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Actualités Recherche – Nouveautés médicales

Édition spéciale : Les communications de la R&D d'Unicancer en 2017

ÉDITORIAL

2017, une nouvelle année de forte croissance

Christian Cailliot, Directeur de la Direction de la Recherche et du Développement d'Unicancer

La complémentarité des 20 Centres de lutte contre le cancer (CLCC), l'interdisciplinarité, la qualité de leurs experts, constituent une base unique sur laquelle l'activité de la R&D d'Unicancer s'appuie pour explorer de nouveaux domaines de la cancérologie. Ainsi, la R&D d'Unicancer participe activement à des avancées capitales en génomique, immunothérapie, radiothérapie ou encore en dépistage précoce et en données de vie réelle.

La progression de l'activité de R&D d'Unicancer a ouvert la voie à de nombreuses coopérations internationales (EORTC, NCIC, CRUK, SAKK, IBCSG…) et à des perspectives de recherche inédites, nous propulsant, et par là même les CLCC dont nous sommes l'émanation, comme une des références internationales de la recherche en cancérologie.

Cependant, nous restons très attachés à la participation de Centres investigateurs hors CLCC à nos essais permettant un accès égal pour tous les patients à l'innovation.

Trois grands projets ont marqué une nouvelle étape de la R&D d'Unicancer dans sa croissance :

- Le financement européen du projet MyPeBS, un essai international comparant le dépistage du cancer du sein basé sur le risque, au dépistage standard
- le lancement de l'étude Check'Up avec la fondation ARC, pour l'identification des facteurs prédictifs de réponse aux immunothérapies,
- le développement de la plateforme ESME poumon / immunologie qui comptera plus de 30 000 patients et évaluera les différentes stratégies thérapeutiques en « vraie vie ».

Ces projets témoignent de par leur portée, leur volume, et l'investissement financier qu'ils représentent, d'une progression significative de la taille des essais menés par la R&D d'Unicancer et par conséquence des enjeux qui y sont attachés.

Pour relever tous ces challenges, la direction R&D d'Unicancer s'est notamment adjoint en juillet 2017 la solide expérience en recherche clinique, à la fois hospitalière et industrielle, du Dr Claire Labreveux, en qualité de directrice scientifique adjoint au directeur de la R&D. Celle-ci sera donc tout naturellement amenée à me succéder dès la fin juin. Je suis persuadé que Claire avec cette formidable équipe seront à même de poursuivre la dynamique de la R&D d'Unicancer de ces sept dernières années.

Merci et à très bientôt certainement

2017, another year of strong growth

**Christian Cailliot,
Unicancer Research and Development Director**

The complementarity of the 20 French Comprehensive Cancer Centres (FCCCs), interdisciplinarity, and the quality of their experts form a unique basis on which Unicancer R&D's activity relies to explore new areas of cancerology. Thus, Unicancer R&D plays an active part in major advances in genomics, immunotherapy, and radiotherapy, as well as early screening and real-world data.

An increase in Unicancer R&D's activity has opened up the way to several forms of international co-operation (EORTC, NCIC, CRUK, SAKK, IBCSG, etc.) and to original research perspectives, making us – and, thus, the FCCCs that gave rise to us – one of the international references for cancerology research.

However, we remain committed to the participation of non-FCCC research centres in our trials, giving all patients equal access to innovation.

Three large-scale projects marked a new stage in the growth of Unicancer R&D:

- European financing for the MyPeBS project, an international trial that compares risk-based breast-cancer screening with standard screening,
- launching the Check'Up study with the ARC foundation, to identify factors that predict response to immunotherapies,
- developing the ESME lung / immunology platform, which will have over 30,000 patients and which will assess various therapeutic strategies in "the real world".

Through their scope, their volume, and the financial investment that they represent, those projects demonstrate a significant increase in the size of trials carried out by Unicancer R&D, and, thus, the challenges that are attached to them.

To take up all those challenges, in July 2017, Unicancer R&D's Directorate added the solid experience in clinical research – in hospitals and industry alike – of Dr. Claire Labreveux, who took up the post of deputy scientific director to the R&D Director, and she will be my natural successor at the end of June. I am convinced that Claire, with this great team, will be up to the task of continuing Unicancer R&D's dynamic built up over the last seven years.

Thank you, and until we meet again very soon.

Scientific articles

Triple-NOTE (Triple Negative OuTcome in ESME). Large recent real-world prognostic data on Triple Negative metastatic breast cancers (mTNBC)

(MP Sablin *et al.*, Journal of Clinical Oncology 2017 35:15_suppl, e12592-e12592).

BACKGROUND

During last decade, therapeutic arsenal has expanded for metastatic breast cancer (mBC), but few data are available about mTNBC, a poor prognosis subtype. In 2014, UNICANCER (composed of 18 French Comprehensive Cancer Centers) launched the Epidemiological Strategy and Medical Economics (ESME) program to centralize real-world data. This base represents a great opportunity to update the outcomes and the treatment practice patterns of this population.

METHODS

The ESME-mBC database was built from information systems, treatment databases and patients' electronic files including quality control processes. All pts who initiated treatment for mBC between 01-Jan-2008 and 31-Dec-2014 were selected. The primary objective of this study was to assess overall survival (OS) of mTNBC pts. TNBC status was defined as ER and PR < 10% in both primary and metastatic disease, as well as the absence of overexpression or amplification of HER2. The secondary objectives were to describe the characteristics of this population, clinical management (duration and sequence of treatments) and to evaluate the prognostic value of several clinical factors (age, distant disease free interval, location and number of metastatic sites).

RESULTS

Among 16703 pts in the ESME-mBC database, 2368 (14%) had mTNBC. Median OS over this time period was 14.8 months (95% CI 14-15.6). Median age at diagnosis of mBC was 57 years. For the pts who relapsed, median metastasis free interval was 24 months, while 25.5% of the pts were de novo metastatic. 61% of the pts presented visceral metastasis and 12% had cerebral metastasis as first metastatic site. The pattern of metastatic involvement (visceral and cerebral) and a short metastasis free interval (< 24 months) were the most important prognostic factors in multivariate analysis. The description of treatment sequences (duration, prognostic value) will be presented.

CONCLUSIONS

In this real-life setting database, mTNBC remain of poor prognosis despite a trend for a better OS than the historical data available (12-13 ms). This TNBC ESME cohort is one of the largest available and offers an updated assessment of the outcomes of this population.

Oral communications

EPICLIN 11 / 24e journée des statisticiens des CLCC

Données de vraie vie en oncologie. Méthodologie de constitution d'une plateforme de données exhaustive Multisource.

(T Guesmia *et al.*, Revue d'Épidémiologie et de Santé Publique 65:S49 · May 2017)

INTRODUCTION

Les données de vraie vie (RWD) ont un rôle important pour l'évaluation de l'efficience des médicaments et des stratégies thérapeutiques, et ce en complément des données provenant des essais cliniques contrôlés. La méthodologie de constitution de la plateforme de RWD ESME repose sur une approche multi sources pour centraliser et standardiser les données nationales relatives à la prise en charge (PEC) des patients dans les 18 centres de lutte contre le cancer.

MÉTHODES

La plateforme ESME, gérée par R&D Unicancer, intègre des variables issues de bases de données structurées (données relatives aux séjours hospitaliers et données sur les médicaments dispensés dans les centres), ainsi que des données non structurées issues du dossier patient informatisé (DPI). L'intégration des données du DPI implique une relecture systématique par des techniciens d'études cliniques spécifiquement formés, tenant compte si disponibles des données des bases locales (données des bases RCP, données issues de l'enquête permanente cancer si poursuivie…). La plateforme pour laquelle la gestion de l'anonymat est gérée centre par centre, regroupe l'ensemble des données anonymisées consolidées des différentes sources. Cette méthodologie fait l'objet de contrôles qualité, d'audit interne sur le recueil et de constitution de listes de présélection, ainsi que de contrôles de data-management systématiques. Les données collectées sont mises à jour annuellement et la plateforme intègre les données des patients nouvellement diagnostiqués.

RÉSULTATS ET DISCUSSION

Le premier volet de ce programme concerne la plateforme ESME « Cancer du sein métastatique » (CSM) pour laquelle les dossiers de 16 736 patients ont été sélectionnés et validés. L'objectif final est de 25 000 dossiers complétés validés attendus d'ici 2019. Il était important de pouvoir capter les patients PEC pour un CSM non hospitalisés et ne recevant pas de traitement dans le centre. Environ 12 % ont ainsi été identifiés comme étant exclusivement pris en charge par des thérapies orales ou hormonothérapie avec un suivi en consultation dans les centres. Le contrôle qualité (CQ) sur site du processus de sélection a été réalisé chez environ 20 % des dossiers non sélectionnés, et 13 % des dossiers sélectionnés ont été contrôlés manuellement pour certains critères majeurs. Ces critères seront détaillés avec les taux d'erreurs par critère et leurs implications pour l'exploitation des données. La plateforme ESME constitue une source unique en Europe de données en vie réelle pour la PEC du CSM. Elle est accessible à l'interrogation par des équipes de recherche ou des partenaires industriels, après validation des questions de recherche par le comité scientifique ESME (CSE), sous le contrôle d'un comité de déontologie et d'un comité consultatif international (dix projets de recherche sont actuellement en cours).

CONCLUSION

La plateforme ESME constituera à terme une source unique et indépendante d'analyse de données dans une grande variété de pathologies d'organes ou de domaines thérapeutiques en oncologie. Elle pourra contribuer à une meilleure compréhension de l'utilisation des stratégies thérapeutiques en vraie vie ainsi que leurs déterminants. Ces données peuvent guider la communauté scientifique vers une prise de décision adaptée au contexte et améliorer la PEC du patient en oncologie.

Posters

ASCO

Assessment of multiple endocrine therapies for metastatic breast cancer in a multicenter national observational study. (O Le Saux *et al.*, abstract # 1052)

Evolution of overall survival according to year of diagnosis (2008-2014) and subtypes, among 16703 metastatic breast cancer (MBC) patients included in the real-life «ESME» cohort (S Delaloge *et al.*, abstract # 1078)

ESMO

Use of Everolimus in advanced hormone receptor positive metastatic breast cancer in a multicenter national observational study (A. Lardy-Cleaud *et al.*, Abstract # 266P)

Survival of patients with aromatase inhibitors sensitive HR+/HER2 - metastatic breast cancer treated with a first-line endocrine therapy or chemotherapy in a multicenter national observational study (E Jacquet *et al.*, Abstract #265P)

FICHE-YOUNG: FIrst-line treatment CHoicE in hormone receptor positive (HR+)/ HER2- negative metastatic breast cancer patients (MBC) ≤45 years old. A large observational multicenter cohort survival analysis. (B Pistilli *et al.*, Abstract #280P)

SABCS

Impact of age at diagnostic of metastatic breast cancer on overall survival in the real-life «ESME» cohort (S Franck ***et al.,*** Abstract # P6-08-10)

Impact of loco-regional treatment (LRT) on overall-survival (OS) in patients with de novo metastatic breast cancer (MBC): results of the French ESME multicenter national observational programme. (E Pons-Tostivint *et al.*, Abstracct # P1-14-02)

Oral etoposide (VP-16) in heavily pre-treated metastatic breast cancer: a multicenter national observational study. (F Lerebours *et al.*, Abstract # P6-14-06)

Real-life activity of eribulin among metastatic breast cancer patients in the multicenter national observational ESME program (W Jacot *et al.*, Abstract # P6-14-02)

Long-term survival in HER2-positive metastatic breast cancer treated with first-line trastuzumab: Real-life results from the Curie ESME database (E Kaczmarek *et al.*, Abstract # P5-21-14)

Impact of prior adjuvant trastuzumab (aT) on clinical characteristics, patterns of recurrence and outcome in 2863 patients with Her2 positive (HER2+) metastatic breast cancer (MBC)- Results from the French ESME UNICANCER program (M Saghatchian *et al.*, Abstract # P5-20-03)

Scientific articles

Longitudinal serum metabolomics evaluation of trastuzumab and everolimus combination as pre-operative treatment for HER-2 positive breast cancer patients.

