR) 0.672, 95% confidence interval (CI) 0.601-0.752; median survival time 27.7 versus 19.8 months]. Results were consistent in all supportive analyses (using a propensity score for adjustment and as a matching factor for nested case-control analyses) and sensitivity analyses. Similar results were observed for the adjusted PFS, favoring the combination (HR 0.739, 95% CI 0.672-0.813; 8.1 versus 6.4 months).

CONCLUSION

In this large-scale, real-life setting, patients with HER2-negative MBC who received paclitaxel plus bevacizumab as first-line chemotherapy had a significantly better OS and PFS than those receiving paclitaxel. Despite robust methodology, real-life data are exposed to important potential biases, and therefore, results need to be treated with caution. Our data cannot therefore support extension of current use of bevacizumab in MBC.

Routinely collected data may usefully supplement randomised controlled data on treatment effects for mortality. (Pérol D, Robain M, Delaloge S, Cailliot C, BMJ. 2016 Dec 16;355:i6745. doi: 10.1136/bmj.i6745.)

Letter to the editor

Programme ESMÉ d'UNICANCER : améliorer la prise en charge des patients à partir des données de vie réelle en cancérologie. (Christian Cailliot, Gaëtane Simon, Camille Baron, Coralie Courtinard & Mathieu Robain, Innovations & Thérapeutiques en Oncologie. 2016;2(4):164-166. doi:10.1684/ito.2016.0053)

Lancé en 2014 par R&D UNICANCER et soutenu par l'ensemble des centres de lutte contre le cancer (CLCC), le programme ESMÉ (« Épidémio-stratégie médico-économique »), initiative académique, consiste en la centralisation de données de vie réelle des patients traités pour un cancer en France. Pour chaque pathologie ou domaine thérapeutique, la plate-forme de données ESMÉ s'appuie sur les données anonymisées documentées par les professionnels de santé des CLCC. L'objectif est de décrire au cours du temps l'évolution de la prise en charge des patients et des stratégies thérapeutiques, dans une approche médico-économique à grande échelle. Ainsi, ce programme permet de générer des connaissances complémentaires de celles issues des essais cliniques randomisés.

À disposition de la communauté scientifique et médicale (chercheurs et cliniciens), cette plateforme de données doit permettre de développer des recherches pour améliorer les connaissances sur le traitement des cancers (stratégies thérapeutiques, déterminants et efficience), qui pourront donner lieu à des publications. Elle fournit également des données indépendantes pour soutenir les autorités françaises de santé dans leurs missions d'évaluation des produits de santé.

Reply to 'The potential and perils of observational studies' by M. Buyse et al. (S Delaloge *et al.*, Ann Oncol (2017) 28 (2): 436-437, doi: 10.1093/annonc/mdw572).

Letter to the editor

Oral Communications

ASCO

Overall survival of patients with HER2-negative metastatic breast cancer treated with a first-line paclitaxel with or without bevacizumab in real-life setting: Results of a multicenter national observational study. (S Delaloge *et al.*, J Clin Oncol 34, 2016 - suppl; abstr 1013)

BACKGROUND

In 2014, UNICANCER (composed of 18 French Comprehensive Cancer Centers) launched the Epidemiological Strategy and Medical Economics (ESME) program to centralize real-world data in oncology. Metastatic breast cancer (mBC) was first selected to address the value of bevacizumab (B) added to paclitaxel (P) as first-line chemotherapy (CT) for HER2-negative tumours, while randomized trials have led to mixed results on outcome.

METHODS

The ESME-mBC database was built from information systems, treatment databases and patients' electronic files including quality control processes. All patients who started a first-line anti-cancer treatment for mBC between 01-Jan-2008 and 31-Dec-2013 were selected. The primary objective of the present study was to assess overall survival (OS) in patients with HER2-mBC treated with a first-line P-based CT ± B. Cox regression with adjustment for the main prognostic covariates was used to estimate the hazard ratio (HR) for OS and progression-free survival (PFS). To adjust for confounders, advanced methodological methods including propensity score, matching factor for nested case-control analyses and sensitivity analyses were performed.

RESULTS

Among 14,014 patients recorded in the ESME-mBC database, 10,605 had HER2-negative tumors. Of these, 2,127 and 1,299 received P+B and P respectively as first-line CT. OS was significantly higher in the P+B group compared with P alone (HR = 0.672 [95%CI, 0.601;0.752]; median survival time, 27.7 versus 19.8 months). Results were consistent across all supportive and sensitivity analyses, including in triple-negative and estrogen receptor-positive tumors subgroups. PFS was also higher for those receiving P+B versus P (HR = 0.739 [0.672; 0.813]; 8.1 versus 6.4 months).

CONCLUSIONS

In this large-scale real-life setting database, patients with HER2-negative mBC who received P+B had a significantly better OS and PFS than those receiving P alone. Despite robust methodology, real-world data should be interpreted with caution. However, these data shed light on the potential interest of real-life data in oncology.

EPICLIN 10 / 23e journée des Statisticiens des CLCC

Plateforme de données de vie Réelle ESME. Constitution d'une liste de sélection exhaustive multi sources (T Guesmia *et al.*, Revue d'Épidémiologie et de Santé Publique, Volume 64, Supplement 3, Ma 2016)

INTRODUCTION

Les données de « vie réelle » sont des données cliniques et thérapeutiques recueillies à grande échelle pour décrire la prise en charge réelle des patients et ses résultats. Ces données sont complémentaires à celles des essais cliniques, chaque approche ayant son intérêt. L'exhaustivité de la population sélectionnée est un point majeur pour la validité des données de vie réelle et repose sur une méthodologie de sélection parfois complexe.

METHODES

La sélection des patients dans le premier projet ESME, patients avec une première prise en charge entre 2008 et 2013 pour un cancer du sein métastatique (CSM) dans les 20 sites des 18 centres de lutte contre le cancer (CLCC), a été réalisée à partir de différentes sources d'information structurées ou non structurées : programme médicalisé des systèmes d'information (PMSI), dossier pharmaceutique, bases locales spécifiques, base des réunions de concertation pluridisciplinaire (RCP), moteurs de recherche internes. La qualification de chaque type de liste a été préalablement réalisée sur échantillons avant de décider l'utilisation de la source d'information dans la démarche. Les listes de présélection issues des différentes sources utilisées ont été fusionnées afin de constituer une liste unique. La méthodologie maximisait la sensibilité tout en essayant de conserver une bonne spécificité. Le retour systématique aux Dossiers patients informatisés (DPI) a permis de valider la sélection de chaque patient. Des contrôles qualités des cas non sélectionnés et sélectionnés ainsi qu'un audit du processus complet de sélection ont été réalisés.

RESULTATS

Au total 34 484 patients ont été présélectionnés. Ce travail de sélection a nécessité de s'appuyer sur les outils et les informations accessibles dans les centres. Après retour à l'ensemble des dossiers des patients présélectionnés, 14 022 patients ont effectivement été sélectionnés. La contribution des sources de présélection à la sélection finale est décrite dans la Tableau 1.

La proportion de patients effectivement sélectionnés (40,7 %) différait d'un centre à l'autre (28 % à 58 %), cependant, le nombre final de patients effectivement sélectionnés dans chaque centre correspondait à l'estimation initiale faite pour chaque centre à partir d'informations extrapolées du PMSI national.

CONCLUSION

L'utilisation de sources d'information différentes était indispensable pour sélectionner l'ensemble des patients de notre population, en particulier ceux suivis uniquement en consultation et accessibles à partir des moteurs de recherche uniquement. Le taux de conversion présélection/sélection était globalement inférieur à celui attendu. Nous considérons cependant avoir approché l'exhaustivité des patients à sélectionner par l'approche multi-sources. Nous avons utilisé les sources d'information communes à l'ensemble des centres et les sources d'information additionnelles propres aux centres afin de maximiser la sensibilité globale de la démarche. Cette méthodologie de sélection menée avec l'ensemble des sources d'information disponibles, variable d'un centre à l'autre, dont plusieurs sont standardisées dans tous les centres, possède une sensibilité très élevée mais implique de poursuivre le travail pour améliorer la spécificité des patients présélectionnés et minimiser le travail de validation du dossier.

SABCS

Real-life activity of oral vinorelbine in metastatic breast cancer patients in the Unicancer ESME database (P Heudel *et al.*, abstract #1053)

Groupe Essais Précoces

Scientific articles

Phase I, Dose-Escalation Trial of Pazopanib in Combination with Cisplatin in Patients with advanced Solid Tumors: A UNICANCER Study. (V Dieras *et al.*, Oncol Ther 2016 4: 211. doi:10.1007/s40487-016-0027-x)

INTRODUCTION

To determine the feasibility, maximum-tolerated dose (MTD), and dose-limiting toxicities (DLT) of pazopanib in combination with cisplatin.

METHODS

Patients with advanced malignancies were included in a 3 + 3 dose-escalation phase I study. Pazopanib administration started 8 days before the first infusion of cisplatin; some patients were treated according to a reverse sequence (cisplatin first). Five dose levels (DLs) were planned. MTD was based on DLT observed during cycles 1 and 2.

RESULTS

Thirty-five patients were enrolled. The MTD was reached at the first DL, (pazopanib 400 mg daily + cisplatin 75 mg/m2 every 21 days). Main DLTs were pulmonary embolism, neutropenia, thrombocytopenia, and elevation of liver enzymes. Overall, most common adverse events were anemia (83%), fatigue (80%), thrombocytopenia (80%), neutropenia (73%), hypertension (59%), neurotoxicity (56%), and anorexia (53%). Sixteen patients (46%) discontinued the study due to toxicity. One patient (sarcoma) had a complete response, and three patients (one with breast cancer and two with ovarian cancers) had a partial response. Pharmacokinetic (PK) analyses showed interactions with aprepitant, resulting in increased exposure to pazopanib, which might explain partly the poor tolerance of the combination.

CONCLUSION

Cisplatin and pazopanib could not be administered at their single agent full doses, partly due to a PK interaction between pazopanib and aprepitant.

Pharmacokinetic interaction between pazopanib and cisplatin regimen. (DC Imbs, Cancer Chemother Pharmacol. 2016 Feb;77(2):385-92. doi: 10.1007/s00280-015-2953-y. Epub 2016 Jan 16.)

A phase I study combining daily oral pazopanib and cisplatin (given iv every 3 weeks) was performed in order to determine the maximum tolerated dose of both drugs in combination. Pharmacokinetic interactions were evaluated.

METHODS

Plasma pazopanib and ultrafilterable cisplatin concentrations were obtained in 32 patients treated according to four levels of dose corresponding to 200, 400 or 600 mg daily dose of pazopanib and 60 or 75 mg/m(2) of cisplatin. Two sequences of treatment were performed in order to explore any interaction of cisplatin on pazopanib pharmacokinetics and inversely. Data were analyzed using the NONMEM program.

RESULTS

Maximum tolerated dose was 400 mg of pazopanib and 75 mg/m(2) of cisplatin. Mean (CV % for inter-individual variability) cisplatin clearance was 10.3 L/h (33.2 %) and appeared not to be influenced by pazopanib. However, pazopanib pharmacokinetics was significantly modified by the cisplatin regimen. Mean (CV %) of oral pazopanib clearance was 0.66 L/h (55 %) at Day 0 (before cisplatin administration), 24.8 % lower at Day 1 and 32.9 % lower at Day 2. The interaction is less likely to be due to cisplatin than to a competitive inhibition of pazopanib metabolism and efflux by aprepitant, an antiemetic drug systematically administered with cisplatin. The plasma pazopanib exposures observed at Day 0 with a 400 mg dose were similar to those observed at the recommended dose of pazopanib in monochemotherapy (800 mg) during the first-in-man phase 1 study.

CONCLUSION

The observed pazopanib plasma overexposure probably contributed to the poor tolerance encountered during this phase 1 study.

How to report toxicity associated with targeted therapies? (B Cabarrou *et al.*, Ann Oncol. 2016 Aug;27(8):1633-8. doi: 10.1093/annonc/mdw218. Epub 2016 May 23.)

BACKGROUND

In the era of personalized medicine, molecularly targeted therapies (MTT) have modified the outcome of some cancer types. The price of tumor control needs to be balanced with toxicity since these new therapies are administered continuously for several months or sometimes for several years. For cytotoxic drugs, the incidence of adverse event (AE) was traditionally reported as frequency and intensity. This simple measure is not sufficient to capture the recurrent nature and duration of AE. This paper presents two methods to better describe the toxicity burden across the time: prevalence and Q-TWiST.

