Conclusion Ngs can help classify rare diseases if the classical pathological diagnostics do not give a satisfying diagnosis. There are currently no clear treatment recommendations for STK11 adenexal tumors yet. International registries and solid clinical follow-up data are urgently needed to enhance our knowledge on these potentially aggressive tumors.

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ANTITUMOUR ACTIVITY OF DOSTARLIMAB BY PD-L1 AND TUMOUR MUTATION BURDEN IN PATIENTS WITHMismatch REPAIR DEFICIENT AND PROFICIENT TUMOURS IN THE GARNET TRIAL

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Introduction/Background Dostarlimab is a programmed death 1 (PD-1) inhibitor approved as monotherapy in patients with mismatch repair deficient (dMMR) recurrent/advanced endometrial cancer (EC) that has progressed on or after platinum-based chemotherapy or solid tumours that have progressed on or after prior treatment, with no satisfactory alternative treatment options. We report a post hoc analysis of antitumour activity by PDL1 expression and tumour mutational burden (TMB) in patients with dMMR and MMR proficient (MMRp) solid tumours in the GARNET trial.

Methodology GARNET (NCT02715284) is a phase 1, multicentre, open-label, single-arm study of dostarlimab in patients with advanced/recurrent solid tumours. Three expansion cohorts enrolled patients based on MMR status: dMMR (A1) and MMRp (A2) advanced/recurrent EC, and dMMR non-EC solid tumours (F). Patients received dostarlimab 500 mg IV Q3W for 4 cycles, then 1000 mg IV Q6W until progression or discontinuation. TMB and PDL1 were exploratory biomarkers. TMB status was determined by FoundationOne test; TMB-high (TMB-H) was defined as ≥10 mutations/Mb. PDL1 expression was determined by combined positive score (CPS) by Ventana assay; PDL1-high (PDL1-H) was defined as CPS ≥1. The study was not powered to assess antitumour activity within subgroups.

Results TMB-H and PDL1-H were common in dMMR solid tumours; PDL1-H was observed in 39.4% of MMRp EC tumours (table 1). Objective response rate (ORR) was higher in patients with TMB-H/PDL1-H tumours (55.6% for all cohorts, combined; Table). Safety for each cohort was previously reported.1 Conclusion PDL1-H and TMB-H were frequently observed in the dMMR EC and non-EC cohorts, regardless of tumour type; PDL1-H was also prevalent in MMRp EC tumours. Although not a powered analysis, ORR by BICR per RECIST v1.1 was higher in patients with TMB-H and PDL1-H solid tumours. Across cohorts, dMMR status was predictive of response.

REFERENCE

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IMMUNOTHERAPY RESPONSE MONITORING USING PERSONALIZED CIRCULATING TUMOR DNA ANALYSIS IN PATIENTS WITH RELAPSED GYNECOLOGIC MALIGNANCIES

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Introduction/Background Immunotherapy has transformed cancer care. Unfortunately, responses within gynecologic malignancies have been modest when compared to other disease sites. Biomarkers for early determination of treatment benefit are urgently needed to spare unnecessary toxicity and cost. We evaluated if circulating tumor DNA (ctDNA) dynamics enable early detection of progressive disease (PD) and treatment response in patients with recurrent, gynecologic malignancies receiving immunotherapy.

Methodology Longitudinal plasma samples (n=138) were collected from 25 patients with recurrent cervical (N=6), endometrial (N=12), or ovarian (N=7) cancers who received immunotherapy. A personalized, tumor-informed multiplex PCR assay (SignaterraTM bespoke mPCR NGS assay) was used for the detection of ctDNA in plasma samples.

Results Pre-treatment samples were available for 9 patients (78% ctDNA detection rate) and all 25 patients had on-treatment samples (68% ctDNA detection rate). Serially ctDNA negative patients (3/15 with imaging) had no evidence of disease on-treatment. ctDNA clearance was observed in 3 (cervical, N=2; endometrial, N=1) of the remaining 12 patients and correlated with clinical benefit. ctDNA decreased in additional 2 patients, both with objective response, while all 7 patients with increased ctDNA had PD. Increased ctDNA
predicted PD prior to imaging by an average of ~2.5 months (lead-time) and was significantly associated with worst progression-free survival (PFS) compared to patients with decreased ctDNA (HR=0.14, 95%CI: 0.03–0.60; p<0.01). TMB and MSI status (binary) were not predictive of response in univariate (p=0.4, p=0.4) analyses.

Conclusion ctDNA dynamics can accurately predict clinical benefit and allow for early prediction of PD in patients with advanced ovarian cancer receiving immunotherapy. Further study is warranted to evaluate the clinical utility of a personalized, tumor-informed ctDNA assay in patients with gynecologic malignancies undergoing systemic therapies.

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HIGH EXPRESSION OF FAP+ CANCER-ASSOCIATED FIBROBLASTS PREDICT POOR OUTCOME IN PATIENTS WITH HIGH-GRADE SEROUS OVARIAN CANCER WITH HIGH CD8-POSITIVE T-CELL INFILTRATION
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Introduction/Background Tumor biology studies have implied that fibroblasts act as negative regulators of immune cell function in cancer. We investigated the impact of FAP-positive cells in high-grade serous ovarian cancer (HGSC) in relation to CD8 expression.

Methodology A discovery cohort (N=113) of HGSC was subjected to immunohistochemistry (IHC) of FAP and CD8. Marker status was correlated with overall survival (OS) and progression-free survival (PFS). Findings were confirmed in a validation cohort (N=121) and in public available datasets (TCGA and GSE9891).

Results We confirmed previous findings that high density of CD8+ cells in HGSC is associated with longer OS compared to low density (HR 0.55; 95% CI 0.33–0.85; p=0.008). In the discovery cohort high intensity of FAP was associated with shorter median PFS in cases with high density of stromal CD8+ cells (11.4 versus 18.6 months) compared to low intensity of FAP (p=0.007). In contrast, high intensity of FAP was not associated with PFS in cases with low density of CD8+ cells. In the validation cohort, high intensity of FAP in the patients with high density of stromal CD8+ cells was associated with shorter OS compared to low intensity of FAP (p=0.01). This association was not seen in the cases with low density of CD8+ cells. The association between high FAP expression and poor outcome in the high density CD8+ group was confirmed in two independent gene-expression data sets, with a shorter PFS in the TCGA dataset and shorter PFS and OS in the GSE9891 dataset.

Conclusion The study shows a specific FAP positive fibroblast-subset of cases with poor prognosis restricted to a CD8 high density group of HGSC. Therapy targeting the immunosuppressive action of fibroblasts may be a tool to enhance the known positive prognostic effect of CD8-cells in ovarian cancer and may be explored in T-cell depended immune therapy.