(E Jobard *et al.*, Oncotarget. 2017 Jun 28;8(48):83570-83584. doi: 10.18632/oncotarget.18784)

ABSTRACT

The mammalian target of rapamycin complex 1 (mTORC1) is an attractive target for HER-2 positive breast cancer therapy because of its key role in protein translation regulation, cell growth and metabolism. We present here a metabolomic investigation exploring the impact of mTOR inhibition on serum metabolic profiles from patients with non-metastatic breast cancer overexpressing HER-2. Baseline, treatment-related and post-treatment serum samples were analyzed for 79 patients participating in the French clinical trial RADHER, in which randomized patients with HER-2 positive breast cancer received either trastuzumab alone (arm T) or a trastuzumab and everolimus combination (arm T+E). Longitudinal series of NMR serum metabolic profiles were exploited to investigate treatment effects on the patients metabolism over time, in both group. Trastuzumab and everolimus combination induces faster changes in patients metabolism than trastuzumab alone, visible after only one week of treatment as well as a residual effect detectable up to three weeks after ending the treatment. These metabolic fingerprints highlight the involvement of several metabolic pathways reflecting a systemic effect, particularly on the liver and visceral fat. Comparison of serum metabolic profiles between the two arms shows that everolimus, an mTORC1 inhibitor, is responsible for host metabolism modifications observed in arm T+E. In HER-2 positive breast cancer, our metabolomic approach confirms a fast and persistent host metabolism modification caused by mTOR inhibition.

Oral communications

ASCO

PREDICTOR (UNICANCER GEP11) : Randomized phase II study of preoperative afatinib in untreated head and neck squamous cell carcinoma (HNSCC) patients

(C Le Tourneau *et al.*, Abstract #6021)

BACKGROUND

Afatinib, a pan-HER irreversible tyrosine kinase inhibitor, demonstrated limited antitumor activity compared to methotrexate in unselected recurrent and/or metastatic HNSCC patients (LUX-HN1, Machiels et al, Lancet Oncol 2015). The UNICANCER (GEP 11) PREDICTOR study's objective was to identify predictive and pharmacodynamic biomarkers of biological activity and efficacy of afatinib (EUDRACT N° 2010-024046-29).

METHODS

This open-label, randomized, multicentric, controlled, phase II study included untreated patients with operable T2-4N0-2M0 HNSCC of the oral cavity, pharynx and larynx, with a PS < 2, adequate organ function and LVEF > 50%. Patients were randomized (2:1) to: oral afatinib (A) 40mg/day (d) for 14-28d or no treatment (NT). Patients had pre-treatment tumor biopsies, tumor imaging, and PET CT scan, with a 2nd tumor imaging before surgery and a PET scan at D15. Adverse events were classified by NCI CTCAE criteria. Based on the biological primary endpoint of tumor reduction the sample size was designed to identify biomarkers associated with a 20% difference between the study arms.

RESULTS

61 patients were included (A: 41/NT: 20). 2 patients in the NT arm were not analyzed (consent withdrawal, no surgery). 7 patients in arm A received < 14d of treatment, including 6 patients with unacceptable toxicity. Afatinib-related toxicities were: grade (G)1 37%, G2 41%, G3 7%, G4 5%, and G5 0%. G≥3 toxicities were mainly gastrointestinal. Partial responses (RECIST1.1) were observed in 3 patients (7.3%) in arm A versus none in the NT arm (p = 0.018). Progressive disease was not observed in arm A versus 3 (16.6%) in the NT arm. Partial responses on PET CT scan by PERCIST were observed in 15/31 evaluable patients (48%) in arm A versus 1/15 (6.7%) in the NT arm (p = 0.005).

CONCLUSIONS

Afatinib given to HNSCC patients in the preoperative setting is safe and is associated with improved response according to RECIST1.1 and PERCIST compared to no treatment. Clinical trial information: NCT01415674

Posters

ASCO GU

Combined Abiraterone, salvage prostate bed Radiotherapy and LH-RH Agonists (CARLHA) in biochemically-relapsing prostate cancer patients following prostatectomy: a phase I study of the GETUG/GEP. (S Supiot *et al*, Abstract #45)

Scientific articles

Chemoradiation in elderly esophageal cancer patients: rationale and design of a phase I/II multicenter study (OSAGE).

(S Servagi *et al.*, BMC Cancer. 2017 Jul 13;17(1):483. doi: 10.1186/s12885-017-3465-4.)

BACKGROUND

The management of elderly patients with cancer is a therapeutic challenge and a public health problem. Definitive chemoradiotherapy (CRT) is an accepted standard treatment for patients with locally advanced esophageal cancer who cannot undergo surgery. However, there are few reports regarding tolerance to CRT in elderly patients. We previously reported results for CRT in patients aged ≥75 years. Following this first phase II trial, we propose to conduct a phase I/II study to evaluate the combination of carboplatin and paclitaxel, with concurrent RT in unresectable esophageal cancer patients aged 75 years or older.

METHOD / DESIGN

This prospective multicenter phase I/II study will include esophageal cancer in patients aged 75 years or older. Study procedures will consist to determinate the tolerated dose of chemotherapy (Carboplatin, paclitaxel) and of radiotherapy (41.4-45 and 50.4 Gy) in the phase I. Efficacy will be assessed using a co-primary endpoint encompassing health related quality of life and the progression-free survival in the phase II with the dose recommended of CRT in the phase I. This geriatric evaluation was defined by the French geriatric oncology group (GERICO)

RESULTS

Among 16703 pts in the ESME-mBC database, 2368 (14%) had mTNBC. Median OS over this time period was 14.8 months (95% CI 14-15.6). Median age at diagnosis of mBC was 57 years. For the pts who relapsed, median metastasis free interval was 24 months, while 25.5% of the pts were de novo metastatic. 61% of the pts presented visceral metastasis and 12% had cerebral metastasis as first metastatic site. The pattern of metastatic involvement (visceral and cerebral) and a short metastasis free interval (< 24 months) were the most important prognostic factors in multivariate analysis. The description of treatment sequences (duration, prognostic value) will be presented.

DISCUSSION

This trial has been designed to assess the tolerated dose of CRT in selected patient aged 75 years or older.

Scientific articles

Patterns of relapse in poor-prognosis germ-cell tumours in the GETUG 13 trial: Implications for assessment of brain metastases

(Y Loriot *et al.*, Eur J Cancer. 2017 Dec;87:140-146. doi: 10.1016/j.ejca.2017.09.029)

BACKGROUND

The GETUG 13 phase III trial tested personalised chemotherapy based on tumour marker decline in patients with poor-prognosis germ-cell tumour (GCT) and demonstrated that a dose-dense regimen improves progression-free survival in patients with an unfavourable decline. We investigated the pattern of relapse for patients included in GETUG 13.

METHOD

We conducted an analysis of relapse events in patients from GETUG 13. Baseline procedures before inclusion in the trial comprised a thoraco-abdomino-pelvic computed tomography scan and a magnetic resonance imaging of the brain.

RESULTS

With a median follow-up of 4.1 years (0.3; 8.8 years), a progression event was observed in 109/254 patients (43%). First event consisted in a marker progression only in 47 patients (43%), a radiographic progression only in 35 patients (32%), a mix progression on both markers and imaging in 12 patients (11%) and death in 15 patients (14%). In patients with radiographic progression only, brain was the predominant site (n = 19/35, 54%). Among patients with unfavourable decline who experienced a radiographic progression (as first and subsequent progression event, n = 58), brain was a site of progression in 28 patients (48%): 12/30 (40%) in patients treated with cisplatin, bleomycin and etoposide and 16/28 (57%) in those treated with dose-dense chemotherapy.

CONCLUSION

Brain metastases develop often, early and frequently as the only site of relapse in the course of poor-prognosis GCT. This raises the question of early detection and optimal treatment of brain metastases in these patients, e.g. by integrating a systematic brain MRI after 2-3 months of chemotherapy.

Q-TWiST analysis of patients with metastatic castrate naive prostate cancer treated by androgen deprivation therapy with or without docetaxel in the randomised phase III GETUG-AFU 15 trial.

(P Marinoi *et al.*, Eur J Cancer. 2017 Oct;84:27-33. doi: 10.1016/j.ejca.2017.07.008)

BACKGROUND

Early chemotherapy has recently become a new standard of care for patients with metastatic castrate-naive prostate cancer (mCNPC). The survival benefit is evident in patients with high-volume disease, but less clear in those with low-volume disease. Here, we assessed the trade-offs between toxicity and survival using a Quality-adjusted Time Without Symptoms of disease and Toxicity of treatment (Q-TWiST) analysis.

PATIENTS AND METHODS

This analysis was performed from the data of the Genito-Urinary Oncology Group (GETUG)-AFU 15 phase III trial evaluating the benefits of docetaxel (D) combined with androgen deprivation therapy (ADT) versus ADT alone in 385 mCNPC patients. Overall survival was partitioned into three periods, namely toxic phase of treatment (TOX), time before progression without toxicity (TWIST), and progression (PROG). These health states were weighted according to patients' utility to determine quality-adjusted survival times. In threshold analyses, utility for TOX and PROG were varied from 0 to 1.

RESULTS

A better quality-adjusted survival was found in the ADT + D arm when the utility for PROG and TOX states were ≤0.2 and ≥ 0.8, respectively. When the utility for PROG was 0.4 or more, ADT + D and ADT alone yielded similar quality-adjusted survival. When patients were stratified into high-volume versus low-volume disease, we found a significant Q-TWiST benefit in favour of the ADT + D arm only for high-volume patients when the utility for PROG was less than 0.35, while we found no benefit in low-volume disease patients, whatever the coefficients tested.

CONCLUSIONS

Early docetaxel may provide significant quality-adjusted survival benefits for patients with mCNPC, especially those with high-volume disease, depending on the values assigned to the times spent in the toxicity phase and after PROG. The Q-TWiST methodology is a useful tool for decision-making regarding trade-offs between survival, PROG and toxicity.

A randomized controlled trial of metastases-directed treatment in patients with metastatic prostate cancer using stereotactic body irradiation: A GETUG-AFU trial

(P Blanchard *et al.*, Cancer Radiother. 2017 Oct;21(6-7):491-494. doi: 10.1016/j)

ABSTRACT

The goal of treatment of metastatic prostate cancer remains palliation. The oligometastatic state could be the right time to intensify therapy by introducing metastases directed treatments. The aim of this trial was to evaluate the benefit of radiotherapy to all macroscopic metastatic sites and to the primary disease in patients with hormone sensitive oligometastatic prostate cancer.