PATIENTS AND METHODS

Limitation of worst-grade method and advantages of prevalence and Q-TWiST in the analysis of toxicity were illustrated using data from a phase II trial and a hypothetically simulated clinical trial.

RESULTS

Prevalence integrates the recurrent nature of AE. Using prevalence, it is possible to obtain a time profile of AE. Q-TWiST method evaluates the weighted time spent in each health state and also considers the recurrent nature of side-effects in order to assess the 'risk-benefit' ratio of a treatment. When interpreting Q-TWiST results, it is necessary to take into account overall survival and progression-free survival and to define a clinically relevant difference according to the setting.

CONCLUSION

The two methods presented here capture different effects. They are helpful for physicians in their treatment choice (balance benefit risk), to counsel patients and to optimize supportive care. In order to ensure consistency and provide critical information required for medical decision-making, it is important to encourage the use of alternative statistical methods in the analysis of toxicities associated with MTT.

ASCO

Predictive value of intratumoral signaling and immune infiltrate for response to pre-operative (PO) trastuzumab (T) *vs* trastuzumab + everolimus (T+E) in patients (pts) with primary breast cancer (PBC) : Unicancer RADHER trial results (M Campone *et al.*, abstract #TPS11620)

GERICO

Posters

SOFOG

ASTER 70s ou Traitement adjuvant systémique du cancer du sein avec récepteurs aux oestrogènes-positifs et HER2-négatif de la femme de plus de 70 ans en fonction du grade génomique (GG). (F Coussy *et al.*)

SIOG

Aster 70s or optimal adjuvant treatment for women over 70 with luminal breast cancer: a gerico/ unicancer phase III trial. (F Coussy *et al.*, abstract #1362)

Final results of gerico 10 getug p03 trial evaluating feasibility of docetaxel in vulnerable or frail elderly (75+) patients with metastatic castration resistant prostate cancer. (L Mourey *et al.*, abstract #1336)

GETUG

UNICANCER Getug

Scientific articles

Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial (C Carrie *et al.*, Lancet Oncol Volume 17, No. 6, p747–756, June 2016)

BACKGROUND

How best to treat rising prostate-specific antigen (PSA) concentration after radical prostatectomy is an urgent clinical question. Salvage radiotherapy delays the need for more aggressive treatment such as long-term androgen suppression, but fewer than half of patients benefit from it. We aimed to establish the effect of adding short-term androgen suppression at the time of salvage radiotherapy on biochemical outcome and overall survival in men with rising PSA following radical prostatectomy.

METHODS

This open-label, multicentre, phase 3, randomised controlled trial, was done in 43 French study centres. We enrolled men (aged ≥18 years) who had received previous treatment for a histologically confirmed adenocarcinoma of the prostate (but no previous androgen deprivation therapy or pelvic radiotherapy), and who had stage pT2, pT3, or pT4a (bladder neck involvement only) in patients who had rising PSA of 0•2 to less than 2•0 µg/L following radical prostatectomy, without evidence of clinical disease. Patients were randomly assigned (1:1) centrally via an interactive web response system to standard salvage radiotherapy (three-dimensional [3D] conformal radiotherapy or intensity modulated radiotherapy, of 66 Gy in 33 fractions 5 days a week for 7 weeks) or radiotherapy plus short-term androgen suppression using 10•8 mg goserelin by subcutaneous injection on the first day of irradiation and 3 months later. Randomisation was stratified using a permuted block method according to investigational site, radiotherapy modality, and prognosis. The primary endpoint was progression-free survival, analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT00423475.

FINDINGS

Between Oct 19, 2006, and March 30, 2010, 743 patients were randomly assigned, 374 to radiotherapy alone and 369 to radiotherapy plus goserelin. Patients assigned to radiotherapy plus goserelin were significantly more likely than patients in the radiotherapy alone group to be free of biochemical progression or clinical progression at 5 years (80% [95% CI 75-84] *vs* 62% [57-67]; hazard ratio [HR] 0•50, 95% CI 0•38-0•66; p<0•0001). No additional late adverse events occurred in patients receiving short-term androgen suppression compared with those who received radiotherapy alone. The most frequently occuring acute adverse events related to goserelin were hot flushes, sweating, or both (30 [8%] of 366 patients had a grade 2 or worse event; 30 patients [8%] had hot flushes and five patients [1%] had sweating in the radiotherapy plus goserelin group *vs* none of 372 patients in the radiotherapy alone group). Three (8%) of 366 patients had grade 3 or worse hot flushes and one patient had grade 3 or worse sweating in the radiotherapy plus goserelin group versus none of 372 patients in the radiotherapy alone group. The most common late adverse events of grade 3 or worse were genitourinary events (29 [8%] in the radiotherapy alone group *vs* 26 [7%] in the radiotherapy plus goserelin group) and sexual disorders (20 [5%] *vs* 30 [8%]). No treatment-related deaths occurred.

INTERPRETATION

Adding short-term androgen suppression to salvage radiotherapy benefits men who have had radical prostatectomy and whose PSA rises after a postsurgical period when it is undetectable. Radiotherapy combined with short-term androgen suppression could be considered as a reasonable option in this population.

Outcome According to Elective Pelvic Radiation Therapy in Patients With High-Risk Localized Prostate Cancer: A Secondary Analysis of the GETUG 12 Phase 3 Randomized Trial. (P Blanchard *et al.*, Int J Radiat Oncol Biol Phys. 2016 Jan 1;94(1):85-92. doi: 10.1016/j.ijrobp.2015.09.020. Epub 2015 Sep 25.)

PURPOSE

The role of pelvic elective nodal irradiation (ENI) in the management of prostate cancer is controversial. This study analyzed the role of pelvic radiation therapy (RT) on the outcome in high-risk localized prostate cancer patients included in the Groupe d'Etude des Tumeurs Uro-Genitales (GETUG) 12 trial.

METHODS AND MATERIALS

Patients with a nonpretreated high-risk localized prostate cancer and a staging lymphadenectomy were randomly assigned to receive either goserelin every 3 months for 3 years and 4 cycles of docetaxel plus estramustine or goserelin alone. Local therapy was administered 3 months after the start of systemic treatment. Performance of pelvic ENI was left to the treating physician. Only patients treated with primary RT were included in this analysis. The primary endpoint was biochemical progression-free survival (bPFS).

RESULTS

A total of 413 patients treated from 2002 to 2006 were included, of whom 358 were treated using primary RT. A total of 208 patients received pelvic RT and 150 prostate-only RT. Prostate-specific antigen (PSA) concentration, Gleason score, or T stage did not differ according to performance of pelvic RT; pN+ patients more frequently received pelvic RT than pN0 patients (P<.0001). Median follow-up was 8.8 years. In multivariate analysis, bPFS was negatively impacted by pN stage (hazard ratio [HR]: 2.52 [95% confidence interval [CI]: 1.78-3.54], P<.0001), Gleason score 8 or higher (HR: 1.41 [95% CI: 1.03-1.93], P=.033) and PSA higher than 20 ng/mL (HR: 1.41 [95% CI: 1.02-1.96], P=.038), and positively impacted by the use of chemotherapy (HR: 0.66 [95% CI: 0.48-0.9], P=.009). There was no association between bPFS and use of pelvic ENI in multivariate analysis (HR: 1.10 [95% CI: 0.78-1.55], P=.60), even when analysis was restricted to pN0 patients (HR: 0.88 [95% CI: 0.59-1.31], P=.53). Pelvic ENI was not associated with increased acute or late patient reported toxicity.

CONCLUSIONS

This unplanned analysis of a randomized trial failed to demonstrate a benefit of pelvic ENI on bPFS in high-risk localized prostate cancer patients.

Oral Communications

ESMO

Metastasis free survival (MFS) is a surrogate for Overall Survival (OS) in Localized Prostate Cancer (CaP). (W. Xie *et al.*, Abstract 7170 - Annals of Oncology (2016) 27 (6): 243-265. 10.1093/annonc/mdw372)

BACKGROUND

Advances in the treatment of localized CaP have led to decreased recurrences and improved OS. The Intermediate Clinical Endpoints in CaP (ICECaP) Working Group is conducting meta-analysis of potential surrogate endpoints for localized CaP trials. We hypothesized that MFS is a surrogate for OS.

METHODS

By June 2013, we systematically identified 102 eligible randomized trials (completed or ongoing) comparing treatments in localized CaP and collected individual patient data (IPD) from trialists. MFS was defined from randomization to the first evidence of distant metastatic disease (excluding pelvic lymph nodes), or death from any cause; or was censored at the date of last follow-up. OS was defined from randomization to death from any cause. We evaluated the surrogacy of MFS with OS using a 2-stage meta-analytic validation model where 2 conditions must hold to claim MFS is a surrogate for OS (Buyse et al, 2000 & 2011 - table). The secondary objective evaluated surrogacy of time to metastasis (TTM) with disease specific survival (DSS), defined analogously to MFS and OS but with non-CaP deaths censored.

RESULTS

By May 2016, IPD from 12,712 men randomized in 19 mature trials between 1987 and 2010 were available for analysis. 90% of the men were from radiation based trials, 30% had intermediate and 57% high-risk disease (NCCN criteria) and 83% were

CONCLUSIONS

MFS can be used as a surrogate of OS and TTM as a surrogate of DSS.

ASCO

Mature results of the GETUG 13 phase III trial in poor-prognosis germ-cell tumors (GCT). (K. Fizazi *et al.*, Abstract #4504, J Clin Oncol 34, 2016 (suppl; abstr 4504))

BACKGROUND

Until 2014, standard treatment for poor-prognosis GCT was 4 BEP plus surgery and cure was achieved in only 50% of patients (pts) (IGCCCG 1997). The tumor marker decline rate identified pts with a better outcome (J Clin Oncol 2004, 22: 3868-76). The GETUG 13 phase III trial established that switching pts with an unfavorable decline to intensified chemotherapy results in improved progression-free survival (PFS) (Lancet Oncol 2014; 15: 1442-50). We assessed the long-term efficacy and toxicity in pts treated in GETUG 13.

METHODS

263 pts with IGCCCG poor-prognosis GCT were treated with 1 BEP. hCG and AFP were assessed at day 21: 1) 51pts with a favorable decline continued BEP (Fav-BEP); 2) 203 pts with an unfavorable decline were randomized to receive either BEP (Unfav-BEP) or a dose-dense regimen (Unfav-dose-dense), consisting of paclitaxel-BEP plus oxaliplatin x 2 cycles, followed by 2 cycles of cisplatin, ifosfamide, and bleomycin + G-CSF. PFS and overall survival (OS) (logrank) and long-term toxicity (NCI-CTC criteria) were assessed.

RESULTS

The median follow-up is 5.6 years (range 0.3; 11.9). The 5-year PFS rate is 60% in the Unfav-dose-dense arm *vs* 47% in the Unfav-BEP arm (HR: 0.65 [0.43-0.97]; p=0.037). The 5-year OS rate is 70.4% and 60.8%, respectively (HR: 0.69 [0.43-1.11]; p=0.12). Side effects evolved favorably, with 3 pts in the Unfav-dose-dense arm reporting grade 3 motor neurotoxicity at 1 year but no reported toxicity ≥ grade 2 after year 2. The prognostic value of the tumor marker decline was confirmed: 70% *vs* 47% for 5-year PFS (p=0.006), and 78% *vs* 61% for OS (p=0.02). Salvage high-dose chemotherapy plus a stem cell transplant was implemented in 8% in the Unfav-dose-dense arm and 17% in the Unfav-BEP arm (p=0.035).

CONCLUSIONS

With a mature follow-up, GETUG 13 shows that pts with poor-prognosis GCT and an unfavorable tumor marker decline after 1 BEP who are treated with intensified chemotherapy achieve significantly improved PFS, numerically better OS, minimal long-term toxicity, and a reduced need for high-dose salvage chemotherapy plus a stem cell transplant. These data support integrating this strategy as a standard of care for these rare pts. Clinical trial information: NCT00104676.

Does short-term androgen depletion add to high dose radiotherapy (80 Gy) in localized intermediate risk prostate cancer? Final analysis of GETUG 14 randomized trial (EU-20503/NCT00104741). (B M. Dubray *et al.*, Abstract #5021, J Clin Oncol 34, 2016 (suppl; abstr 5021))

BACKGROUND

Multi-center randomized trial to evaluate the addition of 4-month androgen deprivation to high dose radiotherapy in intermediate risk localized prostate adenocarcinoma patients (pts).

