Guidance by molecular selection improves the outcome of early phase treatment for gynecological (GYN) cancers

Background: Patients (pts) with advanced gynecological (GYN) cancers have limited therapeutic options and the prognosis is poor. Early phase trials may be a suitable option for pts with good performance status. Increasingly, molecular characterisation guides pt selection for early phase trials. We sought to determine the outcome of GYN pts treated in a phase 1 unit and examined the role of molecular selection to inform therapeutic decision making.
Methods: Medical records of all pts with a GYN malignancy treated within an early phase trial between 2010 and 2016 were reviewed. Data comprising patient and tumor characteristics, prior treatment, trial therapy and outcome were analysed.
Results: 81 pts with a median age of 60 years (range 20-75) with a diagnosis of ovarian (OC, 54), endometrial (EC, 15) or cervical/vulval (CC, 12) cancer were identified. The median number of prior therapies for advanced disease was 3 (OC) and 2 (EC and CC) (overall range 1-6). 9 pts (11%) entered a second and 1 pt a third phase 1 study on disease progression. Next Generation Sequencing (NGS) using a targeted panel was performed in 32 pts (40%) with an actionable mutation identified in 9 including; KRAS (3pts), PIK3CA (2pts) and EGFR (2pts). Germline BRCA (gBRCA) testing was performed in 35 OC pts (65%) with 24 gBRCA mutations identified.
Pts were allocated, in order of priority, where available, to (1) a trial selected on the basis of NGS or gBRCA ('genomic' 35%), (2) a 'tumor specific' cohort within an early phase trial (15%) or (3) a 'generic' study (51%). For the whole cohort there was an overall response rate (ORR) of 18% with 41% stable disease (SD) and median progression free survival (PFS) and overall survival (OS) of 13 and 46 weeks respectively. Outcomes were best for pts in the genomic group. Both PFS and OS were significantly longer with genomic selection ($p < 0.01$ for both, Mantel-cox test) with median PFS of 29.7, 14.2, 8.0 weeks and OS of 84.1, 69.7, 33.6 weeks for genomics, tumor specific and generic studies respectively. The ORR was also greatest for the genomic cohort (32%) compared to the tumour specific (7%) and generic (11%) groups.
Within the heavily pre-treated EC and CC cohorts there was an OS of 30 and 42 weeks respectively. 24% of EC pts had an ORR with a further 24% with stable disease (SD). There was only 1 response (9%) in the CC cohort, however SD was seen in 64%. The OS for the OC was 55 weeks with an ORR of 20% and 46% SD.

Conclusions: Early phase trials represent a good option for pts with advanced GYN malignancies. Whilst applicable to all GYN cancers, this is particularly relevant for EC and CC pts as standard treatment options are limited. For OC patients (median 3 prior lines of chemotherapy in this cohort) where standard treatment options exist, early access to phase 1 genomic trials may result in improved response rates and allow further standard options to be given subsequently. NGS is feasible in real time and may have a positive impact on outcome.