Anticancer Activity and Tolerance of Treatments Received Beyond Progression in Men Treated Upfront with Androgen Deprivation Therapy With or Without Docetaxel for Metastatic Castration-naïve Prostate Cancer in the GETUG-AFU 15 Phase 3 Trial

(P lavaud, *et al.*, Eur Urol. 2017 Oct 23. pii: S0302-2838(17)30791-1. doi: 10.1016/j.eururo.2017.09.022)

BACKGROUND

Androgen deprivation therapy (ADT) plus docetaxel is the standard of care in fit men with metastatic castration-naive prostate cancer (mCNPC) following results from GETUG-AFU 15, CHAARTED, and STAMPEDE. No data are available on the efficacy of treatments used for metastatic castration-resistant prostate cancer (mCRPC) in men treated upfront with ADT plus docetaxel for mCNPC.

OBJECTIVE

To investigate the efficacy and tolerance of subsequent treatments in patients treated upfront with chemo-hormonal therapy for mCNPC.

DESIGN, SETTING AND PARTICIPANTS

Retrospective data from the GETUG-AFU 15 phase 3 trial were collected for treatments received for mCRPC.

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS

For the first three lines of salvage treatment for mCRPC we investigated the biochemical progression-free survival, maximum prostate-specific antigen (PSA) decline, overall survival, and tolerance.

RESULTS AND LIMITATIONS

Overall, 245 patients received at least one treatment for mCRPC. For docetaxel used in first-line, a PSA decline ≥50% was observed in 25/66 (38%) and in 4/20 patients (20%) who had received upfront ADT alone and ADT plus docetaxel (p=0.14). The median biochemical progression-free survival was 6.0 mo (95% confidence interval: 3.6-7.7) and 4.1 mo (95% confidence interval: 1.3-4.9), respectively. For docetaxel used in first- or second-line, a PSA decline ≥50% was observed in 36/80 (45%) and in 4/29 patients (14%) who had received upfront ADT alone and ADT plus docetaxel (p=0.07). PSA declines ≥50% were observed with bicalutamide in 12/28 (43%) and 4/23 patients (17%) who had received upfront ADT alone and ADT plus docetaxel. Among men treated upfront with ADT plus docetaxel who received abiraterone or enzalutamide for mCRPC, 10/19 patients (53%) achieved a PSA decline ≥50%. Few grade 3-4 events occurred. Study limitations include the observational design and retrospective characteristics of this analysis, without standardized therapeutic salvage protocols, and the limited number of patients in some of the treatment subgroups.

CONCLUSIONS

Docetaxel rechallenge following progression to mCRPC after upfront ADT plus docetaxel for mCNPC was active only in a limited number of patients. Available data on abiraterone and enzalutamide support maintained efficacy in this setting. The lack of standardized therapeutic protocols for men developing mCRPC limits the comparability between patients.

PATIENT SUMMARY

Rechallenging docetaxel at castration-resistance was active only in a limited number of patients treated upfront with chemo-hormonal therapy for metastatic castration-naive prostate cancer. Anticancer activity was suggested with abiraterone or enzalutamide in this setting.

Oral Communications

ASCO

The benefit of combining docetaxel to androgen deprivation therapy in localized and metastatic castration-sensitive prostate cancer as predicted by ERG status: An analysis of two GETUG phase III trials.

(S Rajpar *et al.*, Abstract #5012)

BACKGROUND

Combining docetaxel to androgen deprivation therapy (ADT) improves survival in metastatic castration-sensitive prostate cancer (CSPC) (Vale C, Lancet Oncol 2016; 17: 243-56) and it also improves relapse-free survival (RFS) in high-risk localized CSPC (Fizazi K, Lancet Oncol 2015; 16: 787-94). However it is unlikely that all patients (pts) derive a benefit from docetaxel treatment and identifying predictive biomarkers remains a major unmet need. A subset of prostate cancers contains TMPRSS2-ERG gene fusions leading to ERG overexpression.

METHODS

Pre-treatment prostate core biopsies were collected from 255/413 pts and 79/385 pts enrolled respectively in the GETUG 12 and GETUG 15 (Gravis G, Eur Urol 2016; 70: 256-62) phase 3 trials testing early docetaxel in high-risk localized and metastatic CSPC. ERG, PTEN, Ki67 and Rb expression was assessed using immunohistochemistry. RFS curves were compared using the Logrank test.

RESULTS

The median age was 63 years (46-77) and 62 years (49-76) in GETUG 12 and GETUG 15. ERG staining was positive in 88/191 (46%) and 33/79 (42%) pts with available tissue, respectively. In GETUG 12, docetaxel-based chemotherapy was associated with improved RFS in pts with ERG+ expression (HR = 0.55 [0.29-1.03]; 6-year RFS : 80% ADT+docetaxel vs 68% ADT alone), but not in pts with ERG- (HR = 1.10 [0.66-1.85]; 6-year RFS 55% ADT+docetaxel vs 60% ADT alone), interaction test: p = 0.02. Similar findings were observed in GETUG 15, which was used as a validation set: the median RFS was 10.7 (6.5-14.3) and 18.8 (9.8-41) months in pts with ERG+ cancers receiving ADT alone and ADT+docetaxel, and 10.6 (4.8-25.3) and 13.2 (9.4-24) months in pts with ERG- cancers. In contrast, no difference in patient outcome by docetaxel treatment was observed by PTEN, Ki67 and Rb expression.

CONCLUSIONS

Docetaxel-related benefit in men with CSPC is predicted by ERG expression. This biomarker may help better select pts for docetaxel treatment.

Posters

ASCO GU

Results of the GETUG-AFU 19 trial: A randomized phase II study of dose dense Methotrexate, Vinblastine, Doxorubicin and Cisplatin (dd-MVAC) with or without anti-Epidermal Growth Factor Receptor (EGF-R) monoclonal antibody panitumumab (PANI) in advanced transitional cell carcinoma (ATCC) (S Culine *et al.*, Abstract #307)

The acute toxicity results of the GETUG-AFU 22 study: a multicenter randomized phase II trial comparing the efficacy of a short hormone therapy in combination with radiotherapy to radiotherapy alone as a salvage treatment for patients with detectable PSA after radical prostatectomy (S Guerif *et al.*, Abstract #16)

Burden of Metastatic Hormone Sensitive Prostate Cancer Identifies Men More Likely to Benefit from Early Docetaxel (G Gravis *et al.*, Abstract #136)

ASCO

Efficacy and safety of nivolumab in patients with metastatic renal cell carcinoma (mRCC) and brain metastases: Preliminary results from the GETUG-AFU 26 (Nivoren) study. (B Escudier *et al.*, Abstract #4563)

Scientific articles

Development and validation of an ELISA method for the quantification of nivolumab in plasma from non-small-cell lung cancer patients.

(A Puszkiel *et al.*, J Pharm Biomed Anal. 2017 May 30;139:30-36)

ABSTRACT

Nivolumab, an anti PD-1 monoclonal antibody, has been approved for the treatment of previously treated advanced or metastatic non-small-cell lung cancer (NSCLC). The aim of this study was to develop and validate an ELISA method for the quantification of nivolumab in plasma from patients with NSCLC in order to perform future pharmacokinetic/pharmacodynamic (PK/PD) studies. A home-made ELISA was developed and validated according to the general recommendations for the immunoassays. Then, the ELISA method was applied to quantify plasma trough levels (Cmin) of nivolumab (3mg/kg every two weeks) in 27 NSCLC patients at days 14, 28 and 42 after start of treatment. Blood samples were collected just before the infusion on days 0 (baseline), 14, 28 and 42 after start of treatment. The dynamic calibration range for nivolumab assay was 5-100µg/mL. Within- and between-day imprecision for quality controls (5, 20 and 75µg/mL) were less than 5 and 12%, respectively. The mean (±standard deviation) nivolumab Cmin was 17.3±4.8µg/mL (coefficient of variation, CV=27.8%), 25.0±9.7µg/mL (CV=38.8%) and 33.0±12.9µg/mL (CV=39.1%) on days 14, 28 and 42, respectively. IgG (p=0.002) and ALT (p=0.041) were independently associated with plasma nivolumab Cmin at day 42. The present ELISA method for quantification of nivolumab in plasma from NSCLC patients is sensitive and accurate enough to be used for further PK/PD investigations.

Pharmacogenetics of anti-cancer drugs: State of the art and implementation - recommendations of the French National Network of Pharmacogenetics.

(Quaranta S, Thomas F., Therapie. 2017 Apr;72(2):205-215)

ABSTRACT

Individualized treatment is of special importance in oncology because the drugs used for chemotherapy have a very narrow therapeutic index. Pharmacogenetics may contribute substantially to clinical routine for optimizing cancer treatment to limit toxic effects while maintaining efficacy. This review presents the usefulness of pharmacogenetic tests for some key applications: dihydropyrimidine dehydrogenase (DPYD) genotyping for fluoropyrimidine (5-fluorouracil, capecitabine), UDP glucuronosylstransferase (UGT1A1) for irinotecan and thiopurine S-methyltransferase (TPMT) for thiopurine drugs. Depending on the level of evidence, the French National Network of Pharmacogenetics (RNPGx) has issued three levels of recommendations for these pharmacogenetic tests: essential, advisable, and potentially useful. Other applications, for which the level of evidence is still discussed, will be evoked in the final section of this review.

Prevention of fluoropyrimidine toxicity: do we still have to try our patient's luck?

(R Danesi *et al.*, Ann Oncol. 2017 Jan 1;28(1):183.)

Scientific articles

Cabazitaxel in recurrent/metastatic squamous cell carcinoma of the head and neck: phase II UNICANCER trial ORL03.

(J Fayette *et al.* Oncotarget. 2017 Mar 4;8(31):51830-51839. doi: 10.18632/oncotarget.15901. eCollection 2017 Aug 1. PMID: 28881692)

ABSTRACT

Treatments are limited after platinum Cetuximab or anti-PD1 failure for patients with recurrent/metastatic head and neck squamous cell carcinoma. Cabazitaxel has increased overall survival in hormone-refractory metastatic prostate cancer after failure of Docetaxel. Our aim was to detect a signal of activity with Cabazitaxel in patients with head and neck cancer who had failed platinum-, Cetuximab- and taxanes-based chemotherapy. This multicenter phase II trial included progressive patients with an ECOG ≤2. Cabazitaxel was given at 25 mg/m2/3 weeks (maximum of 10 cycles), with growth factors support. Efficacy was centralized and assessed every 6 weeks. The primary endpoint was control rate at six-weeks. A Simon's two-stage optimal design (P0=0.10; P1=0.30) required 29 evaluable patients. At the end of trial, at least 6 non-progressions were required to consider the drug worthy of further study. Out of the 31 enrolled patients, 29 were eligible; 42% had received at least three previous lines of chemotherapy. For the primary end point, 8 patients (27.6%; 95%CI 12.7%-47.2%) had a stable disease at six weeks. Median progression-free survival was 1.05 months (95%CI 0.69-2.07). All patients were analyzed for toxicity: 6 patients had febrile neutropenia. During the 81 cycles administered, 49 grade 3-5 events were observed concerning 81% of the patients, including 35 severe adverse events of which 15 were related to Cabazitaxel. Although Cabazitaxel met its primary endpoint to deserve further investigations, its toxicity makes it difficult to use in frail patients and new schemes are needed (20 mg/m^2 for example) if further investigations are launched.

Scientific articles

Longitudinal serum metabolomics evaluation of trastuzumab and everolimus combination as pre-operative treatment for HER-2 positive breast cancer patients.

(E Jobard *et al.*, Oncotarget. 2017 Jun 28;8(48):83570-83584. doi: 10.18632/oncotarget.18784.)