METHODS

Eligible pts were randomly assigned to high dose conformal radiotherapy (prostate 80 Gy / 40 fractions; seminal vesicles 46 Gy / 23 fractions) either alone (group RT) or in combination with 4-month androgen deprivation (flutamide + triptorelin starting 2 months before radiotherapy, group AD-RT). Lymphadenectomy was mandatory when the risk of node involvement was > 10% (Partin). The primary endpoint was survival without clinical / biochemical relapse at 5 years. Secondary endpoints included overall survival, toxicity (CTCAE v3) and quality of life (QLQ-C30, PR-25). The a-priori sample size was 450 patients, 225 per arm (0.90 power to detect an increase from 75 to 85%, bilateral $\alpha = 0.05$).

RESULTS

377 pts were included between September 2003 and June 2010. The inclusions were prematurely closed, due to slow accrual. Intent-to-treat analysis was made for 370 pts (191 RT, 179 AD-RT). Prognostic factors were well balanced between the two arms. The median follow-up duration was 84 months (range: 3 to 132). At 5 years, the probabilities of survival without clinical / biochemical relapse were 76% [95% CI: 69% – 81%] and 84% [78% – 89%] in RT and AD-RT groups, respectively ($p = 0.02$). Overall survival probabilities were 94% [90% - 97%] and 93% [88% - 96%] respectively ($p = 0.54$). Cumulative incidence of biochemical failure were 21% [15% – 26%] and 10% [6% – 15%], respectively ($p < 0.01$). The probabilities of being free of grade 3-4 toxicities were 96% and 95% ($p = 0.69$) for digestive tract, 93% and 95% ($p = 0.44$) for urinary tract.

CONCLUSIONS

4 months of androgen blockade improves event-free survival at 5 years in pts with intermediate risk prostate adenocarcinoma when treated with high dose radiotherapy. Longer follow-up is required to demonstrate an impact on overall survival. Clinical trial information: EU-20503 / NCT00104741.

Disease free survival (DFS) is a surrogate for Overall Survival (OS) in Localized Prostate Cancer (CaP). (C Sweeney *et al.*, Abstract #5023, J Clin Oncol 34, 2016 (suppl; abstr 5023))

BACKGROUND

Advances in the treatment of localized CaP have led to decreased recurrences and improved OS. The Intermediate Clinical Endpoints in CaP (ICECaP) Working Group is conducting an individual patient data (IPD) meta-analysis of possible surrogate endpoints for localized CaP trials. We hypothesized that DFS is a surrogate for OS.

METHODS

By June 2013, we systematically identified 102 eligible randomized trials (completed or ongoing) comparing treatments in localized CaP and collected IPD from trialists. DFS was defined from randomization (R) to the first evidence of clinical recurrence (loco-regional or distant) or death from any cause; or was censored at the date of last follow-up. OS was defined from R to death from any cause. We evaluated the surrogacy of DFS with OS using a meta-analytic 2-stage validation model where 2 conditions must hold to claim DFS is a surrogate for OS (Buyse et al, 2000 & 2011 - table). The secondary objective evaluated surrogacy of time to disease recurrence (TDR) with disease specific survival (DSS), defined analogously to DFS and OS but with non-CaP deaths censored.

RESULTS

By January 2016, IPD from 16,999 men randomized in 20 mature trials were available for analysis. 32% of the men were from prostatectomy trials, about 30% of the men had intermediate and 50% high-risk disease and 86% were < 74 yo. With median follow-up of 10.2 years, 32% (N = 5,370) men had died and 30% of these deaths (N = 1,592) were due to CaP.

CONCLUSIONS

DFS can be used as a surrogate of OS and TDR as a surrogate of DSS.

Interest of short hormonotherapy (HT) associated with radiotherapy (RT) as salvage treatment for biological relapse (BR) after radical prostatectomy (RP): Results of the GETUG-AFU 16 phase III randomized trial–NCT00423475. (C Carrie *et al.*, J Clin Oncol 33, 2015 (suppl; abstr 5006))

BACKGROUND

RT is the standard as salvage treatment after RP. The role of HT is not demonstrated to date. This trial assessed the efficacy of RT alone *vs* RT+HT on progression-free survival (PFS) (biological or/and clinical relapse) for patients with BR after RP. Secondary objectives were overall survival (OS), toxicity and quality of life.

METHODS

Patients (pts) were randomized (1:1; stratification on risk factors at RP and type of planned RT) to RT alone (66Gy on prostate bed +/- pelvic irradiation according to pN status and risk of initial node involvement) or RT+HT (goserelin, for 6 months). Assuming 5-year PFS of 45% for RT arm, the trial required 369 pts per arm to detect an improvement of 12% on PFS in RT+HT arm (90% power and 5% alpha risk). BR was evaluated according to Astro-consensus.

RESULTS

From Oct. 2006 to Mar. 2010, 743 pts (RT: 374; RT+HT: 369) were randomized. Baseline characteristics were well balanced between the arms, median age: 67 y, pT2ac: 54%, pT3ac: 46%, gleason > 6: 76%, positive margins: 51%, seminal vesicles' involvement 13%. PSA doubling time at relapse was > 6 months in 74%. With a median follow-up of 63.1 months, 216 events were notified (138 in RT *vs* 78 in RT+HT). The intent to treat analysis showed an improved 5-y PFS of 62.1% (CI95%: 57-67) *vs* 79.6% (IC95%: 75-84) for RT and RT+HT, respectively (log-rank: p < 0.0001). The 5-y OS was 94.8% for RT *vs* 96.2% for RT+HT (p = 0.18). Cause of death was progressive disease in 2.1% pts on RT arm *vs* 0.8%. Acute toxicities occured more frequently in RT+HT arm (89% *vs* 79%). No difference was found in grade ^{3}3 acute toxicities (1.9% *vs* 2.2%) and late toxicities (18.8% *vs* 21.9%). No toxic death was observed.

CONCLUSIONS

GETUG-AFU 16 is the first randomized trial comparing RT *vs* RT+ short HT as salvage treatment for BR after RP with undetectable post-op PSA. RT+HT significantly improve the 5-y PFS without increasing acute or late grade 3 toxicities. A longer follow up is required to quantify the impact on OS but RT+HT could be considered as the standard in this situation. Clinical trial information: NCT00423475.

SFRO

Suppression androgénique courte et radiothérapie à haute dose (80 Gy) pour cancer prostatique de risque intermédiaire : analyse finale de l'essai randomisé GETUG 14. (B Dubray *et al.*, Abstract CO 16, Cancer/Radiothérapie, Volume 20, Issues 6–7, October 2016, Pages 711–712)

OBJECTIF DE L'ESSAI

Essai randomisé évaluant l'apport d'une suppression androgénique courte à une irradiation à haute dose chez des patients atteints de cancer localisé de la prostate de risque intermédiaire.

PATIENTS ET METHODE

Les patients ont été randomisés entre une radiothérapie conformationnelle de la prostate de 80 Gy et des vésicules séminales de 46 Gy, exclusive ou associée à 4 mois de suppression androgénique par flutamide et triptoreline, débutant deux mois avant la radiothérapie. Un curage ganglionnaire était requis si le risque d'envahissement était supérieur à 10 % (Partin). Le critère de jugement principal était la survie sans rechute biochimique (Phoenix) ou clinique. L'effectif à inclure était de 450 patients (augmentation de 75 % à 85 %, puissance de 0,90, risque α bilatéral de 0,05).

RESULTATS

Un total de 377 patients a été inclus entre 2003 et 2010 (clôture prématurée en raison des délais de recrutement). L'analyse en intention de traitement a porté sur 370 patients (radiothérapie exclusive : 191, hormonoradiothérapie : 179). Les facteurs pronostiques étaient équilibrés entre les deux groupes. La durée médiane de suivi était de 84 mois (extrêmes : 3 à 132). À 5 ans, les probabilités de survie sans récidive étaient de 76 % (intervalle de confiance à 95 % [IC95 %] : 69 %–81 %) et 84 % [78 %–89 %] respectivement après radiothérapie exclusive et hormonoradiothérapie dans les groupes. Les probabilités de survie globale étaient de 94 % [90 %–97 %] et 93 % [88 %–96 %] (p = 0,54). Les incidences cumulées de rechute biochimiques étaient de 21 % [15 %–26 %] et 10 % [6 %–15 %] (p = 0,001). Les probabilités d'absence de toxicité de grades 3–4 selon (la Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) étaient de 96 % et 95 % (p = 0,69) pour le tube digestif, de 93 % et 95 % (p = 0,44) pour les voies urinaires.

CONCLUSION

Une suppression androgénique courte augmente la probabilité de survie sans rechute clinique ou biochimique à 5 ans chez les patients irradiés à haute dose pour un cancer de prostate localisé de pronostic intermédiaire.

ASCO

Efficacy and tolerance of treatments received beyond progression in men with metastatic hormone-naive prostate cancer treated with androgen deprivation therapy (ADT) with or without docetaxel in the GETUG-AFU 15 phase III trial. (P Lavaud *et al.*, abstract #5080, J Clin Oncol 34, 2016 (suppl; abstr 5080))

ESMO

How should we treat castration-resistant prostate cancer patients who have received androgen deprivation therapy (ADT) plus docetaxel upfront for hormone-sensitive diseae? Mature analysis of the GETUG-AFU 15 phase III trial. (P Lavaud *et al.*, abstract #761P, Ann Oncol 2016; 27 (suppl_6): 761P. doi: 10.1093/annonc/mdw372.45)

Modelling relapse in patients with high-risk localised prostate cancer treated randomly in the GETUG 12 phase III trial reveals two populations of relapsing patients. (C Vicier *et al.*, Abstract #723PD, Ann Oncol (2016) 27 (suppl_6): 723PD.)

Clinical outcome of new metastatic hormone sensitive metastatic prostate (nmHSPC) cancer in real life population, in monocentric study. Comparison with nmHSPC patients included in the GETUG 15 study. (M Guerin *et al.*)

GENETIC Group

Scientific articles

GENESIS: A French national resource to study the missing heritability of breast cancer. (OM Sinilnikova *et al.*, BMC Cancer (2016) 16:13 DOI 10.1186/s12885-015-2028-9)

BACKGROUND

Less than 20% of familial breast cancer patients who undergo genetic testing for BRCA1 and BRCA2 carry a pathogenic mutation in one of these two genes. The GENESIS (GENE SISter) study was designed to identify new breast cancer susceptibility genes in women attending cancer genetics clinics and with no BRCA1/2 mutation.

METHODS

The study involved the French national network of family cancer clinics. It was based on enrichment in genetic factors of the recruited population through case selection relying on familial criteria, but also on the consideration of environmental factors and endophenotypes like mammary density or tumor characteristics to assess potential genetic heterogeneity. One of the initial aims of GENESIS was to recruit affected sibpairs. Siblings were eligible when index cases and at least one affected sister were diagnosed with infiltrating mammary or ductal adenocarcinoma, with no BRCA1/2 mutation. In addition, unrelated controls and unaffected sisters were recruited. The enrolment of patients, their relatives and their controls, the collection of the clinical, epidemiological, familial and biological data were centralized by a coordinating center.

RESULTS

Inclusion of participants started in February 2007 and ended in December 2013. A total of 1721 index cases, 826 affected sisters, 599 unaffected sisters and 1419 controls were included. 98% of participants completed the epidemiological questionnaire, 97% provided a blood sample, and 76% were able to provide mammograms. Index cases were on average 59 years old at inclusion, were born in 1950, and were 49.7 years of age at breast cancer diagnosis. The mean age at diagnosis of affected sisters was slightly higher (51.4 years). The representativeness of the control group was verified.

CONCLUSIONS

The size of the study, the availability of biological specimens and the clinical data collection together with the detailed and complete epidemiological questionnaire make this a unique national resource for investigation of the missing heritability of breast cancer, by taking into account environmental and life style factors and stratifying data on endophenotypes to decrease genetic heterogeneity.

Mutation screening of MIR146A/B and BRCA1/2 3'UTRs in the GENESIS study. (AI Garcia *et al.*, Eur J Hum Genet. 2016 Aug;24(9):1324-9. doi: 10.1038/ejhg.2015.284. Epub 2016 Jan 20.)

