associations of *EPHA3* mutations with tumor mutation burden (TMB), PD-L1 expression, microsatellite instability-high (MSI-H), tumor-infiltrating lymphocytes (TILs), and clinical response to ICIs. This will be very helpful for identifying patients who may benefit from immunotherapy.

Methods: The ICIs cohort from the MSKCC was used for exploring the associations between *EPHA3* mutations and ICIs efficacy. The relationships between *EPHA3* mutations and TMB, PD-L1 expression, and MSI-H were investigated in our Chinese cohort. The TCGA cohort was used for analyzing the link between *EPHA3* mutations and TILs.

Results: First, we analyzed the associations between *EPHA3* mutations and overall survival (OS) after ICIs therapy. For all enrolled patients, those who harbored *EPHA3* mutations had a relatively longer OS compared to those without mutations (40 vs 18 months, $P = 0.0102$). However, *EPHA3* mutations displayed divergent predictive roles in different cancer types. The median OS was significantly longer in the Mut group compared to the WT group for NSCLC (36 vs 11 months, $P = 0.0167$). There were no associations between *EPHA3* mutations and ICIs efficacy for patients with melanoma, glioma, bladder, colorectal, esophagogastric, breast, and head and neck cancers. Second, the results from our cohort showed that the median TMB was higher in the Mut group for NSCLC (14.6 vs 6.6 muts/Mb, $P < 0.0001$). And we did not find the associations of *EPHA3* mutations with PD-L1 expression and MSI-H. Third, the analysis in the TCGA cohort revealed that NSCLC patients with *EPHA3* mutations were infiltrated with increased activated natural killer cells ($P = 0.0131$).

Conclusions: Our data indicated that *EPHA3* mutations were associated with prolonged OS in NSCLC, rather than other cancer types, suggesting that it might act as a predictive biomarker for ICIs therapy in NSCLC. *EPHA3* mutations were also correlated with higher TMB and increased activated natural killer cells in NSCLC.

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87P Clinical development of a predictive biomarker with 58 tumor genes for dovitinib treatment of solid tumors

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Background: Dovitinib is a tyrosine kinase inhibitor that inhibits VEGFR1-3, PDGFR, FGFR1-3, c-KIT, FLT3 and topoisomerase 1 and 2. Dovitinib is in development with a tumor agnostic biomarker based on 58 genes associated with sensitivity and resistance to dovitinib. The most advanced development is in renal cell carcinoma (RCC), which is presented here.

Methods: A multinational phase 3 study enrolled 570 patients treated with either dovitinib or sorafenib in a $\geq 3^{rd}$ line setting. Archival tumor samples were obtained from consenting patients to determine the predictive score in a prospective/retrospective design (pre-specified statistical analysis plan). The biomarker algorithm combines the expression of 58 mRNAs relevant to the *in vitro* sensitivity or resistance of dovitinib that include genes associated with FGFR, PDGF, VEGF, PI3K/Akt/mTOR and topoisomerase pathways as well as ABC drug transport and provides a likelihood score between 0-100%. A cut-point of the median of an RCC reference population was applied to make all statistical analysis categorical. A DRP Dovitinib score of $> 67\%$ was also applied.

Results: 188 patients consented in the dovitinib group, of these 135 passed established biomarker quality criteria. The DRP-dovitinib divided the patients into two groups, sensitive (n=49, DRP score >50%) or resistant (n=86, DRP score $\leq$ 50%) to dovitinib. The DRP sensitive population was compared to the unselected sorafenib group (N=286). The HR for the median PFS and OS was 0.71 and 0.69, respectively (Table). The median PFS using a DRP-Dovitinib score of 67%, is 5.67 M (95% CI 1.87,20.34) HR=0.42 (95% CI 0.21,0.86) (p=0.0174) and the median OS is 20.6 M (95% CI; 9.53, 35.58) in the DRP selected group compared to sorafenib unselected (p=0.08) HR=0.55 (95% CI 0.28,1.08).

Conclusions: The DRP-Dovitinib can be used as a predictive biomarker and thus as a tool for the physician in identifying advanced RCC patients most likely to experiencing clinical benefit from dovitinib treatment.

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88P Efficacy of olaparib in advanced cancers occurring in patients with germline or somatic tumor mutations in homologous recombination (HR) genes, a Belgian Precision phase II basket study

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Background: PARP inhibition with olaparib is a treatment with high efficacy in HR deficient cancers that arise in carriers of a germline mutation in the BRCA1/2 genes, particularly in ovarian cancer, a registered indication. Olaparib is also active in other BRCA1/2 mutation related cancers, including breast, prostate and pancreatic cancer. Olaparib acts through synthetic lethality in HR deficient cancers. Olaparib responses have however also been documented in cancers in which no BRCA1/2 mutations were found. It is possible that other HR deficiencies may play a role in such sensitivities. An array of other genes involved in HR deficiency, when mutated in the germline lead to an increased risk at least for breast and/or ovarian cancer and other cancers and may sensitize to olaparib. These genes include ATM, CHEK2, NBN, BRIP1, MRE11A, RAD50, NBS1, RAD51C, RAD51D, PALB2, and TP53 as well as BARD1.

Methods: The study recruits advanced cancer patients (pts) that harbor a somatic or a germline mutation in a HR gene. For each cohort a Simon minimax two-stage design is used. In the first stage, 13 patients will be accrued in each cohort. If there are no responses in these 13 patients, that cohort will be stopped.

Results: Currently, the BRCA and ATM cohort are the most advanced with regard to recruitment. Due to the low prevalence of other HR mutations, recruitment is slow in these cohorts. Currently, a total of 72 pts are included and 56 pts underwent a response assessment. Twenty-nine out of 56 pts experienced clinical benefit with olaparib. One complete response was observed in a stage IV breast cancer that harbours a PALB2 germline mutation. Six partial responses occurred: a RAD51D breast cancer, a BRCA1 gallbladder cancer, two BRCA1 and two BRCA2 pancreatic cancer pts. Recently we closed the ATM cohort due to the absence of a response in the first 13 pts.

In general, adverse events were mild to moderate (grade 1 and 2). Only 8 pts (11%) presented with a grade 3 adverse event (an allergic reaction, 5 pts anemia, anorexia and neutropenia).

Conclusions: Treatment with olaparib shows activity in cancer pts with a HR gene mutation and is well tolerated.

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Table: 87P

Efficacy Parameter	Dovitinib Dovitinib Score >50% N=49	Sorafenib Unselected N=286	p-value	HR
Median PFS, Months (95% CI)	3.75 (3.68, 5.39)	3.61 (3.48,3.71)	0.0572	0.71 (0.51,1.01)
Median OS, Months (95% CI)	15.0 (12.94, 26.25)	11.2 (9.66,13.37)	0.04	0.69 (0.48,0.99)