ABSTRACT

The mammalian target of rapamycin complex 1 (mTORC1) is an attractive target for HER-2 positive breast cancer therapy because of its key role in protein translation regulation, cell growth and metabolism. We present here a metabolomic investigation exploring the impact of mTOR inhibition on serum metabolic profiles from patients with non-metastatic breast cancer overexpressing HER-2. Baseline, treatment-related and post-treatment serum samples were analyzed for 79 patients participating in the French clinical trial RADHER, in which randomized patients with HER-2 positive breast cancer received either trastuzumab alone (arm T) or a trastuzumab and everolimus combination (arm T+E). Longitudinal series of NMR serum metabolic profiles were exploited to investigate treatment effects on the patients metabolism over time, in both group. Trastuzumab and everolimus combination induces faster changes in patients metabolism than trastuzumab alone, visible after only one week of treatment as well as a residual effect detectable up to three weeks after ending the treatment. These metabolic fingerprints highlight the involvement of several metabolic pathways reflecting a systemic effect, particularly on the liver and visceral fat. Comparison of serum metabolic profiles between the two arms shows that everolimus, an mTORC1 inhibitor, is responsible for host metabolism modifications observed in arm T+E. In HER-2 positive breast cancer, our metabolomic approach confirms a fast and persistent host metabolism modification caused by mTOR inhibition.

Genomic diagnostics leading to the identification of a TFG-ROS1 fusion in a child with possible atypical meningioma

(M Rossing *et al.*, Cancer Genetics 212-213 (2017) 32–37)

ABSTRACT

Meningiomas are rare in children. They are highly complex, harboring unique clinical and pathological characteristics, and many occur in patients with neurofibromatosis type 2. Hereby, we present a case of a two-year-old boy presented with a diagnostically challenging intraventricular tumor. It was incompletely resected 6 times over 14 months but kept progressing and was ultimately deemed unresectable. Histologically, the tumor was initially classified as schwannoma, but extensive international review concluded it was most likely an atypical meningioma, WHO grade II. Comprehensive genomic profiling revealed a TFG-ROS1 fusion, suggesting that ROS1-signaling pathway alterations were driving the tumor growth. In light of this new information, the possibility of a diagnosis of inflammatory myofibroblastic tumor was considered; however the histopathological results were not conclusive. This specific molecular finding allowed the potential use of precision medicine and the patient was enrolled in the AcSé phase 2 trial with crizotinib (NCT02034981), leading to a prolonged partial tumor response which is persisting since 14 months. This case highlights the value of precision cancer medicine in children.

Oral Communications

SABCS

Mutational processes, genome evolution, and outcome in metastatic breast cancers

(A Patsouris *et al.*, Abstract #PD1-08)

BACKGROUND

To determine the distribution and evolution of mutational processes in metastatic breast cancers (mBC), together with their clinical relevance

METHODS

Whole exome sequencing (Hi-Seq, Illumina) and determination of copy number alterations (CNA) (CGH array / SNP6.0) were performed in 240 and 692 metastatic breast cancers respectively. Mutational processes were defined according to Alexandrov (Nature, 2013). Homologous Recombination Deficiency (HRD) was determined by genome wide assessment of loss-of-heteroygosity (LOH) on SNP6.0 (n = 210). Finally, genomic instability was assessed by the % of genome altered assessed by CGH / SNP6.0 Results: Whole exome sequencing showed that HR+/Her2- metastatic breast cancer presented an increased contribution of APOBEC-related signatures, as compared to early breast cancer (TCGA) (58% of the mutations vs 31%, p < 0.0001). Twelve percent of the HR+/Her2- mBC acquired an hypermutator genotype (> 200 non-synonymous mutations). This acquisition of an hypermutator genotype was confirmed in five paired primary-metastatic samples. An operational APOBEC-related signature 13 was associated with a poor outcome in a multivariate analysis (HR: 1.75, 95%CI: 1.1-2.7, p = 0.017). High LOH score (HRD) was observed in 30% of HR+/Her2- mBC as compared to 13% of early HR+/Her2- early BC (p < 0.0001). The opposite was observed in TNBC (43% in mTNBC versus 58% in early TNBC ,p = 0.032). High LOH score was associated with a trend for poor outcome in HR+/Her2- mBC (multivariate 1.67, 95%CI: 0.949-2.951, p = 0.075). The % of genome altered was associated with a poor outcome in multivariate analyses both in the overall and HR+/Her2- mBC (HR / 10 increase:1.144, 95%CI:1.038-1.261, p = 0.007 and HR:1.18, 95%CI:1.037-1.344, p = 0.012 respectively). Copy number analyses identified 143 genes that are more frequently amplified as compared to early breast cancers (FDR < 0.01)

CONCLUSIONS

Metastatic HR+/Her2- metastatic breast cancer present an increased in APOBEC-related mutational burden and in LOH score as compared to early breast cancers. APOBEC-related signature 13 and genome instability are associated with a poor outcome and could be used in the future to better stratify metastatic breast cancer patients.

ASH

Vemurafenib in Advanced Patients with Hairy Cell Leukemia (HCL): Results of the Acsé Phase II Trial

(X Troussard *et al.*, Blood 2017 130:156)

BACKGROUND

Targeted inhibitory therapy with BRAF-inhibitors has been used successfully in HCL patients refractory to or relapsing following previous lines of therapy. The AcSé-Vemurafenib study is the second exploratory multi-tumor 2-stage design phase II trial of AcSé program. We report the preliminary results of the HCL cohort in this nationwide program.

METHODS

BRAF mutational status was assessed on INCa molecular genetic platforms by either direct sequencing or NGS. Patients with BRAF V600E mutation, progressing after at least one standard treatment and who were not amenable to curative treatment could be included in the trial and receive vemurafenib 960 mg BID for up to 16 weeks. Objective Responses (OR) were centrally assessed using clinical and biological parameters every 8 weeks. Careful selection of eligible patients is mandatory since vemurafenib might cause secondary skin malignancies, photosensitivity, QTc-prolongation, liver enzyme elevations and arthralgia. However, vemurafenib has a perfect oral bioavailability, possibility of outpatient treatment, and the lack of hematological toxicity.

A Bayesian approach allows continuous monitoring of the OR. Sequential analyses were planned after 4-month follow-up of the first 10 pts, then every 5 pts until a maximum of 30 to 50 pts, to allow early stopping using an inefficacy bound for OR of 10%. Mean OR rate was estimated with its 95% Credibility Interval (CI). If no early stopping, the treatment was be considered worthy for further evaluation if, the predictive probability that the estimated OR is higher or equal to the efficacy bound p1 =30%, is > 90%.

RESULTS

From 10/2014 to 04/2017, 16/32 HCL harbored BRAF V600E mutation. Ten patients were enrolled, received vemurafenib and had at least one post-baseline assessment. Median age: 68 years [46-80] and 70% men. Median number of prior chemotherapy lines: 3 (0-8). Most frequent grade ≥3 adverse events (AEs) related to vemurafenib were arthralgia (40% of patients). Among the 10 BRAF V600E HCL patients evaluable for the best overall response (BOR) with a minimum follow-up of 4 months, 6 CR and 4 PR were observed. The futility stopping rule was not reached, and the bayesian estimation of the OR rate was 91.7% [95% CI:71.5-99.8]. Median duration of response was 9.2 months [6.4-NA]. Progression-free survival (PFS) rate at 4 months was 100% and median PFS was 14.1 months [8.5-NA]. Overall 1 patient died for progression and 9 are still alive.

CONCLUSION

Vemurafenib offers a feasible outpatient treatment option for relapsed/refractory patient without hematologic toxicity. These preliminary results prompt us to continue the AcSé program. Questions to be answered in the future are the optimal dosage and duration of vemurafenib, retreatment and the possibility to combine treatment with a MEK inhibitor.

Posters

ABC4 Lisbonne

Characteristics of the metastatic breast cancer population with PIK3CA mutation in the randomized phase II study SAFIR02 BREAST (UCBG- 0105/1304) (C Lefeuvre-Plessee *et al.*, Abstract # BP67)

ASCO

An open-label, phase II study of rucaparib, a PARP inhibitor, in HER2- metastatic breast cancer patients with high genomic loss of heterozygosity: RUBY. (A Patsouris *et al.*, Abstract #TPS1117)

ASH

Crizotinib in advanced ALK+ Anaplastic Large Cell Lymphoma in children and adults: results of the AcSé phase II trial (L Brugières *et al.*, Blood 2017 130:2831)

Scientific articles

Results of Methotrexate-Etoposide-Ifosfamide based regimen (M-EI) in osteosarcoma patients included in the French OS2006/Sarcome-09 study

(N Gaspar *et al.*, Eur J Cancer. 2018 Jan;88:57-66. doi: 10.1016/j.ejca.2017.09.036. Epub 2017 Nov 28.)

BACKGROUND

In most countries, reference chemotherapy for osteosarcoma is MAP regimen (M = high-dose methotrexate, AP = doxorubicin-cisplatinum). In France, the standard preoperative chemotherapy for children/adolescents combines M and etoposide-ifosfamide (EI), based on the OS94-trial. We report the safety and efficacy results of patients ≤25 years treated with preoperative M-EI regimen enroled in the French OS2006-study, between 2007 and 2014.

METHODS

Treatment comprised preoperative chemotherapy with the 7 M-courses and 2 EI-courses, then surgery and postoperative chemotherapy assigned by risk's groups: standard-risk (good histological response without metastases) received 12 M-courses, 3 EI-courses; high-risk (poor histologic response, initial metastases or unresectable primary) received 5 M-courses alternated with 5 AP-courses. 253 patients were randomised to receive (n = 128) or not (n = 125) zoledronate.

RESULTS

409/522 patients enroled in the OS2006 study who received preoperative M-EI were analysed. Median age was 14.3 years (4.7-24.5), with 55 patients aged 18-25 years. Primary tumour location was limb in 383 patients (94%) and 85 (21%) presented metastases. Median chemotherapy duration was 37.4 weeks. 381 (96%) patients underwent surgery, 258 patients (65%) had a good histologic response. 187/324 patients (58%) with localised disease did not receive doxorubicin nor cisplatinum. Toxicity was evaluated in the randomised study: most patients experienced ≥1 severe toxicity (grade IV haematological or grade III/IV extra-haematological). Median follow-up was 4.8 years, and 168 patients had events. Five-year event-free survival was 56% (95% CI, 51-62%) and overall survival 71% (66-76%).

CONCLUSION

M-EI regimen/strategy was feasible for patient aged ≤25 years with survival rates are comparable to those obtained with MAP regimen.

CD163-positive tumor-associated macrophages and CD8-positive cytotoxic lymphocytes are powerful diagnostic markers for the therapeutic stratification of osteosarcoma patients: An immunohistochemical analysis of the biopsies from the French OS2006 phase 3 trial.

(A Gomez-Brouchet *et al.*, Oncoimmunology. 2017 Aug 24;6(9):e1331193. doi: 10.1080/2162402X.2017.1331193. eCollection 2017).