Although a wide number of breast cancer susceptibility alleles associated with various levels of risk have been identified to date, about 50% of the heritability is still missing. Although the major BRCA1 and BRCA2 genes are being extensively screened for truncating and missense variants in breast and/or ovarian cancer families, potential regulatory variants affecting their expression remain largely unexplored. In an attempt to identify such variants, we focused our attention on gene regulation mediated by microRNAs (miRs). We screened two genes, MIR146A and MIR146B, producing miR-146a and miR-146b-5p, respectively, that regulate BRCA1, and the 3'- untranslated regions (3'-UTRs) of BRCA1 and BRCA2 in the GENESIS French national case/control study (BRCA1- and BRCA2-negative breast cancer cases with at least one sister with breast cancer and matched controls). We identified one rare variant in MIR146A, four in MIR146B, five in BRCA1 3'-UTR and one in BRCA2 3'-UTR in 716 index cases and 619 controls. Among these 11 rare variants, 7 were identified each in 1 index case. None of the three relevant MIR146A/MIR146B variants affected the pre-miR sequences. The potential causality of the four relevant BRCA1/BRCA2 3'-UTRs variants was evaluated with luciferase reporter assays and co-segregation studies, as well as with bioinformatics analyses to predict miRs-binding sites, RNA secondary structures and RNA accessibility. This is the first study to report the screening of miR genes and of BRCA2 3'-UTR in a large series of familial breast cancer cases. None of the variant identified in this study gave convincing evidence of potential pathogenicity.

8e assises de génétique humaine et médicale

Recherche de nouveaux facteurs génétiques prédisposant au cancer du sein dans l'étude GENESIS-iCOGS : apport de la biologie des systèmes. (C Lonjou *et al.*, abstract # C018)

Parmi les familles de cancer du sein (CS) conduisant à une analyse des gènes BRCA1 et BRCA2, moins de 20% présentent une mutation. De rares mutations de TP53, PTEN, STK11et CDH1 sont également associées au risque de CS ainsi que des variants dans des gènes définis à ce jour comme modérés comme ATM, CHEK2 et PALB2. L'ensemble de ces gènes explique 10% des formes familiales de CS. Les études pan-génomiques (GWAS) en population générale ont mis en évidence des SNPs situés dans une centaine de loci associés à un faible risque de CS (OR<1,2). Cependant, environ 50% du risque familial restent encore inexpliqués.

L'étude GENESIS, composée de paires de sœurs atteintes d'un CS et de témoins, est une ressource nationale pour rechercher des facteurs de prédisposition au CS. Le projet GENESIS-iCOGS a pour objectif de tester dans cette population très sélectionnée les associations identifiées dans les GWAS pour faciliter la cartographie fine des régions d'intérêt et identifier de nouveaux loci au moyen de stratégies d'analyse multi-marqueurs. L'originalité de ces approches est la prise en compte du fait que les SNPs s'intègrent dans des voies ou « pathways » biologiquement fonctionnels et rassemblant de nombreux gènes. 1383 cas index et 1328 témoins non apparentés ont été génotypés avec la puce à ADN iCOGS (Illumina), comprenant 211 155 SNPs choisis en raison de leur localisation dans les régions identifiées dans les GWAS par le consortium COGS (Collaborative Oncological Gene-environment Study). L'analyse d'association simple-marqueur a été menée avec PLINK. Les analyses multi-marqueurs ont été réalisées avec les méthodes suivantes : VEGAS2 qui se focalise sur les gènes, PLINKset et ALIGATOR qui s'intéressent à l'ensemble des gènes d'une voie biologique, et les méthodes d'analyse réseaux dmGWAS et iPINBPA qui prennent en compte les interactions protéine-protéine connues.

Après les contrôles de qualité du génotypage, 1355 cas et 1327 témoins d'origine européenne et 191 423 SNPs ont été inclus dans les analyses. L'analyse simple-marqueur a permis de détecter la région de FGFR2 au seuil de signification p≤10-7 (32 SNPs significatifs). D'autres loci sont détectés au seuil p≤10-6, dont TOX3 (5 SNPs), NEK10 (5 SNPs) et KIAA1244 (1 SNP). L'analyse menée avec VEGAS2 met en évidence 6 autres gènes au seuil p≤10-6 dont CASC16 et SLC4A7. La prise en compte des réseaux biologiques montre l'implication de modules fonctionnels appartenant à plusieurs voies de signalisation dans la prédisposition au CS. En particulier, l'atlas du cancer ACSN souligne l'importance de modules de la réparation de l'ADN, de l'apoptose et de la survie.

Cette étude montre que la combinaison à l'échelle du génome d'analyses simple-marqueur et multi-marqueurs peut non seulement permettre l'identification de nouveaux gènes potentiellement associés au CS mais aussi aider à l'interprétation biologique des associations et à l'identification de marqueurs causaux dans la population à haut risque étudiée.

8e assises de génétique humaine et médicale

Une ressource française unique pour étudier l'héritabilité manquante du cancer du sein : description de la population de l'étude GENESIS. (OM Sinilnikova *et al.*, abstract #2646)

Impact des facteurs de la reproduction sur l'association entre les gènes de la régulation des œstrogènes et le risque de cancer du sein : une stratégie pour l'étude GENESIS. (J Coignard *et al.*, abstract # CS11)

Observatoire Français pour l'Étude du syndrome de Lynch OFELy: base clinico-biologique nationale et ressources biologiques dédiées à la recherche sur le syndrome de Lynch. (C Lasset *et al.*, abstract # #3516)

Détermination du spectre tumoral, de la pénétrance et de l'utilité clinique des mutations constitutionnelles dans les nouveaux gènes de prédisposition aux cancers du sein et de l'ovaire : l'étude TUMOSPEC. (O Caron *et al.*, abstract #3341)

Groupe de Pharmacologie Clinique Oncologique

Scientific articles

Prevention of fluoropyrimidine toxicity: do we still have to try our patient's luck? (R Danesi *et al.*, Ann Oncol. 2016 Sep 29. pii: mdw448. doi: 10.1093/annonc/mdw448.)

The 'ESMO consensus guidelines for the management of patients with metastatic colorectal cancer' [1] is a comprehensive and influential document; however, because of its relevance for clinical practice, we critically appraise the conclusions on the impact of dihydropyrimidine dehydrogenase (DPD) on fluoropyrimidine therapy. The statement that 'DPD testing […] remains an option but is not routinely recommended' is biased on the inappropriate choice of the method to assess levels of evidence and grades of recommendation concerning DPD assessment. More importantly, the evaluation of scientific literature, which strongly associates DPD deficiency with preventable fluoropyrimidine toxicity, would have suggested a less negative opinion and a more differentiated conclusion.

[…]

The statement that 'DPD deficiency is generally not assessed in routine practice before 5-FU administration' does...

Médecine Personnalisée

UNICANCER PERSONALIZED MEDICINE

Scientific articles

Improving the Performance of Somatic Mutation Identification by Recovering Circulating Tumor DNA Mutations. (Y Fu *et al.*, Cancer Res. 2016 Oct 15;76(20):5954-5961. Epub 2016 Aug 17.)

DNA extracted from cancer patients' whole blood may contain somatic mutations from circulating tumor DNA (ctDNA) fragments. In this study, we introduce cmDetect, a computational method for the systematic identification of ctDNA mutations using whole-exome sequencing of a cohort of tumor and corresponding peripheral whole-blood samples. Through the analysis of simulated data, we demonstrated an increase in sensitivity in calling somatic mutations by combining cmDetect to two widely used mutation callers. In a cohort of 93 breast cancer metastatic patients, cmDetect identified ctDNA mutations in 54% of the patients and recovered somatic mutations in cancer genes EGFR, PIK3CA, and TP53 We further showed that cmDetect detected ctDNA in 89% of patients with confirmed mutated cell-free tumor DNA by plasma analyses (n = 9) within 46 pan-cancer patients. Our results prompt immediate consideration of the use of this method as an additional step in somatic mutation calling using whole-exome sequencing data with blood samples as controls.

Analysing patients presenting an 'exceptional and unexpected response' in oncology: recent initiatives (C Ferte *et al.*, Innovations & Thérapeutiques en Oncologie. 2016;2(3):135-140. doi:10.1684/ito.2016.0043)

Most anticancer drugs are approved by making marginal improvements in terms of tumour response or survival in non-selected populations, and are highly heterogeneous at the molecular level. Studying patients who present an exceptional and unexpected response to these drugs could enable the rapid identification of novel treatment response biomarkers, accelerate drug development and, more broadly, lead to a better understanding of the biology of cancer cells. Several studies ("NCI exceptional responders' initiative" in the USA, EXPRESS in France) are currently recruiting to build cohorts of patients, in order to subsequently analyse their tumours and reveal in detail the molecular anomalies associated with exceptional response.

Equal access to innovative therapies and precision cancer care (A Buzyn *et al.*, Nat Rev Clin Oncol. 2016 Jun;13(6):385-93)

Patients with cancers of differing histologies that express certain biomarkers are likely to benefit from treatment with targeted therapies. However, targets can be present in malignancies other than those indicated by a drug's label, and as a result, affected patients will have no access to those potentially useful drugs. To tackle this issue, the French National Cancer Institute developed the AcSé Programme in 2013. This programme is designed to make treatment decisions or recommendations on the basis of the presence of relevant biomarkers for malignancies with no targeted therapies available and also aims to improve safety, and evaluate the efficacy of targeted drugs used outside of their approved indications. Patients across France have access to molecular testing in 28 molecular genetics centres and to targeted therapies within phase II trials provided no other trials exist in which they could reasonably be included. Trials include patients below the age of 18 if safe dosing data are available. As of January 2016, 183 French clinical sites and over 7,000 patients are participating in AcSé led trials. Proof of concept is being demonstrated through trials designed to investigate the effectiveness of crizotinib and vemurafenib in a wide variety of cancers.

Mutational profile of metastatic breast cancers: a retrospective analysis (C Lefebvre *et al.*, PLoS Med. 2016 Dec; 13(12): e1002201.)

BACKGROUND

Major advances have been achieved in the characterization of early breast cancer (eBC) genomic profiles. Metastatic breast cancer (mBC) is associated with poor outcomes, yet limited information is available on the genomic profile of this disease. This study aims to decipher mutational profiles of mBC using next-generation sequencing.

METHODS AND FINDINGS

Whole-exome sequencing was performed on 216 tumor–blood pairs from mBC patients who underwent a biopsy in the context of the SAFIR01, SAFIR02, SHIVA, or Molecular Screening for Cancer Treatment Optimization (MOSCATO) prospective trials. Mutational profiles from 772 primary breast tumors from The Cancer Genome Atlas (TCGA) were used as a reference for comparing primary and mBC mutational profiles. Twelve genes (TP53, PIK3CA, GATA3, ESR1, MAP3K1, CDH1, AKT1, MAP2K4, RB1, PTEN, CBFB, and CDKN2A) were identified as significantly mutated in mBC (false discovery rate [FDR] < 0.1). Eight genes (ESR1, FSIP2, FRAS1, OSBPL3, EDC4, PALB2, IGFN1, and AGRN) were more frequently mutated in mBC as compared to eBC (FDR < 0.01). ESR1 was identified both as a driver and as a metastatic gene (n = 22, odds ratio = 29, 95% CI [9–155], p = 1.2e-12) and also presented with focal amplification (n = 9) for a total of 31 mBCs with either ESR1 mutation or amplification, including 27 hormone receptor positive (HR+) and HER2 negative (HER2–) mBCs (19%). HR+/HER2– mBC presented a high prevalence of mutations on genes located on the mechanistic target of rapamycin (mTOR) pathway (TSC1 and TSC2) as compared to HR+/HER2– eBC (respectively 6% and 0.7%, p = 0.0004). Other actionable genes were more frequently mutated in HR+ mBC, including ERBB4 (n = 8), NOTCH3 (n = 7), and ALK (n = 7). Analysis of mutational signatures revealed a significant increase in APOBEC-mediated mutagenesis in HR+/HER2– metastatic tumors as compared to primary TCGA samples (p < 2e-16). The main limitations of this study include the absence of bone metastases and the size of the cohort, which might not have allowed the identification of rare mutations and their effect on survival.

CONCLUSIONS

This work reports the results of the analysis of the first large-scale study on mutation profiles of mBC. This study revealed genomic alterations and mutational signatures involved in the resistance to therapies, including actionable mutations.

SABCS

High-throughput genome analysis and therapeutic decision for patients with HER2-negative metastatic breast cancer: first feasibility and molecular results of the randomized phase II study SAFIR02 BREAST (UCBG- 0105/1304). (A Gonçalves *et al.*, Abstract #PD1-08)

BACKGROUND

A genomic-driven therapeutic strategy in metastatic breast cancer (MBC) was recently demonstrated as feasible in the clinical practice, but its actual impact on patient outcome remains elusive. SAFIR02 study is an ongoing national multicentric phase II randomized trial evaluating targeted therapies matching specific genomic alterations (GA) administered as maintenance after objective response and/or stable disease obtained with chemotherapy in HER2-negative MBC patients. This analysis reports on feasibility of the procedure and the rate of identified actionable targets.

