Efficacy of spartalizumab across multiple cancer types in patients with *PD1*-high mRNA expressing tumors (SOLTI-1904 ACROPOLI)

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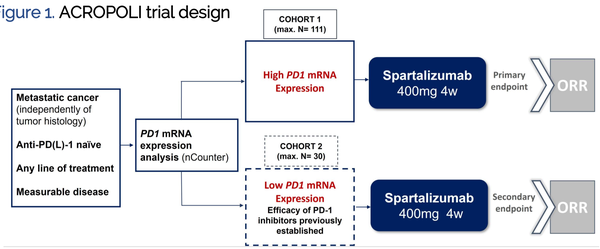
Background

- The **immune checkpoint inhibitors (ICIs)** against programmed death 1 (PD1) or its ligand (PD-L1) have demonstrated **significant efficacy across multiple cancer types**.
- **Microsatellite instability, mismatch repair deficiency, tumor mutational burden and PD-L1 positivity determined by immunohistochemistry (IHC) are the main approved biomarkers** used to guide patient selection for treatment with ICIs.
- Although these markers have a relevant clinical value, their ability for predicting responders can vary across cancer-types, and some results have been controversial. In fact, there is not a common reference standard for PD-L1 protein quantification. Moreover, some studies showed efficacy of anti PD1/PD-L1 independently of PD-L1 expression[1-2].
- **Improved selection of patients** (pts) with cancer most likely to respond to immune checkpoint inhibitors **remains an unmet clinical need.**
- Our earlier findings demonstrate a **strong association between PD1 mRNA levels and response to anti-PD1 monotherapy across several cancer types** both in silico datasets and in clinical samples, being the 80th percentile of PD1 expressing tumors (PD1-high) strongly correlated with ORR[3].

Objectives & Methods

ACROPOLI is an open-label, parallel cohort, non-randomized, multicenter **phase II study to evaluate the efficacy of the anti-PD1 spartalizumab in monotherapy in patients with PD1-high-expressing tumors and no prior exposure to PD(L)-1 inhibitors**[4].

Figure 1. ACROPOLI trial design



❑Primary endpoint: **Overall response rate (ORR) in cohort 1** according to RECIST V1.1.

❑Secondary endpoints:
- ORR in cohort 2, clinical benefit rate (CBR), progression-free survival (PFS), duration of response (DoR), time to response (TtR), Overall Survival (OS).
- Safety and tolerability of spartalizumab.

From April 2021 to May 2022, 73 patients from 10 hospitals in Spain were recruited:
❑58 patients with high levels of PD1 mRNA (Cohort 1), as defined by the pre-specified cutoff, have been enrolled.
❑15 patients with PD1-low tumors where the efficacy of PD1 inhibitors in monotherapy has been previously established have also been recruited (Cohort 2).

Here, we report efficacy results of a prespecified interim analysis (IA) after the first 50 patients in cohort 1 (PD1-high). A successful IA was defined as an ORR of ≥14%. We also report updated efficacy and safety data of all enrolled patients in Cohort 1 (N=58).

Results

Figure 2. CONSORT Diagram.

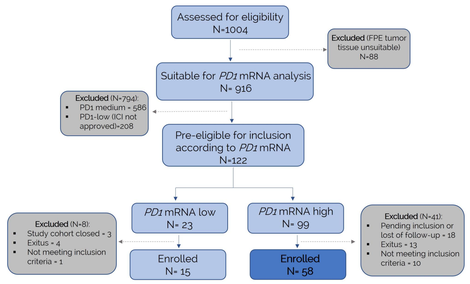


Table 1. Baseline characteristics of patients

	Interim Analysis (N=50)	All patients (N=58)
Age (years)		
Median (Min ; Max)	65 (36 ; 84)	65 (36 ; 89)
Gender		
Female	31 (62%)	35 (60%)
Male	19 (38%)	23 (40%)
ECOG status		
0	20 (41%)	23 (40%)
1	24 (49%)	28 (48%)
2	5 (10%)	7 (12%)
Prior treatments for advanced disease		
Median (Min ; Max)	2 (0 ; 13)	2 (0 ; 13)
Tumor stage at diagnosis		
I-III	24 (41%)	22 (44%)
IV	34 (59%)	28 (56%)