ABSTRACT

The French phase 3 trial (OS 2006) testing zoledronic acid, an osteoclast inhibitor, with chemotherapy and surgery did not improve the outcome of patients with osteosarcoma (OS). To understand this unexpected result, the presence of infiltrating immune cells was investigated in 124 pre-therapeutic biopsies of patients enrolled in the trial. The percentage of CD68/CD163 tumor-infiltrating macrophages (TAMs), CD8+ lymphocytes, osteoclasts, and the PD1/PDL-1 checkpoint were assessed by immunohistochemistry. M1/M2 macrophage polarization was characterized by pSTAT1/CMAF staining. The expression of these biomarkers was correlated with clinical outcome. No statistical correlations were found with response to chemotherapy. High CD163 levels (>50% of cells per core; 43.8% of patients) were associated with CMAF nuclear expression and significantly correlated with better overall survival ($p = 0.0025$) and longer metastasis progression-free survival (MPFS, $p = 0.0315$) independently of metastatic status ($p = 0.002$). Only a trend was observed for patients with high CD68-positive cells ($p = 0.0582$). CD8+ staining was positive in >50% of cases with a median staining of 1%. Lower CD8+ levels were associated with metastatic disease at diagnosis and the presence of CD8-positive cells significantly correlated with improved overall survival in zoledronate-treated patients ($p = 0.0415$). PD1/PDL-1 staining was negative in >80% of cases and was not correlated with outcome. Finally, CD163-positive TAMs and CD8 positive cells are crucial prognostic biomarkers in OS, whereas PD1/PDL-1 checkpoint plays a minor role. For the first time, we described a correlation between CD8 positive cells and survival in zoledronate-treated patients. The immunohistochemical analysis of the microenvironment in biopsies may represent a novel tool for therapeutic stratification.

Prognostic impact of blood and urinary angiogenic factor levels at diagnosis and during treatment in patients with osteosarcoma: a prospective study.

(MD Tabone *et al.*, BMC Cancer. 2017; 17: 419. Published online 2017 Jun 15. doi: 10.1186/s12885-017-3409-z)

BACKGROUND

Angiogenesis is essential for the progression and metastatic spread of solid tumours. Expression of vascular endothelial growth factor (VEGF) has been linked to poor survival among osteosarcoma patients but the clinical relevance of monitoring blood and urine angiogenic factors is uncertain. The aim of this study was to determine the prognostic significance of blood VEGF and blood and urinary basic fibroblast growth factor (bFGF) levels in osteosarcoma patients, both at diagnosis and during treatment.

METHODS

Patients with localised or metastatic osteosarcoma enrolled in OS2005 and OS2006 studies between 2005 and 2011 were prospectively included in this study. VEGF and bFGF levels in serum and plasma and bFGF levels in urine were measured by ELISA at diagnosis, before surgery, and at the end of treatment. Endpoints considered for the prognostic analysis were histological response, progression-free and overall survival. Kruskal-Wallis tests were used to compare the distribution of baseline biomarker values across the different subgroups, and paired sample Wilcoxon rank tests were used to analyze changes over time. Association between biomarker levels and outcomes were assessed in multivariable models (logistic regression for histologic response, and Cox models for survival).

RESULTS

Samples were available at diagnosis for 269 patients (54% males; age ≤ 18 years: 73%; localised disease in 68%, doubtful lung lesions in 17%, and metastases in 15%). High serum VEGF and bFGF levels were observed in respectively 61% and 51% of patients. Serum and plasma VEGF values were not strongly correlated with one another ($r = 0.53$). High serum and plasma VEGF levels were significantly more frequent in patients with large tumours (≥10 cm; $p = 0.003$ and $p = 0.02$, respectively). VEGF levels fell significantly during pre-operative chemotherapy ($p < 0.0001$). No significant correlation was found between this variation and either the histological response, progression-free survival or overall survival ($p = 0.26$, $p = 0.67$, and $p = 0.87$, respectively). No significant association was found between blood or urinary bFGF levels and clinical characteristics, histological response, or survival.

CONCLUSIONS

Levels of VEGF and bFGF angiogenic factors are high in most osteosarcoma patients, but have no significant impact on response to chemotherapy or outcome in this large prospective series.

Oral Communications

ESMO

Results of the LMS03 phase II study evaluating gemcitabine combined with pazopanib as a 2nd-line treatment for metastatic/relapsed leiomyosarcomas (uterine or soft tissue) after failure of anthracyclinebased chemotherapy: the UNICANCER SARCOME 11 study.

(P Pautier *et al.*, Abstract #LBA57)

BACKGROUND

Leiomyosarcomas (LMS) represent 10-15% of soft tissue and visceral sarcomas, most frequently uterine. LMS are moderately chemosensitive. Options in 2nd-line therapy after anthracycline-based chemotherapy for metastatic/advanced disease include Gemcitabine (G), trabectedin and pazopanib (P) monotherapy. Currently no combination therapy is better than monochemotherapy. LMS03 is an open-label multicentre single-group phase II study designed to assess the efficacy and tolerance of G+P in this 2nd-line setting.

METHODS

Patients (pts) aged ≥18 years, ECOG ≤2 with metastatic or relapsed LMS (uterine or soft tissue) after 1st-line anthracycline chemotherapy failure were eligible. Pts were treated with G 1,000 mg/m2 on days 1 and 8 of each 21 day cycle (maximum 8 cycles), in combination with oral daily P (800 mg/day), until disease progression/unacceptable toxicity. Tumour response was assessed every 6 weeks (RECIST) with 9-month PFS rate as primary endpoint. Inacceptable and promising 9-month PFS rates were defined, in Intention-To-Treat (ITT), as 32% (Median PFS=5.5 months (mo)) and 44% (Median PFS=7.5 mo). Secondary objectives included control rate (CR/PR/SD), overall survival, toxicity.

RESULTS

From 2011 to 2016, 18 French centres included 106 pts: mean age of 59.8 years, mainly women (85.8%), ECOG 0 (63.5%), and uterine LMS (61%). Pts were treated with P+G for a median of 3.8 mo; 40 pts (38%) completed the 8 cycles of combination. Pts were treated with P for a median of 4.2 mo. The 9-mo PFS was 32.1% (CI 95% 23.2-41.4; n = 105, ITT) and 34.6% (CI 95% 24.9-44.4; n = 95, per-protocol). Median PFS was 6.5 mo (CI 95% 5.6-8.2; n = 105, ITT) and 7.1 mo (CI 95% 5.7-8.3; n = 95, per-protocol). The 12-week control rate was 83.6% (11 PR and 45 SD; 67 pts evaluable). Grade 3-4 AE (>30%) with P+G were: neutropenia (76 [72.4%]), leucopenia (59 [56.2%]) and thrombocytopenia (40 [38.1%]).

CONCLUSIONS

The study results are negative in ITT with median PFS < 7.5 mo but nearly positive when considering per protocol results. In term of safety the combination P+G could be well managed, without unexpected toxicity.

Scientific articles

QUALIOR Study: the Feasibility and Efficacy of a Home based Standardised Adapted Physical Activity Programme of Patients Receiving Oral Targeted Therapy for Metastatic Cancer Randomised, Phases II–III Unicancer–AFSOS Supportive Care Intergroup Study

(F Joly *et al.*, Oncologie Volume 19, Numéro 1-2, Janvier-Février 2017, 16-20.doi:10.1007/s10269-017-2678-4)

ABSTRACT

The adverse effect most commonly reported by patients treated with oral targeted therapies for advanced cancer is the onset of fatigue, which may be a limiting factor in long-term tolerance of these treatments. Adapted physical activity (APA) has a demonstrated its beneficial effect on the level of fatigue experienced by patients treated for localised cancer and, under certain circumstances, has shown an improvement in survival. The majority of studies were conducted in the post-cancer period or during the treatment phase, with chemotherapy and/or radiotherapy. Very few studies have been carried out on patients treated with oral targeted therapies. APA programmes vary in quality in terms of their objectives and the ways in which they are carried out and assessed. Particularly for patients with fatigue who have an advanced illness, it is important to assess supervised, home-based APA programmes. The QUALIOR study, sponsored by Unicancer, is a phase II–III randomised study, with the aim of thoroughly assessing the implementation of a 3-month home-based APA programme for more than 300 patients treated with targeted therapy for an advanced cancer (including breast, kidney and lung cancer plus a diverse cohort) in improving fatigue and quality of life, as well as full-term treatment compliance. A secondary objective is to evaluate progression-free survival. This programme is also assessed for its medico-economic relevance. The feasibility of the APA programme, which has been designed with various intensity levels, is assessed during the phase II study, which will then be continued with a phase III study to measure the programme's efficacy. The final objective is to provide access to supervised APA sessions, specifically aimed at patients treated with these new targeted therapies, within the framework of a supportive care activity.

L'essai FARADI: efficacité et tolérance du citrate de fentanyl dans les accès douloureux induits lors des examens diagnostiques ou thérapeutiques chez des patients souffrant de cancer

(L labreze *et al.*, Oncologie Vol 19, Numéro 1-2, Janvier-Février 2017,26-31. doi: 10,1007/s10269-017-2680-6)

ABSTRACT

FARADI is a national multicenter protocol that evaluates the efficacy and safety of using transmucosal fentanyl when performing diagnostic examinations (imaging, PET scan) or therapy (radiotherapy). These examinations can induce, during the placement of patients, we can just say effectively: these examinations can induce violent painful episodes that often make it difficult for the patient to complete the program. These painful episodes can be managed with fentanyl citrate that, for now, is authorized for patients who have had an opioid therapy for at least 1 week. We hope to demonstrate that, if the indication is justified, this assessment and monitoring will allow patients to be examined under good conditions of tolerance. An ancillary study will include patients who meet the criteria of the marketing authorization of these products.

Posters

ASCO

A phase II-III, multicenter, randomized, open study evaluating the feasibility and efficacy of a supervised home-based standard physical exercise program, for metastatic cancer patients receiving oral targeted therapy: The UNICANCER SdS 01 QUALIOR study, ID-RCB: 2015-A01922-47 - NCT03169075 (F Joly *et al.*, Abstract #TPS10126)

Scientific articles

Optimal duration of adjuvant chemotherapy for high-risk node negative (N-) breast cancer patients: 6-year results of the prospective randomized multicenter phase III UNICANCER-PACS 05 Trial

(P Kerbrat *et al.*, Eur J Cancer. 2017 Jul;79:166-175.)

PURPOSE

Optimal duration of adjuvant chemotherapy in the treatment of early-stage breast cancer remained to be investigated rigorously for the standard regimens in widespread use in North America (doxorubicin/cyclophosphamide, AC) and Europe (5-fluorouracil/epirubicin/cyclophosphamide, FEC). Whether six cycles of FEC 100 present an advantage, or not, compared with only four cycles was tested directly in a phase III prospective multicentre trial.

PATIENTS AND METHODS

Between 2002 and 2006, 1515 women between 18 and 65°years of age, with node negative N(-) high-risk early-stage breast cancer, were included in the study following breast surgery and axillary lymph node dissection or procedure by sentinel node technique. Inclusion in the study required tumour size T ≥ 1 cm and at least one of the high-risk factors: T > 2 cm, negative oestrogen receptor/progesterone receptor (ER- and PR-), Scarff-Bloom-Richardson (SBR) grade II or III and age ≤ 35°years. Patients were randomly assigned to either six FEC 100 (Arm A) or four FEC 100 (Arm B). The trial was powered to detect an absolute difference ≥6% in disease-free survival (DFS) at 5°years.

RESULTS

At 6.1°years median follow-up, with 91 (12%) events recorded in Arm A versus 106 (14%) in Arm B, no statistically significant risk increase was associated with four versus six FEC 100: DFS (hazard ratio (HR) = 1.18; CI 95% [0.89-1.56], P = .24) and overall survival (OS) (HR = 1.39; CI 95% [0.91-2.13], P = .12).

CONCLUSION

Differences in chemotherapy duration did not induce notably different outcomes in our cohort of high-risk patients.

Circulating Tumour Cells and pathological complete response: independent prognostic factors in inflammatory breast cancer in a pooled analysis of two multicentre phase II trials (BEVERLY 1 & 2) of neoadjuvant chemotherapy combined with bevacizumab.