METHODS

Eligible MBC patients (PS=0/1, first- or second-line of chemotherapy, HER2-negative/hormone receptor (HR)-negative or endocrine resistant HR-positive; measurable per RECIST 1.1; accessible to tumor biopsy; no bone metastases-only disease, no major organ dysfunction) were subjected to tumor biopsy for genomic analysis (CGH arrays, Affymetrix Cytoscan; NGS, Ion Torrent PGM, AmpliSeq, panel of around 50 genes). Actionable GA were identified and corresponding targeted therapies were proposed by a multidisciplinary tumor board (MTB). Patients received cytotoxic-based treatment at physician's choice and those with stable or responding disease after 6 to 8 cycles (or at least 4 if stopped for toxicity reason) and targetable GA, were offered randomization between targeted therapy or chemotherapy maintenance until progression or intolerance (main study). Since January 2016, an amendment was made to propose to patients without targetable alteration a randomization between anti-PD-L1 (MEDI4736) or standard chemotherapy maintenance (substudy).

RESULTS

Between March 2014 and May 2016, 457 patients have been enrolled at 21 centers. Genomic analyses could not be obtained in 107 cases (23%) due to either biopsy failure (n= 40; 9%) or low cellularity (n=67; 14%). Of the 307 patients reviewed by the MTB, 197 (64%) had an actionable GA, including PIK3CA-PIK3CB-PIK3R1 (n=51), FGF4 or FGFR1/2 (n= 42), BRCA1/2 (n=15), AKT1/2/3 (n=13), BRAF/KRAS/NRAS (n=13), HER2/3 (n=10), NF1-FRS2 (n=10), MTOR-RPTOR-TSC2 (n=8), PTEN (n=7), STK11 (n=7), IGF1R (n=7), EGFR (n=5). Therapeutic proposals by MTB included AZD5363 (n=71), AZD4547 (n=42), AZD2014 (n=23), selumetinib (n=23), olaparib (n=16), AZD8931 (n=15), vandetanib (n=5), bicalutamide (n=2). In an exploratory analysis involving 157 patients, the rate of targeted therapy proposal by MTB markedly differed between triple-negative patients (TNBC; 24 of 48, 50%) and HER2-negative/HR-positive patients (92 of 109, 84%; p=6.14. 10-6, Chi-2 test). At the time of the analysis, 85 patients have been randomized (main study, 68; substudy, 17). Causes of randomization failure (n=108) included disease progression (n=45) or death (n=25), non-eligibility criteria (n=27), patient/physician's decision (n=11).

CONCLUSION

A large number of patients had identified targetable GA. Of note, the rate of targeted therapeutic proposal was significantly lower in TNBC than in HER2-negative/HR-positive patients. Rapidly progressing disease may impede ultimate randomization.

ASCO

Crizotinib in children and adolescents with advanced ROS1, MET or ALK-rearranged cancer: results of the AcSé phase II trial. (G Vassal *et al.*, Abstract #11509, J Clin Oncol 34, 2016 (suppl; abstr 11509))

BACKGROUND

Alterations of crizotinib (crz) molecular targets ALK, MET, ROS1 are found in a wide range of adult and pediatric (ped) cancers. Crz is approved for the treatment of adult patients (pts) with ALK+ advanced NSCLC but not developed and licenced in Europe for children. To avoid off-label use and allow for a nationwide safe access to crz for pts with ALK, MET or ROS1+ tumor, the French National Cancer Institute (INCa) launched the AcSé program, funding both access to tumor molecular diagnosis and an exploratory multi tumor phase II trial. We report the results of 11 ped cases out of 159 pts.

METHODS

Molecular diagnosis was performed in 28 regional INCa molecular genetic centers by break-apart FISH assays or sequencing. Rearrangements identified through pangenomic tumor profiling were eligible as well. Pts with ROS1, ALK or MET+ in treatment failure received crz 280 mg/m2 BID (except Anaplastic Large Cell Lymphoma [ALCL] pts who received crz 165 mg/m2BID) in capsules or oral solution. Responses were assessed every-8 weeks using RECIST v1.1.

RESULTS

From Aug. 2013 to Aug. 2015, 107 ped tumors were analyzed. Altered targets were found in 18 tumors (see table). 11 pts were enrolled, median age 9 yrs (range 3–16), 64% boys. 7 pts were still on treatment at the cut-off date, 2 for >12 months; 4 have stopped crz (2 PD, 1 doctor's decision, 1 patient's decision). Among the 8 evaluable pts (3 assessments pending), best responses were 1 CR (ALCL ALK trans), 3 PR (ALCL ALK trans, IMT ROS1 trans, meningioma ROS1 trans), 1 SD (mesothelioma ALK trans), and 3 PD (2 Nb ALK mut, glioma MET trans). Crz was well tolerated with 4 grade ≥3 AEs (QTc prolongation, nausea, loss of appetite, anemia). Mainly AEs were grade 1, were elevated transaminases (60% of pts), vomiting (50%), visual disorders (40%), fatigue (40%).

CONCLUSIONS

Alterations of all crz targets were found in ped tumors and children can benefit from crz therapy. Clinical trial information: NCT02034981

SIOP

Efficacy of crizotinib in ALK+, MET+ or ROS1+ advanced pediatric malignancies: results of the AcSé phase II trial. (G Vassal *et al.*, Abstract #0009)

BACKGROUND/OBJECTIVES

Alterations of crizotinib targets ALK, MET, ROS1 are found in a wide range of adult and paediatric cancers. Crizotinib is approved for the treatment of alk+NSCLC but not developed in Europe for children. To avoid off-label use and allow for a nation-wide safe access to crizotinib for adult and paediatric patients with ALK+, MET+or ROS1+ tumors, the French National Cancer Institute (INCa) launched the AcSé program, funding both access to tumour molecular diagnosis and an exploratory multi-tumour phase II trial.

DESIGN/METHODS

Molecular diagnosis was performed in 28 INCa molecular genetics centers by FISH assay or sequencing, as well as through pangenomic tumour profiling. After failure of standard treatment, patients with an ALK+, MET+or ROS1+ malignancy received crizotinib 80 mg/m2 BID (165 mg/m2 BID for anaplastic large cell lymphoma [ALCL]) in capsules or oral solution. Responses were assessed every-8 weeks using RECIST v1.1.

RESULTS:

From 08/2013 to 08/2015, 17/107 paediatric tumors were positive, including: 7/49 neuroblastomas (4 ALK-mutated, 2 ALK-amplified, 1 ALK-translocated and mutated), 2/3 inflammatory yofibroblastic tumors [IMT] (1 ALK-translocated, 1 ROS1-translocated), 3/16 malignant gliomas (2 MET-amplified, MET-translocated), 5/39 other cancers (3 ALK-translocated, 1 ROS1-translocated, 1 MET-amplified). Twelve patients were enrolled: median age 9 years [3–17], 66% boys. Six patients are still on treatment (2 for > 12 months); 6 have stopped crizotinib (4 PD, 1 doctor's decision, 1 patient's decision). Among 11 evaluable patients, best responses were 1 CR (ALCL), 4 PR (2 ROS1-translocated IMT, ALCL, ROS1-translocated meningioma), 2 SD (ALK-translocated mesothelioma, MET-amplified glioma), 4 PD (2 ALK-mutated neuroblastoma, MET-translocated glioma, MET-amplified xanthoastrocytoma). Crizotinib was well tolerated with a majority of AE grade 1: elevated transaminases, vomiting, fatigue. There were five grade 3 AEs: QTc prolongation, nausea, loss of appetite, anemia, ALT increased.

CONCLUSION:

Responses and clinical benefit with crizotinib were demonstrated in children with ALK+, MET+ and ROS1+ tumors.

ESMO

Vemurafenib (VM) in non-melanoma V600 and non-V600 BRAF mutated cancers: first results of the ACSE trial. (JY Blay *et al.*, Abstract #55PD)

BACKGROUND

BRAF mutations (mut) are observed in several cancer histotypes at low frequency (<5%). VM is active in BRAF mutated melanoma. Recently, non-melanoma BRAF-V600E-mutated cancers were also reported to respond to BRAF inhibitors. The ACSE VM study is the 2nd ACSE program launched by the French National Cancer Institute (INCa). This program aims to avoid off-label use and allows a safe and controlled access to targeted therapies outside their label. Here we report the first results of the ACSE VM study.

METHODS

ACSE VM is a phase II trial in patients (pts) with advanced cancers with a BRAF mut identified through the INCa molecular genetic platforms failing standard treatment. Pts with various BRAF V600 mutated cancers (e.g., lung, ovarian, bladder, thyroid, prostate cancers, [...]

Hôpital Expo

La médecine de précision pour TOUS par la validation de l'utilisation de l'analyse du génome tumoral comme outil de décision thérapeutique. (C Audigier-Valette, JC Soria, F Barlesi)

ASCO

Biomarker-driven access to vemurafenib in BRAF positive cancers: second study of the French National AcSé Program. (JY Blay *et al.*, Abstract # TPS11620)

ESMO

Lower risk of Cutaneous squamous cell carcinomas (cSCCs) induced by vemurafenib (V) in non-melanoma patients. (E Maubec *et al.*, Abstract #1143P)

Journées de Dermatologie de Paris 2016 (JDP)

Carcinomes épidermoïdes cutanés (CE) induits par le Vemurafenib (Vemu) chez les patients atteints de tumeurs non mélanocytaires. (E Maubec *et al.*, Abstract #P360)

WCLC

Vemurafenib in patients with non-small cell lung cancer (NSCLC) harboring BRAF mutation. Preliminary results of the AcSé trial. (J. Mazieres *et al.*, Abstract # P3.02a)

SARCOMA

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Scientific articles

To treat osteosarcoma (OS2006): a randomised, multicentre, open-label, phase 3 trial. (S Piperno-Neumann *et al.*, The Lancet Oncology, Vol. 17, No. 8, p1070–1080, August 2016)

BACKGROUND

Based on preclinical data for the antitumour effect of zoledronate in osteosarcoma, we assessed whether zoledronate combined with chemotherapy and surgery improved event-free survival in children and adults with osteosarcoma.

METHODS

In this randomised, multicentre, open-label, phase 3 trial (OS2006), patients aged between 5 years and 50 years with newly diagnosed high-grade osteosarcoma were randomly assigned to receive standard chemotherapy with or without ten zoledronate intravenous infusions (four preoperative and six postoperative). Adults older than 25 years received 4 mg zoledronate per infusion, patients aged 18–25 years received 0•05 mg/kg for the first two infusions and 4 mg for the remaining eight infusions, and younger patients received 0•05 mg/kg per infusion. Chemotherapy comprised high-dose methotrexate based chemotherapy in patients younger than 18 years, and doxorubicin, ifosfamide, and cisplatin in adults older than 25 years; patients aged 18–25 years were treated with either regime at the discretion of the treating centre. Balanced randomisation between the two groups was done centrally with online randomisation software, based on a minimisation algorithm taking into account centre, age, combined with chemotherapy regimen, and risk group (resectable primary and no metastasis *vs* other). Patients and investigators were not masked to treatment assignment, but the endpoint adjudication committee members who reviewed suspected early progressions were masked to group allocation. The primary endpoint was event-free survival, estimated from the randomisation to the time of first failure (local or distant relapse, progression, death) or to the last follow-up visit for the patients in first complete remission, analysed on a modified intention-to-treat population, which excluded patients found not to have a malignant tumour after central review. Three interim analyses were planned. This trial is registered with ClinicalTrials.gov, number NCT00470223.

FINDINGS

Between April 23, 2007, and March 11, 2014, 318 patients, median age 15•5 years (range 5•8–50•9), were enrolled from 40 French centres; of whom 158 were assigned to the control group (chemotherapy alone) and 160 to the zoledronate group, including 55 (17%) patients with definite metastases. The trial was stopped for futility after the second interim analysis. With a median follow-up of 3•9 years (IQR 2•7–5•1), 125 events occurred (55 in the control group and 70 in the with zoledronate group). Event-free survival at 3 years for all 315 randomly assigned patients was 60•3% (95% CI 64•5–65•9); 3-year event-free survival was 63•4% (55•2–70•9) for the control group and 57•1% (48•8–65•0) for the zoledronate group. The risk of failure was not reduced and was even marginally higher in the zoledronate group than in the control group (hazard ratio [HR] 1•36 [95% CI 0•95–1•96]; p=0•094). No major increase in severe toxic effects of grade 3 or higher associated with zoledronate, barring expected hypocalcaemia (45 [29%] of 153 participants in the zoledronate group *vs* ten [6%] of 155 participants in the control group; p<0•0001) and hypophosphataemia (61 [40%] of 151 in the zoledronate group *vs* 26 [17%] of 156 in the control group; p<0•0001). No significant difference in orthopaedic complications was noted between the two groups (27 in the control group and 29 in the zoledronate group). Two treatment-related deaths were reported (one from cardiomyopathy in the control group and one from multiorgan failure in the zoledronate group before the first zoledronate infusion).

