The Use of Next Generation Sequencing (NGS) to Guide Patient Selection for Phase 1 Clinical Trials.

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Background: Therapeutically targeting actionable mutations in cancer may increase response rates in Phase I clinical trials. We undertook a pilot study to assess the feasibility and therapeutic benefit of incorporating NGS screening into the patient pathway for phase 1 cancer trials.

Methods: NGS tumour profiling was performed using a 22 gene amplicon-based panel (Life Technologies Colon & Lung V2) on 117 consecutive patients (pts) referred for Phase I trials. *BRCA1/2* analysis was performed in pts with epithelial ovarian cancer.

Results: 117 pts (67% female) with a median age of 59 (range 22-78) years were included. Common tumour types were ovarian (n=20), colorectal (n=16), breast (n=13), endometrial (n=12) and lung (n=8) cancer. NGS was successfully performed in 108 (92%) pts with a median time to results of 12 days (range 6-39). 82% of pts (89/108) had a detected variant in ≥ 1 gene with an average of 3 variants (range 0-26) in 2 genes (0-10) per case. Common mutations included *TP53* (69%), *KRAS* (14%), *PIK3CA* (11%) and *SMAD4* (9%). *BRCA1/2* mutations were present in 11 (55%) ovarian cancer pts. Overall, 49 (45%) pts had ≥ 1 actionable mutation. Detected variants were reviewed in a local genomics review board to assess actionability prior to considering therapy. 53 pts were commenced on a Phase I trial; 18 (34%) were genotype directed. Median duration on trial was 73 days for ~~both patients~~ pts on genotype (7-260 days) or non-genotype (20-582) directed trials ~~(range 7-260 days) and non-genotype directed trials (20-582)~~ with 50% and 24% of allocated patients continuing on study respectively. Of pts evaluable for response (n=47), partial response (PR), stable disease (SD) and progressive disease (PD) were observed in 50%, 29% and 21% of pts on genotype directed trials and 20%, 37% and 43% of pts on non-genotype directed respectively. Excluding pts on *BRCA1/2* directed trials, PR, SD and PD were observed in 33%, 33% and 33% of pts respectively in genotype-directed studies.

Conclusions: NGS is feasible in real time and may affect clinical outcome in the phase 1 setting. Almost half of pts had a potentially actionable mutation. Initial response rates for p~~atien~~ts treated on genotype-driven trials are encouraging. Benefit is likely to be augmented using a broader NGS panel which is planned for future assessment.