Functional Precision Medicine Profiling of Patient-Derived Organoids Identifies Effective Targeted Therapies for Patients with Low-Grade Serous Ovarian Carcinoma

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OBJECTIVE

We sought to determine whether functional precision medicine (FPM), which combines functional testing of live cancer cells with genomic profiling, could utilize patient-derived organoids (PDOs) from low-grade serous ovarian carcinomas (LGSOC) to identify effective therapies.

METHODS

Fresh tumor tissue was obtained from 17 patients at 19 timepoints undergoing surgery or image-guided biopsy for LGSOC, 12 at recurrence and 5 at primary surgery.

Short-term tumor PDOs were isolated and profiled for sensitivity to multiple drugs using the SEngine Precision Medicine PARIS test. A filter-based algorithm was applied to each concentration-response curve to generate a sensitivity numerical score (SPM score) ranking drug responses from 15 to 1. Additional metrics were employed to group and assign categories: SPM scores of 15-14 were categorized as exceptional responses, 13-12 as good responses, and 11-9 as moderate to low responses and no response below 9. Tumor origin and driver mutations were confirmed using whole-exome sequencing.

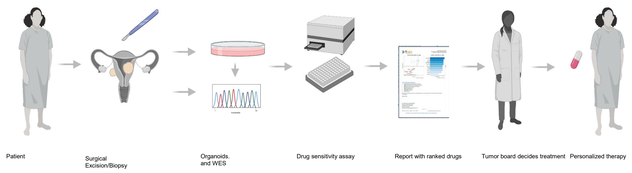


Figure 1. PARIS Test workflow to establish LGSOC PDOs organoids.

RESULTS

PARIS Test clinical characterization of cohort

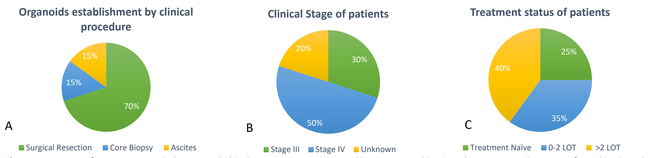


Figure 2. A) Organoid establishment according to clinical procedure B) Clinical stage and C) Treatment status of the patients from whom the LGSOC PDOs were derived.

To date, 20 samples from 17 patients with LGSOC have been evaluated with the PARIS test with 100% success in generating organoids, with median turn around time to test results of 16 days. Of the 17 unique patients, 16 (94%) had at least two drugs identified with good to exceptional responses to drugs targeting a variety of pathways.

RESULTS

Drug sensitivity landscape of LGSOC PDOs recapitulated the clinical resistance to most chemotherapies

Figure 3. Heat map of drug sensitivity screening from the PARIS test comparing the first 15 LGSOCs taken from separate timepoints on the right with a representative group of high-grade serous ovarian carcinomas (HGSCs) on the left. In contrast to frequent LGSOC with targeted drugs identified as responsive, only 3 had any chemotherapy responsiveness, all 3 were a moderate response to gemcitabine. Targeted pathways with common sensitivities included EGFR/HER2, BTK, MEK, mTOR, PI3K/AKT, BET and BCL. These data demonstrate that the PARIS test not only recapitulates the clinical resistance of LGSOC to most chemotherapies and PARP inhibitors compared to HGSOC but can also identify multiple targeted treatments for nearly all patients.

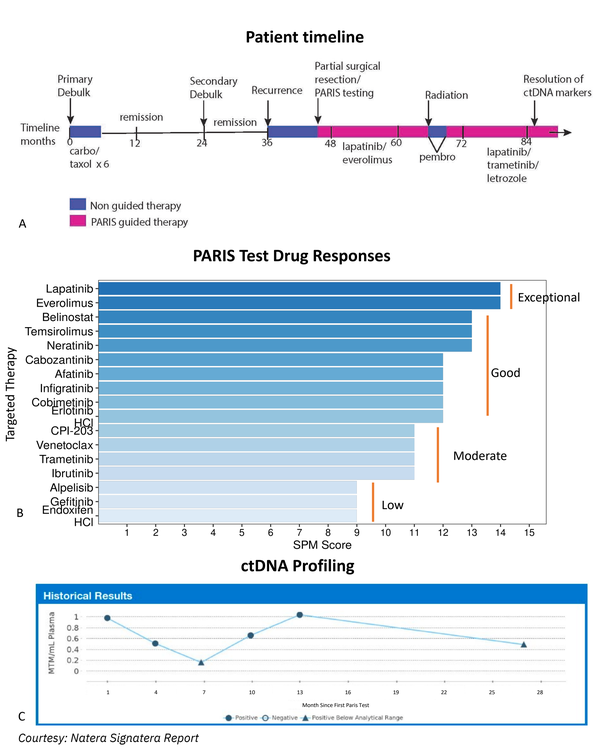
PARIS guided therapy for LGSOC correlated with longer progression-free survival