Figure 3. **Pre-screened cancer types (N = 1004).** Patients with 39 different tumor types were assessed for eligibility being breast cancer (BRCA) and colon/rectal adenocarcinoma (CO/READ) the most common.

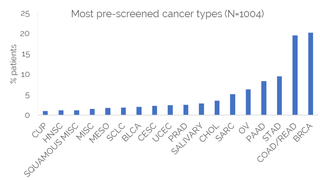


Figure 4. Percentage of TILs in *PD1*-high *vs PD1*-not high. N= 929 (15% vs 4%)

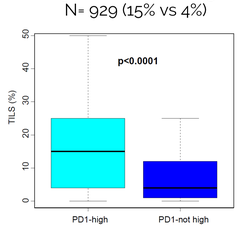


Figure 5. Patients enrolled by tumor type in cohort 1 (*PD1*-high).

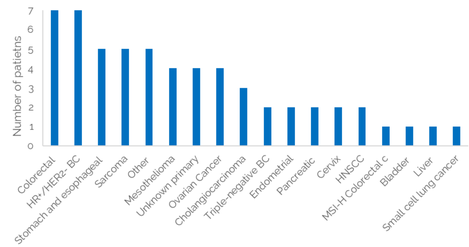


Table 2. **Overall Response.** Partial responses were observed in patients with mesothelioma (N=2), pancreatic carcinoma (N=2), colorectal adenocarcinoma (N=1), ovarian carcinoma (N=1), gastric carcinoma (N=1), carcinoma of primary unknown (N=1), cholangiocarcinoma (N=1), sarcoma (N=1).

	IA (N=50) Cutoff April 2022	All patients (N=58) Cutoff September 2023
Best Overall Response (BOR)		
Partial Response (PR)	8 (16.0%)	10 (17.2%)
Stable Disease (SD) ≥ 24 weeks	7 (14.0%)	8 (13.9%)
Stable Disease (SD) < 24 weeks	9 (18.0%)	9 (15.5%)
Progressive Disease (PD)	22 (44.0%)	26 (44.8%)
Not Evaluable (Clinical Progression)	4 (8.0 %)	5 (8.6%)
Objective Response Rate (ORR)		
No	42 (84%)	48 (82.8%)
Yes	**8 (16.0%)**	**10 (17.2%)**
Clinical Benefit Rate (CBR)		
No	35 (70.0%)	40 (69.0%)
Yes	15 (30.0%)	18 (31.0%)

Figure 6. **Best ORR and duration of response in the 58 patients enrolled in cohort 1 (*PD1*-high).** Percentage of TILs and PDL1 protein expression in tumor samples determined by combined positive score (CPS) are also indicated .Cutoff September 2023.

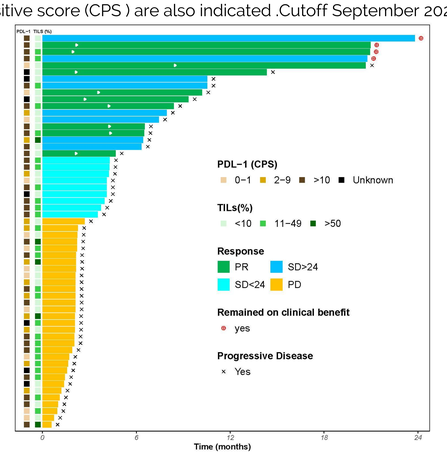


Figure 7. **Change in sum of longest diameters (SLD) in target lesions.** Best percentage changes from baseline in sum of longest diameter CT measurements by RECIST.