(JY Pierga *et al.*, Ann Oncol. 2017 Jan 1;28(1):103-109.)

BACKGROUND

We present a pooled analysis of predictive and prognostic values of circulating tumour cells (CTC) and circulating endothelial cells (CEC) in two prospective trials of patients with inflammatory breast cancer (IBC) treated with neoadjuvant chemotherapy combined with neoadjuvant and adjuvant bevacizumab.

PATIENTS AND METHODS

Nonmetastatic T4d patients were enrolled in two phase II multicentre trials, evaluating bevacizumab in combination with sequential neoadjuvant chemotherapy of four cycles of FEC followed by four cycles of docetaxel in HER2-negative tumour (BEVERLY-1) or docetaxel and trastuzumab in HER2-positive tumour (BEVERLY-2). CTC and CEC were detected in 7.5 and 4 ml of blood, respectively, with the CellSearch System.

RESULTS

From October 2008 to September 2010, 152 patients were included and 137 were evaluable for CTC and CEC. At baseline, 55 patients had detectable CTC (39%). After four cycles of chemotherapy, a dramatic drop in CTC to a rate of 9% was observed ($P < 0.01$). Pathological complete response (pCR) rate was 40%. No correlation was found between CTC or CEC levels and pCR rate. Median follow-up was 43 months. CTC detection (≥1 CTC/7.5 ml) at baseline was associated with shorter 3-year disease-free survival (39% versus 70% for patients without CTC, $P < 0.01$, HR 2.80) and shorter 3-year overall survival (OS) ($P < 0.01$). In multivariate analysis, independent prognostic parameters for shorter survival were absence of hormonal receptors, no pCR and CTC detection at baseline. CEC level at baseline or variations during treatment had no prognostic value.

CONCLUSION

In this pooled analysis of two prospective trials in nonmetastatic IBC, detection rate of CTC was 39% with a strong and independent prognostic value for survival. Combination of pCR after neoadjuvant treatment with no CTC detection at baseline isolated a subgroup of IBC with excellent OS (94% 3-year OS), suggesting that CTC count could be part of IBC stratification in prospective trials.

20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years.

(H Pan *et al.*, N Engl J Med 2017;377:1836-46.)

BACKGROUND

The administration of endocrine therapy for 5 years substantially reduces recurrence rates during and after treatment in women with early-stage, estrogen-receptor (ER)–positive breast cancer. Extending such therapy beyond 5 years offers further protection but has additional side effects. Obtaining data on the absolute risk of subsequent distant recurrence if therapy stops at 5 years could help determine whether to extend treatment.

METHODS

In this meta-analysis of the results of 88 trials involving 62,923 women with ER-positive breast cancer who were disease-free after 5 years of scheduled endocrine therapy, we used Kaplan–Meier and Cox regression analyses, stratified according to trial and treatment, to assess the associations of tumor diameter and nodal status (TN), tumor grade, and other factors with patients' outcomes during the period from 5 to 20 years.

RESULTS

Breast-cancer recurrences occurred at a steady rate throughout the study period from 5 to 20 years. The risk of distant recurrence was strongly correlated with the original TN status. Among the patients with stage T1 disease, the risk of distant recurrence was 13% with no nodal involvement (T1N0), 20% with one to three nodes involved (T1N1–3), and 34% with four to nine nodes involved (T1N4–9); among those with stage T2 disease, the risks were 19% with T2N0, 26% with T2N1–3, and 41% with T2N4–9. The risk of death from breast cancer was similarly dependent on TN status, but the risk of contralateral breast cancer was not. Given the TN status, the factors of tumor grade (available in 43,590 patients) and Ki-67 status (available in 7692 patients), which are strongly correlated with each other, were of only moderate independent predictive value for distant recurrence, but the status regarding the progesterone receptor (in 54,115 patients) and human epidermal growth factor receptor type 2 (HER2) (in 15,418 patients in trials with no use of trastuzumab) was not predictive. During the study period from 5 to 20 years, the absolute risk of distant recurrence among patients with T1N0 breast cancer was 10% for low-grade disease, 13% for moderate-grade disease, and 17% for high-grade disease; the corresponding risks of any recurrence or a contralateral breast cancer were 17%, 22%, and 26%, respectively.

CONCLUSIONS

After 5 years of adjuvant endocrine therapy, breast-cancer recurrences continued to occur steadily throughout the study period from 5 to 20 years. The risk of distant recurrence was strongly correlated with the original TN status, with risks ranging from 10 to 41%, depending on TN status and tumor grade. (Funded by Cancer Research UK and others.)

Oral Communications

ASCO

Standard anthracycline-based vs. Docetaxel-Capecitabine in early breast cancer: results from the chemotherapy randomization (R-C) of EORTC 10041/ BIG 3-04 MINDACT phase III trial

(F Cardoso *et al.*, Abstract #516)

BACKGROUND

The MINDACT trial demonstrated that 46% of breast cancer patients (pts) at high clinical (C) but low genomic (G) risk based on MammaPrint (70-gene signature), might safely forego adjuvant CT (Cardoso NEJM 2016). A second 1:1 randomization (R-C) was optional in all pts for whom CT was decided, between standard anthracycline-based regimens (AT) and experimental docetaxel 75 mg/m² IV + oral capecitabine 825 mg/m² bid x 14 days (DC), q3wks for 6 cycles after surgery.

METHODS

MINDACT included 6693 pts, of whom 2895 received CT. C-low/G-low pts were allocated to no CT, C-high/G-high to CT and those with discordant G/C results were randomized to use either G or C risk to decide use of CT. Primary endpoint for R-C was disease-free survival (DFS). Secondary endpoints included OS and safety. Statistical hypothesis: HR-0.76 in favour of DC.

RESULTS

A total of 1301 pts (45%), of whom 787 (61%) were C-high/G-high, 351 (27%) C-high/G-low, 137 (11%) C-low/G-high, and 26 (2%) C-low/G-low, were randomized to AT or DC. Main reason for not inclusion in R-C was CT given outside the trial. Compliance rates for R-C were 97% overall. At 5-years median follow-up, DFS was not significantly different between AT (649 pts) and DC (652 pts) [HR = 0.83 (0.60- 1.15, p = 0.263], and OS was similar in both arms (HR 0.91, 95% CI, 0.54- 1.53). For the relevant C-high/G-high group, DFS was also not different (5-years DFS 86.1 vs 88.1%; HR 0.83, 95% CI, 0.58-1.21). Of note, number of events is still small (AT: 30; DC: 27). Commonest adverse events in DC were grade 2 hand/foot syndrome (28.5% vs 3.3%), grade 2 diarrhea (13.7% vs 5.8%) and grade 1 peripheral neuropathy (27.1% vs 11.2%). Grade 2 anemia (14.2% vs 5.1%) and grade 4 neutropenia (24.6% vs 20.5%) were higher in AT. Cardiac events occurred in 9 pts overall, including 1 cardiac failure (AT), while 53 pts developed secondary cancers (AT: 32; DC: 21; leukemia: 2 in AT vs. 1 in DC). Four deaths occurred (AT:1 and DC:3) while on therapy.

CONCLUSIONS

Docetaxel-capecitabine did not improve DFS or OS, compared with standard anthracycline-based CT, including for the C-high/G-high group. Safety profile of both regimens was as expected. Clinical trial information: NCT00433589

ESMO

Not all small, node- negative (T1a-b N0) breast cancers are similar: Outcome results from an EORTC 10041/ BIG 3-04 MINDACT trial substudy

(K Tryfonidis *et al.*, Abstract # 150O_PR)

BACKGROUND

Adjuvant systemic therapy for pT1abN0 breast cancer is controversial, as these tumors overall have a low relapse risk. The best tool to identify a subgroup that would benefit from adjuvant treatment is unknown.

METHODS

This subgroup included patients with pT1abN0 tumors enrolled in MINDACT who had both their genomic risk G (per MammaPrint®) & clinical risk C (per a modified version Adjuvant! Online) assessed. Patients characterized as low-risk in both assessments were spared chemotherapy (CT), while in those characterized as C&G high CT was advised. Discordant cases were randomized to receive CT based on the C or the G result. Here, we report the 5-year rates of distant metastasis-free survival (DMFS), distant metastases-free interval (DMFI) & overall survival (OS) for pT1abN0 patients who received or not CT based on their G or C risk result.

RESULTS

826/6693 (12.3%) patients with pT1abN0 tumors were enrolled in MINDACT. 310/826 (37.5%) were ≥ 60 years & 525/826 (63.6%) postmenopausal. 727/826 samples were reviewed by central pathology; 585/727 (80.5%) were invasive ductal, 662/727 (91.1%) ER positive, 46/727 HER2 positive (6.3%) & 81/727 (11.1%) were grade 3 tumors. IHC subtype classification identified 426/727 (58.6%) as Luminal A; 193/727 (26.5%) Luminal B; 38/727 (5.2%) Luminal B/HER2 positive; 8/727 (1.1%) HER2- positive; 37/727 (5.1%) triple-negative tumors. Almost all patients (820/826; 99.3%) were clinical low-risk (CL). Overall, 624/826 (75.5%) were CL/GL & 196/826 (23.7%) were CL/GH (5 patients were CH/GL, no cases were CH/GH, 1 missing). 5-year DMFS for patients with CL/GH pT1abN0 tumors who received CT was 97.3% (95% CI, 89.4-99.3) vs 91.4% (95% CI, 82.6-95.9) for those who did not. 5-years DMFI & OS for these patients treated with CT were 98.8% (95% CI, 91.9-99.8) & 98.5% (95% CI, 89.6- 99.8) vs 91.4% (95% CI, 82.6- 95.9) & 95.8% (89.1- 98.4%) respectively for those who did not receive CT.

CONCLUSIONS

Biological characteristics can be used as determinants of adjuvant CT administration for T1abN0 tumors. An important portion (23.7%) of these small tumors was CL but GH (MammaPrint®) risk and derived a benefit from CT.

CLINICAL TRIAL IDENTIFICATION

The main MINDACT study: ClinicalTrials.gov number: NCT00433589, EudraCT number:2005-002625-31

Letrozole and palbociclib as neoadjuvant treatment in luminal breast cancer. Results of the UNICANCER-NeoPal study.

(P Cottu *et al.*, Abstract #LBA9)

BACKGROUND

Benefit of neoadjuvant chemotherapy in patients (pts) with luminal breast cancer (LBC) is limited. Palbociclib combined with endocrine treatment has shown impressive results in advanced LBC. We conducted a randomized parallel phase II study, assessing letrozole + palbociclib (LP) as neoadjuvant treatment in LBC.

METHODS

Postmenopausal women were eligible if they had a stage II-III ER-positive HER2-negative BC, not candidate for breast conserving surgery (BCS), with either a PAM50 luminal B, or a PAM50 luminal A profile with proven lymph node involvement (N+). A parallel 1:1 randomization proposed 6 courses of 3rd generation chemotherapy (FEC100 x 3 - docetaxel 100 x 3), or 19 weeks (wks) of L 2.5 mg/day plus P 125 mg/day, 3 wks/4. Surgery was performed at wk 20. Primary endpoint was locally assessed Residual Cancer Burden (RCB) rate. Main secondary endpoints included safety, response rate, positive and negative predictive values of PAM50 ROR (risk of recurrence)-defined status, centrally reviewed RCB, and BCS rates. The protocol planned that the trial should be stopped for futility if ≤ 5 local RCB 0-I events (16.7%) were observed in the first 30 pts in the LP arm.