INTERPRETATION

From the results observed in this study, we do not recommend zoledronate in osteosarcoma patients. Further biological studies are required to understand the discordance between the results of OS2006 trial and preclinical data.

The ENCCA-WP7/EuroSarc/EEC/PROVABES/EURAMOS 3rd European Bone Sarcoma Networking Meeting/ Joint Workshop of EU Bone Sarcoma Translational Research Networks; Vienna, Austria, September 24–25, 2015. Workshop Report. (L Kager *et al.*, Clin Sarcoma Res. 2016 Mar 16;6:3. doi: 10.1186/s13569-016-0043-5.)

This report summarizes the results of the 3rd Joint ENCCA-WP7, EuroSarc, EEC, PROVABES, and EURAMOS European Bone Sarcoma Network Meeting, which was held at the Children's Cancer Research Institute in Vienna, Austria on September 24–25, 2015. The joint bone sarcoma network meetings bring together European bone sarcoma researchers to present and discuss current knowledge on bone sarcoma biology, genetics, immunology, as well as results from preclinical investigations and clinical trials, to generate novel hypotheses for collaborative biological and clinical investigations. The ultimate goal is to further improve therapy and outcome in patients with bone sarcomas.

ASCO

Efficacy of Busulfan-Melphalan high dose chemotherapy consolidation in localised high-risk Ewing sarcoma: Results of EURO-E.W.I.N.G 99 R2Loc randomised trial. (J Whelan *et al.*, Abstract #11000)

BACKGROUND

EE99R2Loc (ISRCTN61438620) was conducted in 12 countries, by 4 cooperative groups: GPOH, SFCE/GSF, UK-CCLG, and EORTC. It evaluated effects on event-free (EFS, main endpoint) and overall survival (OS) of BuMel compared to standard chemotherapy in ES presenting with localized disease and either a poor histologic response to induction chemotherapy or large tumor volume (> 200ml) unresected or initially resected.

METHODS

Eligible pts were aged < 50, received 6 VIDE courses (vincristine, ifosfamide, doxorubicin, etoposide) and 1 VAI (vincristine, actinomycin-D, ifosfamide) before randomization to BuMel with stem cell rescue or VAI x 7 courses. The estimate of hazard ratio (HR) and the p-value were corrected for the 4 previous interim analyses by the Inverse Normal Method.

RESULTS

Between 2000 and 2013, from 477 pts classified as high-risk pts, 216 pts (median age, 17 yrs) were randomized to VAI (107) or BuMel (109). Some pts requiring radiation therapy (RT) to the primary site were excluded to avoid excess organ toxicity from interaction between RT and Busulfan. 80% entered the trial because of poor histologic response after chemotherapy alone. Median follow up is 8.0 yrs, with only 3 pts lost to follow up before 3 yrs. Overall, 3yr EFS is 60.0% and OS, 73.9%. In an intention to treat analysis, the risk of an event was significantly decreased by BuMel compared to VAI: HR = 0.63 (95%CI, 0.42-0.94) p = .023 ; 3yr-EFS of 66.9% (57.6-75.0) *vs*. 53.1% (43.6-62.3). OS also favored BuMel, 77.8 *vs*. 69.9%, HR = 0.60 (0.39-0.92) p = .019. Results were consistent across subgroups, and in sensitivity analyses. Two pts died of BuMel-related toxicity and 1 after standard chemotherapy. Significantly more BuMel pts experienced severe acute toxicities, but these arose from a single high-dose course *vs*. multiple VAI courses.

CONCLUSIONS

BuMel conferred improvement in EFS and OS with acceptable toxicity for pts with localized ES and poor histological response to chemotherapy or large tumor volume unresected or initially resected. It should be considered as a standard of care for this group of pts with localized high-risk ES and no contra-indication to BuMel. Clinical trial information: 61438620.

Comparison of VAI standard chemotherapy & whole lung irradiation and Busulfan-Melphalan high dose chemotherapy in Ewing sarcoma (EwS) patients with pulmonary metastases: Results of EURO-E.W.I.N.G. 99 R2pulm randomised trial. (U Dirksen *et al.*)

SIOP

Results of Methotrexate-Etoposide-Ifosfamide based regimen in osteosarcoma patients included in the French OS2006 study. (L Brugières *et al.*)

Local relapse in patients treated n the French OS2006 study: incidence, risk factors and outcome. (E Mascard *et al.*)

EMSOS

Ewing sarcoma of the head and neck: local treatment evaluation of the French population of Euro-Ewing99. (J Bouaoud *et al.*)

Local relapse in patients treated in the French OS2006 study: incidence, risk factors and outcome. (E Mascard *et al.*)

CTOS

Busulfan-Melphalan with blood stem cell rescue (BuMel) for high risk localised Ewing Sarcoma (ES): results of R2Loc randomised study. (J Whelan *et al.*)

Results of Methotrexate-Etoposide-Ifosfamide based regimen in osteosarcomas patients included in the French OS2006/Sarcome-09 study. (M Bérard *et al.*)

Comparison of Methotrexate-Etoposide-Ifosfamide and API-AI based regimen in 18-25yr osteosarcoma patients included in the French OS2006/Sarcome-09 study. (V Laurence *et al.*)

Results of API-AI based regimen in Osteosarcoma patients in the French OS2006/Sarcome-09 study. (S Piperno-Neumann *et al.*)

SIOP

Osteosarcoma with several bone localisations at diagnosis: experience of the OS2006 study. (C Lervat *et al.*)

UCBG

French breast cancer intergroup UNICANCER

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Scientific articles

Factors associated with patient-reported cosmetic outcome in the Young Boost Breast Trial. (PJ Brouwers et al., Radiother Oncol. 2016 Jul;120(1):107-13.)

PURPOSE

To investigate which factors are related to patient reported cosmetic outcome (PRCO) after breast conserving therapy.

METHODS

From 2004 to 2011, 2421 cT1-2N0-2a breast cancer patients were randomised in the Young Boost Trial between a 16 and a 26Gy boost to the tumour bed. Cosmesis was scored subjectively by the patient and physician, and objectively using BCCT.core, at baseline, one and four years after treatment. Presence of fibrosis, QoL and rib pain at four years were also scored. Data were complete for 864 patients. The relation between the separate components was investigated using a proportional odds model.

RESULTS

Of the 7 BCCT.core parameters, the distance from nipple to inframammary fold and the length of the breast contour were significantly related to the overall PRCO at four years. Patients with more fibrosis and poorer QoL scored their cosmesis worse, while rib pain was not related. The agreement between the different scores was low (kappa 0.26-0.42).

CONCLUSION

The distance from nipple to inframammary fold, the length of the breast contour and the severity of fibrosis were the main factors related to patient-reported cosmetic outcome. Patients with better QoL scored their cosmesis better.

Dépistage du cancer du sein: en route vers le futur. (S Delaloge *et al.*, Bull Cancer. 2016 Jul 26.)

Breast cancer remains a potentially lethal disease, which requires aggressive treatments and is associated with long-term consequences. Its prognosis is linked to both tumor biology and burden at diagnosis. Although treatments have allowed important improvements in prognosis over the past 20 years, breast cancer screening remains necessary. Mammographic screening allows earlier stage diagnoses and a decrease of breast cancer specific mortality. However, breast cancer screening modalities should be revised with the objective to address demonstrated limitations of mammographic screening (limited benefit, imperfect sensitivity and specificity, overdiagnoses, radiation-induced morbidity). Furthermore, both objective and perceived performances of screening procedures should be improved. Numerous large international efforts are ongoing, leading to scientific progresses that should have rapid clinical implications in this area. Among them is improvement of imaging techniques performance, development of real time diagnosis, and development of new non radiological screening techniques such as the search for circulating tumor DNA, development of biomarkers able to allow precise risk evaluation and stratified screening. As well, overtreatment is currently addressed by biomarker-based de-escalation clinical trials. These advances need to be associated with strong societal support, as well as major paradigm changes regarding the way health and cancer prevention is perceived by individuals.

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. (F Cardoso *et al.* N Engl J Med. 2016 Aug 25;375(8):717-29.)

BACKGROUND

The 70-gene signature test (MammaPrint) has been shown to improve prediction of clinical outcome in women with early-stage breast cancer. We sought to provide prospective evidence of the clinical utility of the addition of the 70-gene signature to standard clinical-pathological criteria in selecting patients for adjuvant chemotherapy.

METHODS

In this randomized, phase 3 study, we enrolled 6693 women with early-stage breast cancer and determined their genomic risk (using the 70-gene signature) and their clinical risk (using a modified version of Adjuvant! Online). Women at low clinical and genomic risk did not receive chemotherapy, whereas those at high clinical and genomic risk did receive such therapy. In patients with discordant risk results, either the genomic risk or the clinical risk was used to determine the use of chemotherapy. The primary goal was to assess whether, among patients with high-risk clinical features and a low-risk gene-expression profile who did not receive chemotherapy, the lower boundary of the 95% confidence interval for the rate of 5-year survival without distant metastasis would be 92% (i.e., the noninferiority boundary) or higher.

RESULTS

A total of 1550 patients (23.2%) were deemed to be at high clinical risk and low genomic risk. At 5 years, the rate of survival without distant metastasis in this group was 94.7% (95% confidence interval, 92.5 to 96.2) among those not receiving chemotherapy. The absolute difference in this survival rate between these patients and those who received chemotherapy was 1.5 percentage points, with the rate being lower without chemotherapy. Similar rates of survival without distant metastasis were reported in the subgroup of patients who had estrogen-receptor-positive, human epidermal growth factor receptor 2-negative, and either node-negative or node-positive disease.

CONCLUSIONS

Among women with early-stage breast cancer who were at high clinical risk and low genomic risk for recurrence, the receipt of no chemotherapy on the basis of the 70-gene signature led to a 5-year rate of survival without distant metastasis that was 1.5 percentage points lower than the rate with chemotherapy. Given these findings, approximately 46% of women with breast cancer who are at high clinical risk might not require chemotherapy. (Funded by the European Commission Sixth Framework Program and others; ClinicalTrials.gov number, NCT00433589; EudraCT number, 2005-002625-31).

A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic breast cancer (UCBG 12-1). (H Bonnefoi *et al.*, Annals of Oncology 0: 1–6, 2016 doi:10.1093/annonc/mdw067)

BACKGROUND

Several expression array studies identified molecular apocrine breast cancer (BC) as a subtype that expresses androgen receptor (AR) but not estrogen receptor α. We carried out a multicentre single-arm phase II trial in women with AR-positive, estrogen, progesterone receptor and HER2-negative (triple-negative) metastatic or inoperable locally advanced BC to assess the efficacy and safety of abiraterone acetate (AA) plus prednisone.

PATIENTS AND METHODS

Patients with a metastatic or locally advanced, centrally reviewed, triple-negative and AR-positive (≥10% by immunohistochemistry, IHC) BC were eligible. Any number of previous lines of chemotherapy was allowed. AA (1000 mg) was administered once a day with prednisone (5 mg) twice a day until disease progression or intolerance. The primary end point was clinical benefit rate (CBR) at 6 months defined as the proportion of patients presenting a complete response (CR), partial response (PR) or stable disease (SD) ≥6 months. Secondary end points were objective response rate (ORR), progression-free survival (PFS) and safety.

RESULTS

One hundred and forty-six patients from 27 centres consented for IHC central review. Of the 138 patients with sufficient tissue available, 53 (37.6%) were AR-positive and triple-negative, and 34 of them were included from July 2013 to December 2014. Thirty patients were eligible and evaluable for the primary end point. The 6-month CBR was 20.0% [95% confidence interval (CI) 7.7%-38.6%], including 1 CR and 5 SD ≥6 months, 5 of them still being under treatment at the time of analysis (6.4+, 9.2+, 14.5+, 17.6+, 23.4+ months). The ORR was 6.7% (95% CI 0.8%-22.1%). The median PFS was 2.8 months (95% CI 1.7%-5.4%). Fatigue, hypertension, hypokalaemia and nausea were the most common drug-related adverse events; the majority of them being grade 1 or 2.

