**Epreuve de l’UE O3 M2 Pharmacologie Filière Pro 2020-2021**

**19 janvier 2021 Durée de l’épreuve : 2 h (rédiger sur 2 copies différentes)**

**Question A (sans aucun document)  :**

1. Définition d’une inspection d’essai clinique. Différence avec un audit.
2. L’ANSM vous contacte afin de diligenter une inspection dans un essai médicamenteux dont vous vous occupez : Expliquez le déroulement d’une inspection A l'aide d'exemples, proposez un calendrier.

**Question B (documents autorisés, sans accès internet) :** Olaparib and durvalumab in patients with germline *BRCA* -mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study

Susan M Domchek et al Lancet Oncology, The, 2020-09-01, Volume 21, Numéro 9, Pages 1155-1164

**Summary**

Background. Poly (ADP-ribose) polymerase inhibitors combined with immunotherapy have shown antitumour activity in preclinical studies. We aimed to assess the safety and activity of olaparib in combination with the PD-L1-inhibitor, durvalumab, in patients with germline *BRCA1* -mutated or *BRCA2* -mutated metastatic breast cancer.

Methods. The MEDIOLA trial is a multicentre, open-label, phase 1/2, basket trial of durvalumab and olaparib in solid tumours. Patients were enrolled into four initial cohorts: germline *BRCA* -mutated, metastatic breast cancer; germline *BRCA* -mutated, metastatic ovarian cancer; metastatic gastric cancer; and relapsed small-cell lung cancer. **Here, we report on the cohort of patients with breast cancer**. Patients who were aged 18 years or older (or aged 19 years or older in South Korea) with germline *BRCA1* -mutated or *BRCA2* -mutated or both and histologically confirmed, progressive, HER2-negative, metastatic breast cancer were enrolled from 14 health centres in the UK, the USA, Israel, France, Switzerland, and South Korea. Patients should not have received more than two previous lines of chemotherapy for metastatic breast cancer. Patients received 300 mg olaparib in tablet form orally twice daily for 4 weeks and thereafter a combination of olaparib 300 mg twice daily and durvalumab 1.5 g via intravenous infusion every 4 weeks until disease progression. Primary endpoints were safety and tolerability, and 12-week disease control rate. Safety was analysed in patients who received at least one dose of study treatment, and activity analyses were done in the full-analysis set (patients who received at least one dose of study treatment and were not excluded from the study). Recruitment has completed and the study is ongoing. This trial is registered with [ClinicalTrials.gov](http://clinicaltrials.gov/) , [NCT02734004](http://clinicaltrials.gov/ct2/results?term=NCT02734004) .

Findings. Between June 14, 2016, and May 2, 2017, 34 patients were enrolled and received both study drugs and were included in the safety analysis. 11 (32%) patients experienced grade 3 or worse adverse events, of which the most common were anaemia (four [12%]), neutropenia (three [9%]), and pancreatitis (two [6%]). Three (9%) patients discontinued due to adverse events and four (12%) patients experienced a total of six serious adverse events. There were no treatment-related deaths. 24 (80%; 90% CI 64·3–90·9) of 30 patients eligible for activity analysis had disease control at 12 weeks.

Interpretation. Combination of olaparib and durvalumab showed promising antitumour activity and safety similar to that previously observed in olaparib and durvalumab monotherapy studies. Further research in a randomised setting is needed to determine predictors of therapeutic benefit and whether addition of durvalumab improves long-term clinical outcomes compared with olaparib monotherapy.

**Introduction**

*BRCA1* and *BRCA2* are tumour suppressor genes closely linked to breast cancer susceptibility. Pathogenic germline variants of *BRCA1* and *BRCA2* occur in approximately 5% of patients with breast cancer. 3 BRCA proteins help repair DNA double-strand breaks via the homologous recombination repair pathway. 4 Poly (ADP-ribose) polymerases (PARPs) are a family of enzymes involved in the repair of single-strand DNA breaks through base excision repair.

