2015 EUROPEAN CANCER CONGRESS

25-29 September 2015

Vienna, Austria

SUMMARY

The European Cancer Congress (ECC 2015) combined the 40th European Society for Medical Oncology (ESMO) congress with the 18th congress of the European CanCer Organisation (ECCO) and was held 25 to 29 September, 2015. The meeting was organised in partnership with the European Society of Radiation and Oncology (ESTRO), the European Society of Surgical Oncology (ESSO), the European Academy for Cancer Research (EACR), the European Oncology Nursing Society (EONS), and International Society of Paediatric Oncology (SIOPE). The efforts of all partner organisations were united to continue advancing multidisciplinarity as the way forward to optimise the prevention, diagnosis, treatment, and care of cancer patients by encouraging participants to leverage knowledge, promote education and build awareness for patient-centred oncology.

Contents

GYNAECOLOGICAL CANCERS

ARIEL2: Genetic analysis of the tumour prospectively identifies patients with ovarian cancer most likely to respond to rucaparib

The phase II ARIEL2 trail aimed to identify BRCA mutations in patients with ovarian cancer and to evaluate patient outcome by mutation type. According to Rebecca Kristeleit, University College London, UK at least 50% of high-grade serous ovarian cancer may have homologous recombination deficiency (HRD), of which germline BRCA1 and BRCA2 mutations account for approximately one-third. A next generation sequencing (NGS) tumour-based HRD assay and a novel algorithm were used to assess the tumour BRCA status and to identify HRD tumours likely to respond to rucaparib, an inhibitor of (ADP-ribose) polymerase (PARP).

In part 1 of ARIEL2, patients with platinum-sensitive high-grade serious or high-grade endometrioid ovarian cancer patients with RECIST measurable disease were enrolled and stratified according to HRD tumour subgroups that had been assessed in archival and pre-treatment biopsies: mutated BRCA ($BRCA^{mut)}$, BRCA wild-type/high loss of heterozygosity [LOH^{high}] (BRCA-like), and $BRCA^{wt}/LOH^{low}$ (biomarker negative). Rucaparib was given to 204 patients with a median age of 65 (range: 31 to 86) years; 67% of patients had ECOG 0, 96% of patients were high-grade serious, and 43% had received 2 or more prior treatments.

Analysis of efficacy data from 171 patients showed that the primary endpoints, progression-free survival (PFS), and objective response rate (ORR; RECIST v1.1) criteria were met. Patients in the $BRCA^{mut}$ and BRCA-like cohorts demonstrated improved PFS and ORR following rucaparib compared to the biomarker negative subgroup: In 39 $BRCA^{mut}$, and 72 BRCA-like patients, PFS was median 285 (95%CI 222, not reached) days and 216 (95%CI 110, 430) days, respectively compared to median PFS of 111 (95%CI 107,166) days in 60 biomarker negative patients. The ORR (RECIST) was 69%, 29% and 13% in the $BRCA^{mut}$, BRCA-like, and biomarker negative cohorts, respectively. The median duration of ORR was 232, 170, and 127 days in the respective cohorts. The authors noted that the ORR by RECIST plus CA125 were similar in patients with germline and somatic BRCA mutations: 80% versus 84%, respectively.

Treatment-related adverse events (AEs) occurring in at least 15% of patients were generally low grade and comprised nausea, fatigue, dysgeusia, transient transaminases, decreased appetite, vomiting, constipation, anaemia, and diarrhoea. Part 2 of the ARIEL2 trial will evaluate the HRD response signature in 300 additional patients with ovarian cancer receiving ≥3 prior

chemotherapies to assess the utility of the signature, and the response to rucaparib in heavily pre-treated patients. NCT01891344. Kristeleit *et al.* Abstract 2700.

Practice point and future research opportunities

Rucaparib showed superior efficacy in patients with high-grade serious ovarian cancer and tumours showing HRD that were either BRCA mutated or BRCA-like, and was generally well tolerated.

Ovarian cancer patients likely to benefit from rucaparib prospectively identified by quantification of genomic loss of heterozygosity

PARP inhibitors target tumour cells with homologous recombination deficiency (HRD), which are thought to result from deleterious BRCA1/2 mutations ($BRCA^{mut}$) or other mechanisms that have not been fully elucidated. HRD displays a common phenotype of genome-wide loss of heterozygosity (LOH), leading Amit Oza, Princess Margaret Hospital, Toronto, Canada, and colleagues to evaluate whether the genomic phenotype of LOH can be used to identify BRCA-like HRD tumours most likely to be sensitive to the PARP inhibitor, rucaparib. They used comprehensive next generation sequencing (NGS)-based tumour genomic profiling to develop an HRD assay, which was used to profile pre-treatment screening biopsies and archival FFPE tumour samples from patients participating in part 1 of the phase II ARIEL2 study; genomic LOH was assessed by sequencing >3,500 evenly-distributed SNPs across the genome, the extent of genomic LOH (G_{LOH}) was quantified. The optimal G_{LOH} cut-off separating overall survival curves was determined and used to pre-specify high and low G_{LOH} (LOH^{high}, LOH^{low}) tumours. Known germline $BRCA^{mut}$ patient enrollment was capped. Response (by RECIST and GCIG CA-125) in 187 patients was then evaluated.