RESULTS

Out of 184 screened pts, 106 women with Stage II-IIIA, PAM50-ascertained LBC were randomized. Pts had T1-2 (73%) or T3 (27%); N + (26.5%); luminal B (89%) tumors. Median ROR score was 68 (22-93). At interim analysis, RCB 0-I was observed in 1 pt in the LP arm and inclusions were stopped. At final analysis, local RCB 0/I/II/III was observed in 3.8%/3.8%/52%/40.4% of pts in the LP arm, and in 5.9%/9.8%/37.3%/47.1% in the chemo arm, respectively. Central and local RCB results were identical. ROR score was not predictive of RCB 0/1. Clinical objective response rates were 74.5% and 76%, and BCS rates 69.2% and 68.6%, in the LP and chemo arms, respectively. Ki67 final median value was significantly lower in the LP arm [3% (range 1-40) vs 8% (2-15), p=.017). Of 19 serious adverse events, 2 occurred in the LP arm and 17 in the chemo arm (p

CONCLUSIONS

Neoadjuvant LP led to a slightly lower pCR/RCB 0-I rate than chemo, however clinical response and BCS rates were similar in both arms and LP had a much better safety profile. Extensive analyses are ongoing.

SABCS

MAAT: Menses after Adjuvant Treatment. Prediction of menses recovery after chemotherapy for early breast cancer (BC) by using a nomogram model in UNICANCER PACS04 and PACS05 trials

(B Pistilli *et al*, Abstract # PD7-06)

BODY: PURPOSE

The likelihood of menses recovery (MR) is largely variable in premenopausal patients (pts) receiving adjuvant chemotherapy for BC. Quantifying this probability for each single patient could impact discussion of chemotherapy side effects and better individualize fertility counseling.We performed a pooled analysis from PACS04 and PACS05 randomized trials aiming to develop a nomogram to estimate the probability of menses recovery at 6 and 18 months (mos) after the end of adjuvant chemotherapy (CT) for premenopausal pts with early BC.

PATIENTS AND METHODS

The analyzed population consisted of 1683 pts who were premenopausal and ≤ 50 (out of 4524 enrolled in both trials). In PACS05 node-negative BC pts were randomized to 4 or 6 cycles of FE100C (standard arm); in PACS04 node-positive pts were randomized to 6 cycles of FE100C or 6 cycles of Epirubicin 75mg/m2 and Docetaxel 75 mg/m2 (ED75).Endocrine therapy (ET) (Tamoxifen) x 5 years was mandatory for ER+ BC. Variables significantly associated with MR in the univariate analysis (P<0.20) were included in the multivariate analysis. Using this data set, a logistic regression-based nomogram was developed to predict MR at 6 and 18 mos.

RESULTS

Pts' characteristics were: median age 43 (22-50), median body mass index (BMI) at baseline 22.6 (15.6-54.7), at the end of chemotherapy 22.8 (15.8-58.6). ED75 was administrated to 517 (30.7%), while 802 (47.7%) received 6FE100C, 364 (21.6) 4FE100C. Trastuzumab was given to 122 (7.2%), ET to 1229 (73%) pts. CT-induced amenorrhea was observed in 1407 (83.6%) pts. Factors associated to MR were assessed on 1210 pts (excluding pts who recovered menses during CT or of whom date of recovery was not specified). At a median follow-up of 90 mos, 28.2% (342/1210) of pts had recovered menstrual cycles: 11% (133/1210) at 6 mos and 24.3% (294/1210) at 18 mos. Multivariate analysis showed that younger age, higher BMI at the end of CT, non-alkylating agents and absence of ET were independently associated to MR.

Table1 Multivariate Cox regression analysis of menses recovery

Variables	HR (95%CI)	P value
Age	1.49 (1.16-1.93)	< 0.002
Age²*	0.99 [0.98-0.99]	<0.0001
BMI after CT	1.02 (0.99-1.04)	0.07
Alkylating agents	0.72 (0.57-0.90)	0.004
Endocrine Therapy	0.50 (0.40-0.62)	<0.001

** The quadratic term in the age variable accounts for the non-linearity of the relation between the age and the probability of recovering menses. Overall this probability tend to decrease when age increase with a greater decrease for the older patients.*

Nomogram concordance-index was 0.749 and 0.750 for predicting MR at 6 and 18 mos respectively. A better calibration was observed at 18 mos, comparing nomogram predictions with the actual probability of MR in the 1210 women.

CONCLUSION

Our analysis confirmed the possibility of developing a user-friendly nomogram for predicting menses recovery after adjuvant chemotherapy. As next step, we will externally validate our nomogram on CANTO premenopausal population, one of the biggest national cohorts aiming to assess the long-term impact of cancer treatments toxicities (UNICANCER NCT01993498 - http://etudecanto.org/)

FGFR1 / ZNF217 copy numbers and outcome in patients with node positive, HR+/Her2- early breast cancer: A genomic analysis of PACS04 trial

(F André *et al.*, Abstract # PD4-10)

BODY

Purpose: There is a need to identify which patients present a high risk of relapse after optimal adjuvant therapies, in order to better define which population of early breast cancer patients is eligible to new drugs. Previous studies have shown that gene copy numbers drive breast cancer progression. In the BIG1-98 trial, FGFR1 (8p11) and ZNF217 (20q13) amplifications were associated with poor outcome in patients with HR+/Her2- early breast cancers. In the present study, we aim to validate these findings using retrospective analysis of samples prospectively collected in a randomized trial (PACS04).

PATIENTS AND METHODS

Tumor DNA was extracted from FFPE samples obtained from patients included in PACS04 trial. This trial compared FEC to ED75 in patients with node positive, early breast cancer and included 3000 patients between 2001 and 2004. The biomarker study focuses on HR+/Her2- breast cancer. 500 samples were collected and hybridization was performed on 390. DNA copy numbers were assessed on 900 genes using Oncoscan FFPE assay kit. Prognostic value of FGFR1 (8p11) and ZNF217 (20q13) copy numbers was assessed in a Cox model that included prognostic parameters. Prognostic value was assessed using CNA as continuous variable, and with a predefined cut-off (CN>=3). Metastases-free survival (MFS) was chosen as endpoint for this biomarker study.

RESULTS

Tumor copy numbers alterations were obtained in 390 patients with HR+/Her2-, node positive, early breast cancer. 31% of the patients presented more than 3 lymph node involved, and 25% a poorly differenciated tumor. The median tumor size was 20 mm. 120 (30%) and 112 (28%) patients presented FGFR1 and/or ZNF217 gene gain with a cut-off for amplification predefined at 3 copies. When assessed as continuous variable, FGFR1 (HR: 1.02, 95%CI:1.007-1.04, p=0.0045) and ZNF217 (HR: 1.011, 95%CI:1.003-1.01, p=0.006) copy numbers were associated with MFS. The 10 years MFS rates were 68% (95%CI: 59-78%) and 85% (95%CI: 81-91%) in patients with FGFR1-gained and FGFR1-normal tumors respectively (HR: 2.51, 95%CI:1.56-4.01, p=0.0001). The 10 years MFS rates were 72% (95%CI:65%-83%) and 83% (95%CI: 77-87%) in patients with ZNF217-gained and ZNF217-normal tumors (HR: 1.79, 95%CI:1.12-2.86, p=0.013). In a multivariate analysis, FGFR1-gain (HR: 2.45, 95%CI:1.42-4.22, p=0.0012) and ZNF217-gain (HR:1.78, 95%CI:1.00-3.17, p=0.049) were associated with a higher likelihood of metastases and/or death. The 10 MFS rate was 88% (95%CI: 83-94%) for patients who presented FGFR1- and ZNF217-normal tumor (n=191), and 71% (95%CI: 66-76%) in patients presenting FGFR1 and/or ZNF217 gene gain.

CONCLUSION

Using samples prospectively collected in a randomized trial, this study validates the prognostic value of FGFR1- and ZNF217- copy numbers in patients who present HR+/Her2- early breast cancer. Exploratory analyses on copy number alterations, together with targeted sequencing are ongoing and will be presented.

Posters

ASCO

Pharmacogenetics revisits bevacizumab in breast cancer patients – An ancillary analysis of the UCBG trial COMET, a French multicentric prospective study from R&D UNICANCER. (G Milano *et al.*, Abstract #1079)

UNICANCER: prospective cohort study of treatment related chronic toxicities in patients (pts) with localized breast cancer (BC) (CANTO) (IM Vaz Duarte Luis *et al.*, Abstract #TPS10125)

SABCS

Overtime distribution and predictors of local recurrences (LRs) in patients with hormone receptor positive (HR+) and node positive (N+) breast cancers (BCs): 10 -year follow-up analysis of UNICANCER-PACS 01 and PACS04 trials (B Pistilli *et al.*, Abstract # P1-07-07)

CANTOCHEM: analysis of chemotherapy practice and early side effects in the 6090 first patients from the prospective CANTO cohort (P Cottu *et al.*, Abstract # P6-12-18)

Heterogeneity and variability of human epidermal growth factor receptor 2 (HER2) expression on Circulating Tumor Cells (CTC) in HER2 negative metastatic breast cancer patients treated with first line weekly paclitaxel and bevacizumab in a prospective cohort from the French Breast Cancer InterGroup Unicancer (UCBG): COMET study (JY Pierga *et al.*, Abstract # P2-01-02)

MammaPrint is cost-effective compared to clinical risk assessment in early stage breast cancer. (VR Retèl *et al.*, Abstract # P4-12-01)

Young age and the risk of disease recurrence as assessed by the 70-gene signature – an analysis from the EORTC 10041/BIG 03-04 MINDACT trial (K Aalders *et al.*, Abstract # P1-07-08)

Scientific articles

Health-related quality of life results from the PRODIGE 5/ACCORD 17 randomised trial of FOLFOX versus fluorouracilecisplatin regimen in oesophageal cancer

(C Bascoul-Mollevi *et al.*, Eur J Cancer. 2017 Oct;84:239-249)

BACKGROUND

A recent prospective randomised trial did not reveal significant differences in median progression-free survival between two chemoradiotherapy (CRT) regimens for inoperable non-metastatic oesophageal cancer patients. This secondary analysis aimed to describe the impact of CRT on health-related quality of life (HRQOL), physical functioning, dysphagia, fatigue and pain and to evaluate whether baseline HRQOL domains can predict overall survival.

Patients and methods

A total of 267 patients were randomly assigned to receive with 50 Gy of radiotherapy in 25 fractions six cycles of FOLFOX or four cycles of fluorouracil and cisplatin on day 1. HRQOL was prospectively assessed using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire version 3.0 with the oesophageal cancer module (QLQ-OES18).

RESULTS

Both groups showed high baseline compliance. Subsequently, compliance reduced to 41% at the 6-month follow-up. Baseline HRQOL scores showed no statistical differences between treatment arms. During treatment, both groups exhibited lower physical and social functioning and increased fatigue and dyspnoea, although dysphagia moderately improved in the fluorouracil-cisplatin arm only ($p = 0.047$). During follow-up, HRQOL scores revealed no significant differences between chemotherapy regimens. Linear mixed model exhibited a treatment-by-time interaction effect for dysphagia ($p = 0.017$) with a greater decrease in dysphagia in the fluorouracil-cisplatin group. Time until definitive deterioration analysis showed no significant differences in global HRQOL, functional or main symptom domains. However, time until definitive deterioration was significantly longer for the fluorouracil and cisplatin arm compared with FOLFOX for appetite loss ($p = 0.002$), QLQ-OES-18 pain ($p = 0.008$), trouble swallowing saliva ($p = 0.011$) and trouble talking ($p = 0.020$).