In the OlympiAD study, olaparib showed a significant benefit over standard chemotherapy in patients with germline *BRCA1* -mutated or *BRCA2* -mutated metastatic breast cancer. … 6

Durvalumab is a human IgG1 κ monoclonal antibody that inhibits binding of PD-L1 to its receptors PD-1 and CD80. Durvalumab is approved for the treatment of urothelial carcinoma 7 and unresectable stage 3 non-small-cell lung cancer. 8…

Immunotherapies combined with chemotherapy or a PARP inhibitor are being explored in various studies. …

**Methods**

Study design and participants

MEDIOLA is a phase 1/2, open-label, basket study done in 14 medical centres in the UK, the USA, Israel, France, Switzerland, and South Korea. The aim of the study is to evaluate safety and tolerability, pharmacokinetics, and antitumour activity of durvalumab in combination with olaparib in patients with advanced solid tumours in four patient cohorts: breast cancer associated with germline *BRCA1* and *BRCA2* mutations, ovarian cancer associated with germline *BRCA1* and *BRCA2* mutation, gastric cancer, and relapsed small-cell lung cancer. Results from the other cohorts have been reported previously. **Here, we present the breast cohort.**

Eligible patients were aged 18 years or older, had a deleterious germline *BRCA1* or *BRCA2* mutation (locally or centrally determined) with histological confirmation, had progressive, locally advanced, or metastatic, HER2-negative breast cancer, and had either triple negative metastatic breast cancer or were hormone-receptor positive.

…. Other inclusion criteria included Eastern Cooperative Oncology Group performance status 0–1, life expectancy 12 weeks or longer, and normal baseline organ and bone marrow function. Patients could not have received more than two previous lines of cytotoxic chemotherapy for metastatic breast cancer. …

Procedures

Patients received olaparib monotherapy 300 mg in tablet form orally twice daily for the first 4 weeks, and then a combination of olaparib 300 mg twice daily and durvalumab 1.5 g intravenously was administered every 4 weeks (28-day cycle) until disease progression or intolerable toxicity. The fixed durvalumab dose of 1.5 g every 4 weeks is equivalent in exposure to weight-based dosing (10 mg/kg every 2 weeks), but with greater ease of use. This dose was the recommended phase 2 dose determined in a phase 1 dose-escalation study of the combination. 12 Patients were able to withdraw from the study at any time. …

Tumours were assessed by investigator review of CT or MRI at baseline, 4 weeks after starting olaparib, and every 8 weeks thereafter using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Safety and tolerability were assessed by recording adverse events and serious adverse events as graded by Common Terminology Criteria for Adverse Events (version 4.03) and by documenting dose interruptions or reductions and treatment discontinuations. Safety assessments comprised measurements of haematology and clinical chemistry (on days 1, 8, 15, 22, and 29; then every 2 weeks until week 9; and then every 4 weeks thereafter).

For the biomarker analysis, archival tumour tissue was collected for all patients. Analysis of tumour cell and immune cell (PD-L1) expression was done using the VENTANA PD-L1 (SP263) assay (Roche, Basel, Switzerland) and quantified by a pathologist. PD-L1 tumour cell and immune cell cutoffs for positivity were set at 1% or higher. …. For this study, tumour mutational burden was assessed by Foundation Medicine (Cambridge, MA, USA) using methods previously described. …

Outcomes

The primary efficacy endpoint was disease control rate at 12 weeks, defined as the percentage of patients who had at least one complete or partial response in the first 12 weeks or stable disease that was maintained until RECIST 1.1 assessment at 12 weeks. Safety and tolerability were primary safety endpoints. Efficacy endpoints included disease control rate at 28 weeks, objective response rate, duration of response, progression-free survival, percentage change from baseline in tumour size at 12 and 28 weeks, best percentage change from baseline in tumour size, time to study treatment discontinuation or death, and overall survival.