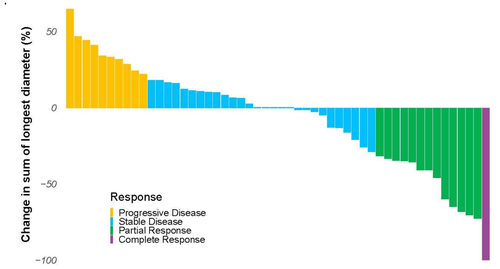


Figure 8. **A) Progression-free survival (PFS). B) Overall survival (OS).** N= 58 patients included in cohort 1. Cutoff September 2023.

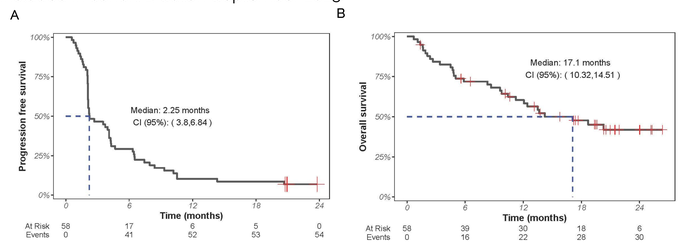


Table 3. **Safety data in patients enrolled in cohort 1 (*PD1*-high).**

TRAEs in > 3 % of patients, N (%)	All grades	Grade 3
Fatigue	7 (12.1%)	1 (1.7%)
Hypothyroidism	5 (8.6%)	-
Diarrhea	3 (5.2%)	1 (1.7%)
Transaminases increased	2 (3.4%)	1 (1.7%)
Anorexia	2 (3.4%)	1 (1.7%)
Blood alkaline phosphatase increased	2 (3.4%)	-
Dry mouth	2 (3.4%)	-
Dyspnoea	2 (3.4%)	-
Gamma-glutamyltransferase increased	2 (3.4%)	1 (1.7%)
Hyperthyroidism	2 (3.4%)	-
Pneumonitis	2 (3.4%)	2 (3.4%)
Pruritus	2 (3.4%)	-
Rash	2 (3.4%)	-

- ❑ 50% of patients (N=29) experienced at least one treatment-related adverse event (TRAE).
- ❑ 5 patients (8.6%) experienced grade 3-5 toxicities related to spartalizumab.
- ❑ One fatal event was reported (pneumonitis).

Conclusions

- ❑ Spartalizumab monotherapy demonstrated promising efficacy (ORR=17.2%) and favorable safety profile in heavily treated patients with immune-inflamed solid tumors expressing high levels of *PD1* mRNA, including patients with pancreatic cancer, colorectal adenocarcinoma MSS and sarcoma, among others.
- ❑Premature discontinuation of the trial's recruitment occurred due to the termination of the spartalizumab development program. Nevertheless, the trial has begun enrolling a new cohort of 111 patients with PD1-high tumors with tislelizumab

References: [1]*Brahmer, J., et al. N Engl. J. Me. (2015);* [2]*Rizvi, N.A., et al. Lancet Oncology. (2015);* [3]*Paré, L., et al. Ann Oncol.(2019);* [4]*Prat et al. Future Oncology (2022)*

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Conflicts of interest of the first author: A.P. reports advisory and consulting fees from Roche, Pfizer, Novartis, Amgen, BMS, Puma, Oncolytics Biotech, MSD, Guardan Health, Peptomyc and Lilly, lecture fees from Roche, Pfizer, Novartis, Amgen, BMS, Nanostring Technologies and Daiichi Sankyo, institutional financial interests from Boehringer, Novartis, Roche, Nanostring, Sysmex Europa GmbH, Medica Scientia inno. Research, SL, Celgene, Astellas and Pfizer; stockholder and consultant of Reveal Genomics, SL; the DNADX patent filed. For more details, please refer to the original abstract.

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