CONCLUSION

Analyses of HRQOL scores revealed no statistically significant differences between patients with inoperable non-metastatic oesophageal cancer treated by FOLFOX versus those treated with a fluorouracil-cisplatin regimen as part of definitive CRT.

Dynamic evaluation of circulating tumour cells in patients with advanced gastric and oesogastric junction adenocarcinoma: Prognostic value and early assessment of therapeutic effects.

(S Pernot *et al.*, Eur J Cancer. 2017 Jul;79:15-22. doi: 10.1016/j.ejca.2017.03.036. Epub 2017 Apr 26.)

BACKGROUND:

The identification of dynamic biomarkers in advanced gastric and oesogastric junction adenocarcinoma (GOA) could help to tailor strategies for each patient. Enumeration of circulating tumour cells (CTCs) is approved by the US Food and Drug Administration in breast, colon and prostate cancer but is not in advanced GOA. Our study aims to establish the optimal threshold and the clinical significance of CTC count in advanced GOA before and during treatment.

METHODS

One hundred six patients with untreated advanced GOA were included in the ancillary study of the PRODIGE 17-ACCORD 20 trial. CTCs were detected in the peripheral blood using the CellSearch system on day 0 (D0) and day 28 (D28). The prognostic value of CTCs at D0 and D28 was analysed by testing several thresholds.

RESULTS

At baseline, median CTC count was 1 (range, 0-415). While CTCs ≥1, 2 or 3 at D0 were all significantly associated with worse overall survival (OS) and progression-free survival (PFS), CTCs ≥2 were the optimal threshold, on D0 or D28. CTCs ≥2 at D28 were also predictive of disease control. Taking into account both D0 and D28 CTC count defined 3 groups (low/low, high/low and low-high/high) with significantly different PFS ($p = 0.0002$) and OS ($p = 0.003$).

CONCLUSION

Quantification of CTCs at baseline and during treatment may be a useful prognostic tool in advanced GOA, as it is associated with worse PFS and OS. A threshold ≥2 CTCs seems to have the best discriminant value. Change in CTC count between baseline and D28 could help to tailor treatment to each individual patient.

Retrospective analysis of CA19-9 decrease in patients with metastatic pancreatic carcinoma treated with FOLFIRINOX or GemcitabIne in a randomized phase III study (ACCORD11/PRODIGE4).

(M Robert *et al.*, Oncology 2017;93:367-376; (DOI:10.1159/000477850))

OBJECTIVES

Carbohydrate antigen 19-9 (CA19-9) is a sensitive and specific serum marker in pancreatic cancer. Our retrospective analysis aims to evaluate CA19-9 decrease in patients with metastatic pancreatic cancer treated in ACCORD11/PRODIGE4 (FOLFIRINOX vs. gemcitabine).

METHODS

A total of 342 patients were treated. CA19-9 was measured at 8 weeks (±2) in 160 patients from a total of 282 with abnormal CA19-9 values at baseline (gemcitabine arm, n = 75; FOLFIRINOX arm, n = 85). In the present study, 8-week CA19-9 decrease or greater CA19-9 decrease according to the 20 and 90% thresholds were analyzed. Progression-free survival (PFS) and overall survival (OS) were estimated in each subgroup.

RESULTS

In the FOLFIRINOX arm, patients with an 8-week CA19-9 decrease or greater CA19-9 decrease ≥20% showed improved median OS, PFS, and objective response rate. In the overall study population, median OS and PFS were significantly improved in patients with an 8-week CA19-9 decrease ≥20% (vs. <20%). The 8-week CA19-9 decrease was predictive of PFS (interaction test significant according to treatment arm; p = 0.006).

Conclusion

An 8-week CA19-9 decrease ≥20% is a prognostic factor for OS and PFS. The 8-week CA19-9 decrease (20% threshold) is predictive of PFS. It could help to evaluate the efficacy of FOLFIRINOX and gemcitabine regimens.

Late toxicities and clinical outcome at 5 years of the ACCORD 12/0405-PRODIGE 02 trial comparing two neoadjuvant chemoradiotherapy regimens for intermediate-risk rectal cancer.

(D Azria et al., Ann Oncol. 2017 Oct 1;28(10):2436-2442. doi: 10.1093)

BACKGROUND

Outcome of intermediate risk rectal cancer may be improved by the addition of oxaliplatin during 5-fluoruracil concomitant neoadjuvant chemoradiotherapy. The purpose of this study is to analyze the main clinical results of the ACCORD12 trial (NCT00227747) in rectal cancer after 5 years of follow-up.

PATIENTS AND METHODS

Inclusion criteria were as follows: rectal adenocarcinoma accessible to digital examination staged T3-T4 Nx M0 (or T2 Nx distal anterior rectum). Two neoadjuvant chemoradiotherapy regimens were randomized: CAP45 (RT 45 Gy + capecitabine) and CAPOX50 (RT 50 Gy + capecitabine and oxaliplatin). Main end point was sterilization of the operative specimen. Acute and late toxicities were prospectively analyzed with dedicated questionnaires.

RESULTS

Between November 2005 and July 2008, 598 patients were included in the trial. After a median follow-up of 60.2 months, there was no difference between treatment arms in multivariate analysis either for disease-free survival or overall survival (OS) [P = 0.9, hazard ratio (HR)=1.02; 95% confidence interval (CI), 0.76-1.36 and P = 0.3, HR = 0.87; 95% CI, 0.66-1.15, respectively]. There was also no difference of local control in univariate analysis (P = 0.7, HR = 0.92; 95% CI, 0.51-1.66). Late toxicities were acceptable with 1.6% G3 anal incontinence, and <1% G3 diarrhea, G3 rectal bleeding, G3 stenosis, G3-4 pain, G3 urinary incontinence, G3 urinary retention and G3 skeletal toxicity. There was a slight increase of erectile dysfunction over time with a 63% rate of erectile dysfunction at 5 years. There was no significant statistical difference for these toxicities between treatment arms.

CONCLUSIONS

The CAPOX50 regimen did not improve local control, disease-free survival and overall survival in the ACCORD12 trial. Late toxicities did not differ between treatment arms.

Oral Communications

Bevacizumab (Bev) or cetuximab (Cet) plus chemotherapy after progression with bevacizumab plus chemotherapy in patients with wild-type (WT) KRAS metastatic colorectal cancer (mCRC): final analysis of a randomized, multicenter, phase II study (PRODIGE 18).

(J Bennouna *et al.*, Abstract #4770)

BACKGROUND

Second-line treatment with chemotherapy plus Bev or Cet is now established as a valid option in mCRC. The main objective of this French multicenter, randomized open phase II trial, was to evaluate the Progression Free Survival (PFS) rate at 4 months with chemotherapy plus Bev or Cet in patients with disease progression after Bev plus chemotherapy.

METHODS

The main eligibility criterion was disease progression after bevacizumab + 5-FU with irinotecan or oxaliplatin in patients with WT KRAS exon 2 mCRC. Patients were randomized in Arm A (FOLFIRI or mFOLFOX6 plus Bev) or in Arm B (FOLFIRI or mFOLFOX6 plus Cet); the chemotherapy doublet was chosen according to the first line (cross over). Analyses were performed in ITT population. They were repeated on the KRAS + NRAS WT population and in the triple negative population (KRAS, NRAS, and BRAF negative).

RESULTS

From October 2010 to May 2015, 133 patients were included in 25 sites (1 patient ineligible): 85 males (64%), PS 0 (74, 56%), 1 (54, 41%), unknown (4, 3%). The 4-month PFS rate was 80.3% [95%CI (68.0% - 88.3%)] in Arm A and 66.7% [95%CI (53.6% - 76.8%)] in Arm B. Median PFS was 7.1 months in Arm A vs 5.6 months in Arm B (p = 0.060). Median OS reached 15.8 months in Arm A vs 10.4 months in Arm B (p = 0.073). Tumors samples were collected by a central laboratory and 95 were analysed using the KRAS/BRAF mutation analysis panel kit (KRAS exon 2,3,4 and BRAF V600E) and NRAS mutation detection kit (exons 2,3,4; Entrogen). On the whole, 81 patients were KRAS and NRAS WT (41 in Arm A and 40 in Arm B). Median PFS was respectively 7.8 months and 5.6 months in Arm A and Arm B (p = 0.076); median OS was 21.0 months in Arm A vs 10.7 months in arm B (p = 0.324). 73 were negative for the 3 genes (n = 36 and 37). Their median PFS were 8.2 months in Arm A) vs 5.7 months in arm B (p = 0.100). Median OS was 21.1 months vs 12.6 months (p = 0.365).

CONCLUSIONS

PRODIGE18 study is in favour of bevacizumab continuation beyond progression with chemotherapy cross over in WT RAS mCRC initially treated with first-line Bev plus chemotherapy.

Adjuvant GEMOX for biliary tract cancer: updated relapse-free survival and first overall survival results of the randomized PRODIGE 12-ACCORD 18 (UNICANCER GI) phase III trial.

(J Edeline *et al.*, Abstract #LBA29)

BACKGROUND

No standard adjuvant treatment is currently recommended in localized biliary tract cancer (BTC). Standard treatment for advanced BTC is gemcitabine combined with platinum-based chemotherapy. We aimed to assess whether GEMOX would increase relapse-free survival (RFS) while maintaining health-related quality of life (HrQoL).

METHODS

We performed a multicenter, randomized phase III trial. Patients were randomized, within 3 months of R0 or R1 resection of a localized BTC, to receive either GEMOX for 12 cycles (Experimental Arm A) or surveillance (Standard Arm B). Co-primary endpoints were RFS and HrQoL. 190 patients and 126 RFS events were required to show an increase of median RFS from 18 to 30 months.

RESULTS

Between July 2009 and February 2014, 196 patients were included in 33 French centers. Baseline characteristics were balanced: R0 resection rate was 86% (Arm A) vs 88% (Arm B), lymph node invasion was present in 37% vs 36%. In Arm A, a median of 12 cycles was delivered. Maximal grade of adverse events was grade 3 in 58% (Arm A) vs 22% (Arm B), and grade 4 in 17% vs 9%. After a median of 46.5 months, 126 RFS events and 82 deaths were recorded. The final RFS analysis did not show any statistically significant difference between the 2 arms, with a median of 30.4 months in Arm A vs 18.5 months in Arm B (log-rank p=0.47), Hazard Ratio (HR)=0.88 [95%CI: 0.62-1.25] (p=0.48). The Overall Survival (OS) was not different between the 2 arms, with a median of 75.8 months [95%CI: 34.4–NE] in Arm A vs 50.8 months [95%CI: 38.0–NE] in Arm B (log-rank p=0.74), HR=1.08 [95%CI: 0.70-1.66] (p=0.74). 24-months, 48-months and 72-months OS were 69%, 51% and 51% in Arm A vs 76%, 52% and 48% in Arm B, respectively. No benefit of adjuvant chemotherapy was seen in any subgroup analyses of RFS or OS.

CONCLUSIONS

Final RFS and first OS analysis confirmed the lack of benefit from adjuvant GEMOX in the PRODIGE 12 study. Combined analysis with other adjuvant trials is warranted.

Posters

Impact of Immune response-associated gene Polymorphisms on tumor response in Rectal Cancer Patients Treated with capecitabine +/- oxaliplatine and Radiation in the ACCORD-12/PRODIGE-2 phase III trial (V Boige *et al.*, Abstract #560P)

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