Additional secondary endpoints included serum concentrations of durvalumab and olaparib at steady state during the monotherapy and combination therapy periods …

Statistical analysis

… A disease control rate of 55% or less was considered undesirable. These values resulted in a target sample size of 30 patients, the minimum sample size that results in type I error rates under 0.10 and type II error rates under 0.20.

… Kaplan-Meier methods were used to generate time-to-event curves and calculate medians (95% CIs) and IQRs for time to treatment discontinuation or death, overall survival, progression-free survival, and duration of response. 95% CIs for objective response rate and 90% CIs for disease control rate were calculated using exact

**Results**

Between June 14, 2016 and May 2, 2017, 34 patients were enrolled and received study treatment. Four patients were excluded from the activity analyses because they did not fulfil the predefined eligibility criteria (three patients had received more than two previous lines of chemotherapy for metastatic breast cancer and one had non-measurable bone-only disease); therefore, the full-analysis set comprised 30 patients. Baseline characteristics are shown in [table 1](https://www.clinicalkey.fr/tbl1) .

Table 1

Baseline characteristics

|  |  | **Patients (n=34)** |
| --- | --- | --- |
| Age, years | | 46 (37–52) |
| Sex | | |
|  | Female | 33 (97%) |
|  | Male | 1 (3%) |
| Race | | |
|  | White | 18 (53%) |
|  | Asian | 7 (21%) |
|  | Not available | 9 (26%) |
| *BRCA*mutation status | | |
|  | *BRCA1* | 16 (47%) |
|  | *BRCA2* | 18 (53%) |
| Hormone receptor status | | |
|  | Hormone receptor positive (ER positive or PgR positive) | 16 (47%) |
|  | Triple-negative breast cancer | 18 (53%) |
| Previous lines of chemotherapy | | |
|  | 0 | 9 (26%) |
|  | 1 | 11 (32%) |
|  | 2 | 10 (29%) |
|  | 3 | 2 (6%) |
|  | 4 | 1 (3%) |
|  | Not available | 1 (3%) |
| Previous platinum therapy | | 13 (38%) |
| PD-L1 expression in tumour cells | | |
|  | Positive (≥1%) | 10 (29%) |
|  | Negative (<1%) | 21 (62%) |
|  | Not available | 3 (9%) |

**\* Collection of these data not permitted in France.**

… . Immune-mediated adverse events were reported in 12 (35%) of 34 patients …. The most commonly reported durvalumab-related adverse events of special interest were diarrhoea (one [3%]) and hypothyroidism (five [15%]). 19 (56%) deaths occurred during the study, all of which were due to the disease under investigation. There were no treatment-related deaths. …

… Plasma concentration–time curves showed good overlap between the profile of olaparib as monotherapy (on day 1 and at steady state on day 22) and the combined therapy period ( [appendix p 12](https://www.clinicalkey.fr/sec1) ), suggesting no effect of durvalumab on olaparib exposure. Durvalumab exposure reached steady state at approximately week 16. Durvalumab exposure in combination therapy with olaparib was consistent with that observed in durvalumab monotherapy (data not shown). …

**Discussion**

The MEDIOLA trial tested the hypothesis that olaparib activity could be further enhanced by adding the PD-L1 inhibitor durvalumab without compromising safety. Here, we report the results in a cohort of patients with germline *BRCA1* -mutated or *BRCA2* -mutated, HER2-negative metastatic breast cancer. The combination of olaparib and durvalumab was well tolerated over the follow-up period. By contrast with other studies exploring other combinations of PARP inhibitors and immunotherapy, 11 MEDIOLA employed full doses of both drugs, based on a phase 1 study that showed the absence of dose-limiting toxicity in a heavily pretreated population. 12 No new safety signals, including no excess in immune-mediated adverse events, were observed, in line with those previously seen in respective monotherapy studies. …. 31

The observed primary endpoint of 12-week disease control rate of 80% exceeded the prespecified target of 75%; however, this target was based on a phase 2 trial 24 of more heavily pre-treated patients before the OlympiAD results were available…. 5 Although studies have suggested that adding immune checkpoint inhibitors to standard of care can lead to improved clinical outcomes, 10 we were not able to determine this in this study.