CONCLUSIONS

AA plus prednisone treatment is beneficial for some patients with molecular apocrine tumours and five patients are still on treatment.

A Systematic Evaluation of Blood Serum and Plasma Pre-Analytics for Metabolomics Cohort Studies. (E Jobard *et al.*, Int. J. Mol. Sci. 2016, 17, 2035)

The recent thriving development of biobanks and associated high-throughput phenotyping studies requires the elaboration of large-scale approaches for monitoring biological sample quality and compliance with standard protocols. We present a metabolomic investigation of human blood samples that delineates pitfalls and guidelines for the collection, storage and handling procedures for serum and plasma. A series of eight pre-processing technical parameters is systematically investigated along variable ranges commonly encountered across clinical studies. While metabolic fingerprints, as assessed by nuclear magnetic resonance, are not significantly affected by altered centrifugation parameters or delays between sample pre-processing (blood centrifugation) and storage, our metabolomic investigation highlights that both the delay and storage temperature between blood draw and centrifugation are the primary parameters impacting serum and plasma metabolic profiles. Storing the blood drawn at 4 °C is shown to be a reliable routine to confine variability associated with idle time prior to sample pre-processing. Based on their fine sensitivity to pre-analytical parameters and protocol variations, metabolic fingerprints could be exploited as valuable ways to determine compliance with standard procedures and quality assessment of blood samples within large multi-omic clinical and translational cohort studies.

Bevacizumab plus neoadjuvant chemotherapy in patients with HER2-negative inflammatory breast cancer (BEVERLY-1): a multicentre, single-arm, phase 2 study. (F Bertucci et al, Lancet Oncol. 2016 May;17(5):600-11.)

BACKGROUND

Addition of bevacizumab to standard chemotherapy in the neoadjuvant setting in patients with HER2-negative metastatic breast cancer improves progression-free survival and the proportion of patients achieving pathological complete response. In the BEVERLY-1 (UCBG-0802) trial we aimed to assess the addition of bevacizumab to neoadjuvant and adjuvant chemotherapy in the treatment of patients with HER2-negative inflammatory breast cancer.

METHODS

We did this phase 2, single-arm trial at 20 hospitals in France. We enrolled women aged 18 years or older who had non-metastatic HER2-negative inflammatory breast cancer. Patients underwent 3-week treatment cycles, receiving neoadjuvant intravenous fluorouracil (500 mg/m2), epirubicin (100 mg/m2), cyclophosphamide (500 mg/m2), and bevacizumab (15 mg/kg) during cycles 1–4, then docetaxel (100 mg/m2) and bevacizumab during cycles 5–8. 2–4 weeks after surgery, patients received adjuvant radiotherapy, hormone therapy (if they had a hormone receptor-positive tumour), and adjuvant intravenous bevacizumab. The primary endpoint was pathological complete response in breast and axillary lymph nodes after neoadjuvant treatment, determined after centralised review in accordance with Sataloff classification and assessed in the intention-to-treat population. Our analysis of toxic effects included all patients who received at least one dose of bevacizumab. The trial is complete and follow-up is ongoing. This study is registered with ClinicalTrials.gov, number NCT00820547.

FINDINGS

Between Jan 16, 2009, and Sept 8, 2010, we enrolled 101 patients, one of whom withdrew consent before treatment, leaving 100 patients in the primary endpoint analysis. After neoadjuvant therapy, 19 (19% [95% CI 12–28]; p=0•16) of 100 patients achieved a pathological complete response according to centralised review. The most frequent grade 3–4 events during the neoadjuvant phase were neutropenia (89 [89%] of 100 patients), febrile neutropenia (37 [37%]), and mucositis (23 [23%]) and during the adjuvant phase the most frequent grade 3–4 adverse event was proteinuria (5 [7%] of 75 patients). One (1%) patient died of thrombotic microangiopathy after cycle 1, which was thought to be related to bevacizumab. Two patients (3%) developed transitory heart failure. 48 (48%) patients had serious adverse events, the most frequent of which was febrile neutropenia (28 [28%]).

INTERPRETATION

Our results suggest that the addition of bevacizumab to neoadjuvant and adjuvant chemotherapy does not provide clinical benefit to patients with non-metastatic HER2-negative inflammatory breast cancer. Longer follow-up and correlative studies to identify patients who might benefit from bevacizumab are needed.

Randomized phase 2 neoadjuvant trial evaluating anastrozole and fulvestrant efficacy for postmenopausal, estrogen receptor-positive, human epidermal growth factor receptor 2-negative breast cancer patients: Results of the UNICANCER CARMINA 02 French trial (UCBG 0609). (F Lerebours *et al.*, Cancer. 2016 Oct;122(19):3032-40.)

BACKGROUND

Treatment strategies for locally advanced breast cancer in elderly patients too frail to receive neoadjuvant chemotherapy and the introduction of new classes of drugs in the early 2000s have led to the consideration of endocrine therapy as a neoadjuvant treatment for younger hormone receptor (HR)–positive, postmenopausal patients not eligible for primary breast-conserving surgery (BCS).

METHODS

This was a multicenter, phase 2, randomized trial designed to evaluate as its primary objective the clinical response rate after up to 6 months of neoadjuvant endocrine therapy (NET) alone in HR-positive/human epidermal growth factor receptor 2 (HER2)–negative patients with 1 mg of anastrozole (arm A) or 500 mg of fulvestrant (arm B). Secondary objectives included the BCS rate, tumor response assessment (breast ultrasound and magnetic resonance imaging), pathological response (Sataloff classification), safety profile, relapse-free survival (RFS), and predictive markers of responses and outcomes.

RESULTS

From October 2007 to April 2011, 116 women (mean age, 71.6 years) with operable infiltrating breast adenocarcinoma (T2-T4, N0-N3, M0) were randomized to receive anastrozole or fulvestrant. The clinical response rates at 6 months were 52.6% (95% confidence interval [CI], 41%-64%) in arm A and 36.8% (95% CI, 25%-49%) in arm B. BCS was performed for 57.6% of arm A patients and 50% of arm B patients. The RFS rates at 3 years were 94.9% in arm A and 91.2% in arm B. The Preoperative Endocrine Prognostic Index status was significantly predictive of RFS. Both treatments were well tolerated.

CONCLUSIONS

Both drugs are effective and well tolerated as NET in postmenopausal women with HR-positive/HER2-negative breast cancer. NET could be considered a treatment option in this subpopulation.

Can Surrogate Pathological Subtyping Replace Molecular Subtyping? Outcome Results from the MINDACT Trial. (F Cardoso *et al.*, Abstract #PD7-01)

BACKGROUND

Molecular subgroups within early breast cancer (EBC), such as Luminal A, Luminal B, HER-2+, Basal-like may help to best to identify patients for specific treatment regimens. Controversy exists as to which methodology is best at identifying these molecular subgroups. Immunohistochemistry (IHC) may be used as a surrogate method to stratify patients. Molecular subtyping gene expression based tests, such as BluePrint, measure a greater number of genes than pathological criteria. ER, PgR, HER-2 and Ki67 are measured individually at the protein level, while BluePrint is designed to capture the functional underlying biologic pathway regulated by these receptors.

METHODS

The MINDACT trial is an international, prospective, randomized, phase III trial which has proventhe clinical utility of MammaPrint in selecting EBC patients who can safely avoid chemotherapy. Here we present the results of a preplanned MINDACT sub-study to compare outcome based on molecular subtyping (MS) to surrogate pathological subtyping (PS) as endorsed by 2013 St. Gallen Consensus. MS data were obtained by MammaPrint (MP) and BluePrint classifying patients in the following subtypes: Luminal A (MP Low Risk); Luminal B (MP High Risk); HER2-type; and Basal-type. ER, PgR, HER2 and Ki67 protein status were centrally assessed by IHC/FISH. The primary hypothesis was that among PS Luminal patients, patients with HER-2+ or Basal-type tumors by MS would have a decreased DMFS compared to MS Luminal patients. At α=5% with 220 events, the study has 80% power to demonstrate this for HR=2.44.

[…]

CONCLUSIONS

1) MS was able to re-stratify 16% of patients to a low risk Luminal A-type group with an excellent outcome. 2) Among TN EBC, 5% were classified as Luminal by MS and had an excellent outcome. 3) Albeit limited by low numbers of patients in each subgroup, this study suggest that MS is better correlated with outcome. 4) The observed subtype discrepancies may have an impact on treatment decision making. 5) Centrally assessed Ki67 labeling index of 20% may be the best cut-off for surrogate differentiation between Luminal A and B.

ISMRC

Circulating Tumor Cells (CTC) and pathological complete response (pCR) are strong independent prognostic factors in inflammatory breast cancer (IBC) in a pooled analysis of two multicentre phase II trials of neoadjuvant chemotherapy combined with bevacizumab (BEVERLY 1 & 2 studies). (FC Bidard *et al.*)

BACKGROUND

We have previously demonstrated that CTC detection in blood is an independent prognostic factor in primary HER2 positive inflammatory breast cancer with a detection rate of 35 % (Pierga, CCR 2014) in 52 patients included in a prospective trial. We present here the results in a pooled analysis of two prospective trials including more than 150 patients. Predictive and prognostic value of circulating endothelial Cells (CEC) for response to bevacizumab was also analyzed.

METHODS

CTC and CEC were detected in 7.5 ml and 4 ml of blood respectively in the neoadjuvant setting in IBC (T4d) patients (pts) enrolled in two phase II multicentre trials, evaluating bevacizumab (15mg/kg q3w) in combination with sequential neoadjuvant CT of 4 cycles of FEC followed by 4 cycles of Docetaxel in HER2 negative tumor (BEVERLY 1) or docetaxel, trastuzumab in HER2 positive (BEVERLY 2). The CellSearch™ System, combining EpCAM immunomagnetic selection followed by anti-cytokeratin (A45B/B3) and anti-HER2 staining for CTC and CD146 IMS and CD105 staining for CEC.

RESULTS

From 10/08 to 09/10, 152 pts were included and 137 were evaluable for CTC and CEC. Median follow-up was 43 months. At baseline, 55 pts had ≥ 1 detectable CTC (39%). A dramatic drop in CTC was observed during treatment with a rate of 9% after 4 cycles of chemotherapy. pCR rate was 40% and was associated with absence of hormonal receptor and HER2 positive status (pCR of 63% HER2+ and 36% in HER2 negative IBC). No correlation was found between CTC and CEC levels or pCR rate. CTC detection at baseline independently predicted 3-year DFS: (70% *vs*. 39% for patients with <1 *vs*. ≥1 CTC/7.5 mL [p<0.001, HR 2.80 (1.65-4.76)]) and 3-year OS (p<0.01). At multivariate analysis, independent prognostic parameters for DFSr were absence of hormonal receptors, no pCR and CTC detection at base-line. CEC level at baseline or variations during treatment had no prognostic value for DFS and OS.

CONCLUSIONS

This is the largest series of non-metastatic inflammatory breast cancer included in prospective trials evaluating CTC detection at baseline and during treatment. We observed a high CTC detection rate of 39% with a strong and independent prognostic value for DFS and OS. Combination of pCR after neoadjuvant treatment, with CTC at baseline, isolates a subgroup of inflammatory breast cancer with excellent survival. CTC count should be part of IBC stratification in prospective trials.

Carrefour pathologie

Analyse globale de l'environnement immunitaire des cancers du sein triple négatif de l'essai multicentrique Unicancer-PACS08. (E Lardenois *et al.*)

INTRODUCTION

Le cancer du sein triple négatif (TNBC) représente 15% des cancers du sein, et est de mauvais pronostic avec un risque élevé de rechute précoce et de métastases. Le traitement repose essentiellement sur la chimiothérapie, mais la réponse histologique complète n'est obtenue que dans 25% des TNBC. Des études d'expression génique ont montré que la réponse immunitaire est corrélée positivement à la survie et à la réponse à la chimiothérapie dans les TNBC. Par ailleurs, un nombre élevé de lymphocytes infiltrant la tumeur (TIL) est associé à une augmentation de la survie et une diminution des rechutes à distance dans les TNBC, indépendamment des autres facteurs pronostiques. Toutefois, une analyse approfondie de l'infiltrat immunitaire dans les TNBC n'a jamais été réalisée à ce jour.

OBJECTIF

L'objectif de cette étude était de réaliser une analyse globale de l'environnement immunitaire des TNBC afin d'identifier i) les paramètres immunitaires critiques liés à l'évolution clinique des TNBC et ii) de nouvelles cibles thérapeutiques ou stratégies pour augmenter la réponse immunitaire anti-tumorale dans les TNBC.