As of April 8 2015, review of 192 archival and 152 screening tumour samples produced 140 matched pairs from 206 patients with high-grade ovarian cancer enrolled in ARIEL2 part 1, which were profiled using the NGS-based HRD assay. These samples included 20% of enrolled patients were $BRCA^{mut}$ (10% germline, 10% somatic), and 7% of patients with genomic alteration in another known HR-pathway gene. Analysis of the matched pairs exhibited similar genomic LOH profiles (r=0.86). Consistent with BRCA mutations conferring HRD, $BRCA^{mut}$ tumours had significantly higher G_{LOH} than BRCA wild-type tumours ($p < 1e^{-7}$).

Receiver operating characteristic analysis of G_{LOH} cut-off showed it could be useful in identifying patients likely to respond to rucaparib (AUC=0.71, $p < 1e\text{-}^{4}$). The pre-specified G_{LOH} cut-off, was

used to detect LOH^{high} tumours in 54% of patients with BRCA wild-type. The response rates varied in patients according to G_{LOH} cut-off; the response rate following rucaparib in patients with LOH^{high} tumours was 43% versus 22% in patients with LOH^{low} tumours (p = 0.0072). The authors plan to apply the HRD signature prospectively to the primary analysis of the ongoing portion of the phase II ARIEL2 part 2 and the phase III maintenance studies of rucaparib in patients with high-grade ovarian cancer. NCT01968213. Oza *et al.* Abstract 2701.

Practice point and future research opportunities

This study demonstrated that a BRCA-like HRD signature assessing genomic LOH can be used to prospectively identify patients with high grade ovarian cancer and tumours expressing BRCA wild-type who may benefit from rucaparib. The signature will be further tested in the ongoing ARIEL3 trial of rucaparib.

Patients with rare tumours benefit from management by the French National Network dedicated to Ovarian Malignant Rare Tumours (TMRO)

Patricia Pautier, Institut Gustave-Roussy, Villejuif, France, and the PathGyn Group conducted an audit of the prospective collection of clinical data, dedicated multidisciplinary staff decisions, central pathological review, and patient follow-up recorded in the Ovarian Malignant Rare Tumours (TMRO) database since 2011. Rare ovarian tumours (ROT) have such a low incidence that the natural history, prognostic factors and definitive histological diagnostics have not been clearly identified, even though they represent more than 20% of all ovarian cancers. Adding to the complexity of devising treatment strategies is the extreme variability of the characteristics of patients who develop ROT, such as age, histologic subtypes, and the stage at diagnosis. In order to monitor the management of ROT in France, a national network with a dedicated system for referral and information gathering that includes 22 regional expert centers (REC) and 3 national centres was put into place in 2011 to provide equal access to expertise and new treatments for all patients with ROT.

This audit revealed that patients with ROT have increased yearly from 468 patients in 2011 to 1058 patients in 2014. Among patients diagnosed with ROT, 18% represent serous borderline tumours that required pathologist expertise to determine the degree of invasiveness. In 2014, 544 (45%) of these patients' tumours were reviewed by an expert pathologist and discussed within multi-disciplinary staff in reference centres, which compared favourably to just 166 (25%) patients having access to multidisciplinary staff in 2011. In all, 742 patients with ROT in the 2014 database are managed in REC compared to 294 cases in 2011. National centres were involved in carrying out

histological review and induced medical decision modifications for 9% of ROT cases. An increased number of uterine and cervix rare tumours, 216 in all, were also determined by clinicians to need histological and/or clinical advice in 2014. During the years of the network, the number of cases of all tumour types recorded has risen from a total of 468 cases in 2011 to 1058 cases in 2014. The tumour types contained in the network (cumulative number of cases) was stromal and sex-cord tumours (1030), germ cell (534), mucinous borderline (681), mucinous carcinoma (371), clear cell carcinoma (362), serous borderline tumours (556), low grade serous carcinoma (62), carcinoma (180), and small cell carcinoma (37). Research in this field should be vastly aided by the more than 30% of patients who signed informed consent for biology research in 2014. Pautier *et al.* Abstract 2705.

Practice point and future research opportunities

This audit demonstrates how networks improve disease management and research possibilities. The study clearly shows the patient benefit in management of rare ovarian tumour obtained with the organisation and coordination between reference centres and also the enhanced opportunities for epidemiology and research.

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AFFILIATION AND DISCLOSURE

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Disclosure

No conflicts of interest to disclose.

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