Limitations of the MEDIOLA study include the fact that it is a single-arm, open-label study with a small patient population and no comparator group. The study also enrolled a population with differing prognoses (hormone receptor positive and triple-negative breast cancer; zero, one, or two prior lines of chemotherapy), introducing potential confounders into subgroup analyses. The olaparib run-in reduced the exposure of some patients to durvalumab, which might have influenced the results.

In conclusion, findings from the MEDIOLA trial show that the combination of olaparib and durvalumab produced promising antitumour activity and was tolerable in patients with germline *BRCA1* -mutated or *BRCA2* -mutated metastatic breast cancer. Further research is needed to determine whether there are subsets of patients who benefit from the addition of durvalumab to olaparib, …

**QUESTIONS (et réponses attendues –mots clés-)**

1. En quoi ont pu consister les études précliniques évoquées ligne 16 ?

R : Modèles tumoraux animaux montrant que l’association est plus efficace qu’une molécule seule

1. Quels résultats préalables à cette étude ont pu justifier le choix d’une dose de 1,5 g administrée toutes 4 semaines en lieu et place du schéma d’administration qui avait été initialement utilisé lors du développement clinique : 10 mg/kg toutes les 2 semaines (lignes 72-75) ?

R : études pharmacocinétiques montrant que exposition (AUC) équivalentes (en moyenne et en termes de variabilités inter-individuelles)

1. Justifier la détermination du niveau d’expression de PD-L1 et du taux de mutations au niveau tumoral (lignes 83-87).

R : expression de PD-L1 et taux de mutations somatiques ont été identifiés comme facteurs prédictifs de réponse à l’immunothérapie et notamment au anti-PD1 et anti-PD-L1

1. A quels organes est-il fait référence ligne 68 et justifier ce critère d’inclusion.

R : fonctions rénales et hépatiques normales, critère d’inclusion des phases précoces (phase 1 ntamment)

1. Les résultats pharmacocinétiques (lignes 118-122) étaient-ils attendus?

R : oui, absence d’interaction PK entre 2 molécules de structure très différentes (un anti-corps monoclonal et une « petite molécule ») qui ont des voies d’élimination différentes (par les mêmes processus métaboliques

1. Justifier le terme “Basket” (lignes 11, 13 et 59) pour cette étude.

R : étude qui a inclus des patients ayant des localisations tumorales différentes (mais toutes porteurs de mutations de BRCA1/2)

1. Quelles sont, parmi les données du Tableau 1 (ligne 113), celles qui dont le recueil n’a pas été permis en France (justifier votre réponse).

R : Origine ethnique

1. Le critère principal d’efficacité (lignes 89-91) est-il le même que celui qui est utilisé pour les études de phase 2 consistant à évaluer l’activité antitumorale d’un cytotoxique ? Justifier une éventuelle différence.

R : pour les cytotoxiques, les patients « répondeurs » sont ceux ayant soit réponse complète, soit réponse partielle ; contrairement à ici où patients en maladie stable sont considérés comme « succès thérapeutiques » ce qui se justifie par les bénéfices cliniques prolongés qui peuvent être associés à cette situation

1. Les résultats obtenus pour cette cohorte de patients sont-ils encourageants pour la poursuite du développement de cette association? (justifier votre réponse).

R : Oui car tolérance acceptable et efficacité mais décevant car apparement pas supérieure à la monothérapie (PARP inhibiteur)

1. Quel(s) autre(s) essai(s) clinique(s) peut/doit envisager le promoteur à la suite de cette étude ?

Etude contrôlée vs. PARPi seul : mise en évidence d’un bénéfice de l’adjonction de l’immunothérapi globale ; ou, à défaut, identification de sous-groupes de patients pour lequel le bénéfice existe.