METHODE

Une analyse rétrospective du microenvironnement immunitaire des TNBC a été réalisée par immunohistochimie sur la cohorte Unicancer PACS 08 regroupant sur tissue micro-array 500 cas de TNBC (N+/N-) et 161 cas de tumeur du sein ER+ PR- Her2- (N+). Différentes populations immunitaires infiltrantes ont été analysées grâce aux marqueurs CD3/CD8 pour les lymphocytes T (LT), FoxP3 pour les LT régulateurs, NKp46 pour les cellules NK, CD20 pour les lymphocytes B, DC-LAMP pour les cellules dendritiques (CD) matures, BDCA2 pour les CD plasmocytoides, CD163 pour les macrophages et MPO pour les polynucléaires neutrophiles. L'évaluation de l'expression de points de contrôle immunitaire (PDL1, ICOS) a également été réalisée.

RESULTATS

Les analyses statistiques de cette étude sont en cours afin de corréler i) les paramètres immunitaires entre eux et ii) les paramètres immunitaires aux données cliniques (médiane de suivi de 5.5ans) comme la survie des patientes, la progression tumorale et à la réponse thérapeutique.

DISCUSSION/CONCLUSION

Cette étude permettra l'identification de nouveaux biomarqueurs pronostiques des TNBC et pourraient avoir des implications thérapeutiques futures pour ce sous-type de cancer du sein agressif.

SABCS

Prognostic and predictive values of High Endothelial Venules (HEV) and tumor infiltrating CD8+ lymphocytes (CD8) in tumors of patients included in the adjuvant PACS04 trial: HEV is predictive of outcome for HER2+ tumors exposed to trastuzumab. (H Roché *et al.*, Abstract # P6-09-05)

Circulating tumor cells (CTC) and endothelial cells (CEC) prognostic value in HER2 negative metastatic breast cancer patients treated with first line weekly paclitaxel and bevacizumab: first results of a prospective cohort from the French Breast Cancer InterGroup Unicancer (UCBG): COMET study. (JY Pierga *et al.*, Abstract #P4-01-02)

Predictive value of FDG-PET/CT after neoadjuvant endocrine treatment in breast cancer. (S Boughad *et al.*, Abstract #P04-01-03)

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Prognostic and predictive values of High Endothelial Venules (HEV) and tumor infiltrating CD8+ lymphocytes (CD8) in tumors of patients included in the adjuvant PACS04 trial: HEV is predictive of outcome for HER2+ tumors exposed to trastuzumab. (H Roché *et al.*, Abstract #P6-09-05)

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Results of a phase II trial of abiraterone acetate plus prednisone in patients with a molecular apocrine HER2-negative locally advanced or metastatic breast cancer (UCBG 2012-1). (T grellety *et al.*)

Gastro-Intestinal

UNICANCER GASTRO INTESTINAL

Scientific articles

Applying the longitudinal model from item response theory to assess health-related quality of life in the PRODIGE 4/ACCORD 11 randomized trial. (A Barbieri *et al.*, Med Decis Making 2016, 36(5) : 615-628)

INTRODUCTION

A new longitudinal statistical approach was compared to the classical methods currently used to analyze health-related quality-of-life (HRQoL) data. The comparison was made using data in patients with metastatic pancreatic cancer

METHODS

Three hundred forty-two patients from the PRODIGE4/ACCORD 11 study were randomly assigned to FOLFIRINOX versus gemcitabine regimens. HRQoL was evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30. The classical analysis uses a linear mixed model (LMM), considering an HRQoL score as a good representation of the true value of the HRQoL, following EORTC recommendations. In contrast, built on the item response theory (IRT), our approach considered HRQoL as a latent variable directly estimated from the raw data. For polytomous items, we extended the partial credit model to a longitudinal analysis (longitudinal partial credit model [LPCM]), thereby modeling the latent trait as a function of time and other covariates.

RESULTS

Both models gave the same conclusions on 11 of 15 HRQoL dimensions. HRQoL evolution was similar between the 2 treatment arms, except for the symptoms of pain. Indeed, regarding the LPCM, pain perception was significantly less important in the FOLFIRINOX arm than in the gemcitabine arm. For most of the scales, HRQoL changes over time, and no difference was found between treatments in terms of HRQoL.

DISCUSSION

The use of LMM to study the HRQoL score does not seem appropriate. It is an easy-to-use model, but the basic statistical assumptions do not check. Our IRT model may be more complex but shows the same qualities and gives similar results. It has the additional advantage of being more precise and suitable because of its direct use of raw data.

An assessment of the benefit-risk balance of FOLFIRINOX in metastatic pancreatic adenocarcinoma (J Péron *et al.*, Oncotarget, 2016, DOI: 10.18632/oncotarget.12761)

BACKGROUND

We sought to assess the benefit-risk balance of FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic adenocarcinoma.

METHODS

We used generalized pairwise comparisons. This statistical method permits the simultaneous analysis of several prioritized outcome measures. The first priority outcome was survival time (OS). Differences in OS that exceeded two months were considered clinically relevant. The second priority outcome was toxicity. The overall treatment effect was quantified using the net chance of a better outcome, which can be interpreted as the net probability for a random patient treated in the FOLFIRINOX group to have a better overall outcome than a random patient in the gemcitabine group.

RESULTS

In this trial 342 patients received either FOLFIRINOX or gemcitabine. The net chance of a better outcome favored strongly and significantly the FOLFIRINOX group (24.7; P<.001), suggesting a favorable benefit-risk balance of FOLFIRINOX versus gemcitabine. The positive benefit-risk balance of FOLFIRINOX was observed throughout all sensitivity analyses.

CONCLUSIONS:

Generalized pairwise comparisons are useful to perform a quantitative assessment of the benefit-risk balance of new treatments. It provides a clinically intuitive way of comparing patients with respect to all important efficacy and toxicity outcomes. Overall the benefit-risk balance of FOLFIRINOX was strongly positive.

FOLFIRINOX combined to targeted therapy according RAS status for colorectal cancer patients with liver metastases initially non-resectable: A phase II randomized Study—PRODIGE 14 – ACCORD 21 (METHEP-2), a unicancer GI trial. (M Ychou *et al.*, Abstract #3512)

BACKGROUND

Liver metastases (LM) from colorectal cancer (CRC) are initially resectable in only 10-15% of patients (pts). The conversion to resectability following induction chemotherapy is an important strategy to increase survival. Our study was designed to determine the most appropriate chemotherapy (associated with a targeted therapy) for CRC pts with LM considered as initially unresectable.

METHODS

This French phase II, multicenter, prospective trial, randomized pts between bi-chemotherapy (BiCT) versus tri-chemotherapy (TriCT). The population was initially stratified by targeted therapy depending on KRAS status and then by RAS status (from 02 Dec 2013 due to the change in cetuximab's [Cet] marketing authorization): Cet for wt(K)RAS pts and bevacizumab (Bev) for mtRAS pts. The hypothesis was to increase the rate of LM resection (R0-R1) from 50% with BiCT to 70% with TriCT (bilateral α-test 5%; power 90%).

RESULTS

256 patients were randomized in 33 sites from February 2011 till April 2015: 126 BiCT (FOLFIRI [56 pts]; FOLFOX4 [70 pts]) and 130 TriCT (FOLFIRINOX). The resection rate (R0 or R1; CI95%) of the LM was 45.2% [36; 54] for pts treated with BiCT *vs* 56.9% [48; 66] for TriCT (p = 0.062).The LM resection rate (R0 or R1; CI95%) was 44.7% [35; 55] for pts treated with Bev (mtRAS) *vs* 55.6% [47; 64] for Cet (wtRAS) (p = 0.087). At the time of data analysis, the median follow-up (CI95%) was 22.5 months [19.6;29.5] for the BiCT pts and 23.5 months [19.8; 28.8] for the TriCT pts and at analysis 78 patients had died. The median overall survival (OS) is significantly different (p = 0.048): in the TriCT Arm the median OS was not reached and is 36 months [23.5;40.6] in the BiCT Arm. The severe toxicity rate was 37.6% for BiCT *vs* 41.7% for TriCT (p = 0.503). 38 BiCT pts and 34 TriCT pts had surgical complications, with two deaths in each arm.

CONCLUSIONS

First line FOLFIRINOX chemotherapy, in association with a targeted therapy, showed a higher rate of LM R0/R1 resections than standard BiCT (FOLFIRI or FOLFOX4) combined with the same targeted therapy, with a statistically significant difference in terms of OS. Clinical trial information: 2009-012813-22.

Bevacizumab or cetuximab plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wtKRAS metastatic colorectal cancer: A randomized phase II study (PRODIGE 18 – ACCORD 22 UNICANCER GI). (S Hiret *et al.*, Abstract #3514)

BACKGROUND

Second-line treatment with chemotherapy plus bevacizumab (Bev) or cetuximab (Cet) is now recognized as a standard treatment in mCRC. The main objective of this French multicenter, prospective open randomized trial was to evaluate the Progression Free Survival (PFS) rate at 4 months in patients receiving chemotherapy plus Bev or Cet after failure with Bev plus chemotherapy.

METHODS

The main eligibility criteria were disease progression after first-line chemotherapy: 5-FU with irinotecan or oxaliplatin associated with bevacizumab in wtKRAS mCRC. Patients were treated with cross over chemotherapy (FOLFIRI or mFOLFOX6) with bevacizumab (Arm A) or cetuximab (Arm B) until progression or limiting toxicity. The tumor response was evaluated every 6 weeks until progression using RECIST 1.1.

RESULTS

133 patients, 86 male(64.7%), PS 0 (n = 74, 57.8%), 1 (n = 54, 42.2%), in 25 sites in France, were included between October 2010 and May 2015. Most frequent chemotherapy regimens delivered were mFOLFOX6 + Bev (n = 41) or Cet (n = 42); FOLFIRI + Bev (n = 25) or Cet (n = 25). The PFS rate at 4 months was 79% in Arm A and 66.7% in Arm B (p = 0.09). Secondary objectives included median PFS: 7.1 months (Arm A) *vs* 5.6 months (Arm B) (HR = 1.43; 95%CI [0.99-2.06] p = 0.06), and median OS: 15.9 months (Arm A) *vs* 10.6 months (Arm B) (HR = 1.44; 95%CI [0.95-2.18] p = 0.08).

CONCLUSIONS:

In wtKRAS mCRC patients progressing after bevacizumab plus chemotherapy, continuation beyond progression with bevacizumab and crossover chemotherapy is associated with a numerically higher but not statistically significant median PFS and OS compared to cetuximab plus chemotherapy. Final data with KRAS and NRAS analysis will be presented at the meeting. Clinical trial information: NCT01442649

ASCO

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Head & Neck

Posters

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ESMO

Pazopanib in patients with progressive or metastatic (R/M) salivary gland carcinoma (SGC) : further evaluation of efficacy including tumor growth rates (TGR) analysis. H&N Unicancer Group, PACSA trial with the REFCOR. (J Guigay *et al.*, Abstract #986P)

Recherche et Développement

UNICANCER HEAD & NECK Group

Scientific articles

What specifications for a centre or network of excellence in clinical research? (V Diebolt *et al.*, Therapie. 2016 Feb;71(1):43-57. doi: 10.1016/j.therap.2015.11.003. Epub 2016 Feb 3.)

The Giens 2015 Workshop Round Table entitled "What specifications for a centre or network of excellence in clinical research?" took a viewpoint distinct from earlier work and studies on changes in clinical research activities in France. The purpose of the present work was to identify, starting from concrete examples, the main strengths and advantages of clinical research activity in France related, in part, to the background environment and also to the specific characteristics of the investigation centres considered to be among the most high-performance units in activity. The criteria retained were grouped into a set of specifications that could be used to establish a "label of excellence" upon which the different teams and clinical research centres could model themselves. It was thus considered that belonging to a centre or structured network with at least a national configuration, when this is possible for the medial topic in question, constitutes a real advantage. Four benchmarks were identified: the scientific and clinical expertise of the head investigator, as well as the qualification and operational capacity of the centre's team; definition and measurement of performance using clearly displayed indicators and evaluation procedures; the quality of the overall trial "process" and of each of its component steps; communication, because know-how and promotion go hand in hand, with the main objective of informing the professional and general public about the value of the research centre meeting the above-mentioned criteria, about its networks of competencies, and more generally, about the important assets of the background of clinical research in France. This sector of research is funded by the public authorities via calls for public grants, financial aids for structures supporting clinical research in the University Hospital Centres and other healthcare institutions allowing for a professionalization of the research occupations, and the national public health plans (cancer, rare disease, HIV).

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POSTERS

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