Case ID	Age at diagnosis (years)	Turn-around time (days)	# prior regimens	Actionable molecular findings	PARIS good and exceptional responses	FPM-guided therapy	Prospective Tx	PFS (months)
Recurrent LGSOC								
Pt#1	27	45	4	ESR1 p.Y537S	neratinib, lapatinib, everolimus, fulvestrant	Yes	fulvestrant/ everolimus	7
Pt#2 (Sample#1)	57	16	1	None	Everolimus, ibrutinib,	No	bevacizumab / letrozole	19
Pt#2 (Sample#2)	57	14	3	None	navitoclax, azacitadine, afatinib, lapatinib, neratinib	No	trametinib	4
Pt#3	50	22	1	None	ibrutinib, afatinib, CPI-0610, adavosertib, erlotinib, neratinib	Yes	ibrutinib afatinib	14.5 8.5
Pt#4	25	20	1	KRAS p.G12D	alpelisib,ipatasertib, everolimus, ibrutinib	Yes	trametinib	NE*
Pt#5	40	23	1	None	everolimus, lapatinib, neratinib, temsirolimus, belinostat, erlotinib, cabozatinib, infigratinib, afatinib, cobimetiminib, ibrutinib, trametinib, venetoclax, CPI-203	Yes Yes	Lapatinib/ everolimus lapatinib/ trametinib/ letrozole	16 16+
Pt#6	32	14	5	None	bortezomib, venetoclax, alpelisib,	No	trametinib Carboplatin/ gemcitabine	5 3
Pt#7	31	18	3	None	alpelisib, VS-6766, trametinib, selumetinib, gemcitabine	No	letrozole	9
Pt#8	60	17	4	None	alpelisib, infigratinib	No	Docetaxel/Bev	3
Pt#9	25	15	5	None	afatinib, lapatinib, erlotinib, neratinib, trametinib, ibrutinib, endoxifen, alpelisib, venetoclax, midostaurin, VS-6766, letrozole, cobimetinib, gemcitabine	Yes	Letrozole + ribociclib	6
Pt#10	29	20	2	None	afatinib, lapatinib ibrutinib neratinib erlotinib, gemcitabine	No	Palbociclib/ fulvestrant	3
Pt#11	39	19	4	None	Lapatinib, Venetoclax, Ceritinib, Trametinib, Alpelisib, Ibrutinib, Letrozole, Midostaurin, Abemaciclib, Selumetinib, Etposide, Detuxecan	No	Bispecific ab targeting PRAME	2
Pt#15	52	17	3	KRAS p.G12V	None	No	NA	NA
Primary LGSOC								
Pt#12	43	13	0	KRAS p.G12D	lapatinib, CPI-203, midostaurin	No	letrozole (GY019) trametinib	3 NA
Pt#13	41	14	0	None	infigratinib, midostaurin, endoxifen, CPI-203	No	Carboplatin/taxol + maintenance letrozole (GY019)	25+
Pt#14	68	16	0	KRAS p.G12C	lapatinib, geftinib, erlotinib, encorafenib, ibrutinib, trametinib, cobimetinib, neratinib	No Yes	Carbo/taxol/bev trametinib	5 NE
Pt#16	23	16	0	None	Ibrutinib, Zanubritinib, Azacitidine, Lapatinib, Alpelisib, Gemcitabine, Cisplatin	NA	NA	NA
Pt#17	34	16	1	None	Azacitidine, Lapatinib, Alpelisib, Copanlisib, Ipatasertib	NA	NA	NA

NA; Not available, *NE: Non-evaluable: Tumor responded to trametinib, but stopped after 6 weeks secondary to side effects and declined further tx.

Table 1. The case series in Table 1 includes all LGSOC cases evaluated with the PARIS test having available previous treatment status, PARIS test results along with prospective treatments, and progression free survival. In the recurrent setting, of the 6 patients treated with FPM -informed therapy, two had exceptional (defined as 12 months or greater) responses and the mean PFS was 10.0 months (range 6-16 months). In contrast, of the 7 cases treated with non-guided therapy, there was one exceptional response, and the two longest responses were to letrozole, which is now standard of care for frontline therapy or maintenance of LGSOC. For those receiving non-guided treatment, the mean PFS was 6.4 months (range 2-19 months).

Case report highlighting exceptional response to PARIS guided therapy



Courtesy: Natera Signatera Report

Figure 4. Case #5: A. 40-year-old female was diagnosed with LGSOC stage IIIB involving the omentum and peritoneum. After 4 years from diagnosis and initial treatments, tissue was obtained via surgical resection for PARIS testing. Tumor sequencing revealed no actionable alterations. The patient has been on PARIS-guided treatment for >34 months with a brief 3 month pause during which she had radiation and immunotherapy. The patient currently has ctDNA below detection level, consistent with near complete response. A) The patient's disease timeline indicating the PARIS Test and prospective treatments. B) Drug sensitivity assay indicates multiple top scoring drugs as potential treatments. C) The most recent ctDNA report by Natera Signatera test indicates the level below analytical range.

SUMMARY

- PDO can be generated and profiled from LGSOC within a clinically useful turn around time to test results (median 16 days)
- FPM using PDOs from LGSOC can identify therapeutic sensitivities to unique targeted agents that would not be identified by standard molecular profiling and recapitulates known chemoresistance.
- Ibrutinib and lapatinib were frequently identified top drugs for LGSOC PDO, and there were patients with LGSOC who had exceptional responses to these agents consistent with their PDO prediction.
- FPM-directed therapy holds promise for the therapy of recurrent LGSOC and should be tested in a prospective clinical trial.

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