480P – CATRIPCA - A Phase 1 of pembrolizumab combined with xevinapant (Debio 1143) in patients (pts) with non MSI-high advanced/metastatic pancreatic ductal adenocarcinoma (PDAC) or colorectal cancer (CRC).

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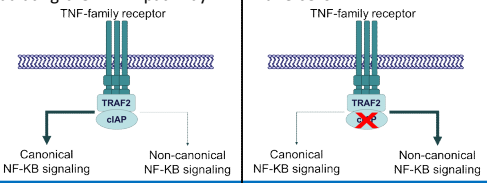
RATIONALE

Xevinapant is a potent, oral, small-molecule IAP (inhibitor of apoptosis protein) inhibitor. Preclinical data suggest that IAP inhibition may synergize with immune checkpoint blockers (ICB) by modulating the NF-κB pathway in immune cells.



STUDY DESIGN

- 3+3 dose escalation design, 21-day DLT window.
- Adverse Event (AE) graded according to NCI CTCAE v5.0
- **DLT definition:** grade 4 non-laboratory AEs, grade 3 non-laboratory AEs lasting more than 7 days, and grade 3-4 laboratory AEs requiring medical intervention (including hematological AEs) or lasting more than 7 days,

Dose escalation part
(n= Up to 18 patients with PDAC or CRC)

pembrolizumab
(IV, Q3W, 1 fixed dose of 200mg)
+
xevinapant
(orally, 14 days on – 7 days off)

MTD & RP2D

Expansion part
(n=14 PDAC and n=14 CRC)

pembrolizumab
(IV, Q3W, 1 fixed dose of 200mg)
+
xevinapant
(RP2D)

Key eligibility criteria:

- Adult pts with non-MSI-H advanced/ metastatic PDAC or CRC. ECOG Performance Status (PS) 0 or 1.
- At least one prior line of chemotherapy for advanced disease.
- Adequate organ function.

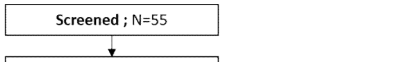
[ClinicalTrials.gov Identifier: NCT03871959]

BASELINE CHARACTERISTICS

	DOSE ESCALATION PART N=13	EXTENSION PART N=28	ALL N=41
Gender			
Male	7 (53.8%)	19 (67.9%)	26 (63.4%)
Female	6 (46.2%)	9 (32.1%)	15 (36.6%)
Age at ICF signature			
Mean (std)	63.8 (8.8)	62.4 (8.5)	62.9 (8.5)
Median (min; max)	65.0 (50; 80)	63.5 (42; 82)	64.0 (42; 82)
ECOG performance Index			
0	3 (23.1%)	3 (10.7%)	6 (14.6%)
1	10 (76.9%)	25 (89.3%)	35 (85.4%)
Primary tumor site			
Colorectal adenocarcinoma	8 (61.5%)	14 (50.0%)	22 (53.7%)
Pancreatic adenocarcinoma	5 (38.5%)	14 (50.0%)	19 (46.3%)
PRIOR THERAPY			
Surgery of the primary tumor			
Yes	9 (69.2%)	15 (53.6%)	24 (58.5%)
Radiotherapy of the primary tumor			
Yes	2 (15.4%)	4 (14.3%)	6 (14.6%)
Number of prior chemotherapy lines (for advanced disease)			
≤ 2	2 (15.4%)	14 (50.0%)	16 (39.0%)
≥ 3	11 (84.6%)	14 (50.0%)	25 (61.0%)
Number of metastatic site(s) at inclusion			
≤ 2	3 (23.1%)	15 (53.6%)	18 (43.9%)
≥ 3	10 (76.9%)	13 (46.4%)	23 (56.1%)
Liver metastases	10 (76.9%)	26 (92.9%)	36 (87.8%)
Peritoneal metastases	6 (46.2%)	7 (25.0%)	13 (31.7%)

Table 1: Patient's characteristics at baseline.

STUDY POPULATION



Dose escalation part ; N = 13

DL	Dose (mg/d)	Enrolled	Efficacy population	Safety population
DL1	100	3	3	3
DL2	150	3	3	3
DL3	200	7	6	7

Extension part ; N = 28

Cohort	Enrolled and treated
CRC	14
PDAC	14

Thirteen pts (7M/6F, median age, 65 y [range, 50-80y]) were enrolled in 3 dose levels (DL) (X 100 and 150mg/d: 3 pts each and X 200mg/d: 7 pts). One pt who received less than 10 doses of xevinapant during cycle 1 was considered non-evaluable for DLT at DL3 and efficacy, and was replaced.

SAFETY DATA

No DLT was observed during dose-escalation.

Thirty-six (88%) pts had at least one AE related to xevinapant and/or pembrolizumab. Fifteen pts (37%) presented at least one immune-related adverse event (irAE). IrAEs were grade 1-2, except three grade 3 (stomatitis, myocarditis and rash). The most frequent irAE was rash (6 patients -15%-)

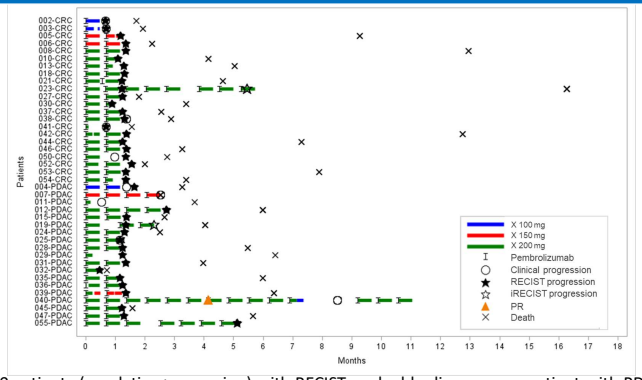
	DOSE ESCALATION PART All N=13		EXTENSION PART CRC N=14		EXTENSION PART PDAC N=14		ALL N=41	
GRADE	**Grade 1-2**	**Grade 3-4**	**Grade 1-2**	**Grade 3-4**	**Grade 1-2**	**Grade 3-4**	**Grade 1-2**	**Grade 3-4**
NAUSEA	3 (23.1%)	0 -	3 (21.4%)	0 -	4 (28.6%)	0 -	10 (24.4%)	0 -
STOMATITIS	0 -	0 -	3 (21.4%)	0 -	1 (7.1%)	1 (7.1%)	4 (9.8%)	1 (2.4%)
FATIGUE	8 (61.5%)	0 -	3 (21.4%)	0 -	3 (21.4%)	1 (7.1%)	14 (34.1%)	1 (2.4%)
LIPASE INCREASED	2 (15.4%)	1 (7.7%)	0 -	1 (7.1%)	1 (7.1%)	0 -	3 (7.3%)	2 (4.9%)
DECREASED APPETITE	5 (38.5%)	0 -	6 (42.9%)	0 -	4 (28.6%)	0 -	15 (36.6%)	0 -
PRURITUS	1 (7.7%)	0 -	3 (21.4%)	0 -	4 (28.6%)	0 -	8 (19.5%)	0 -
DRY SKIN	2 (15.4%)	0 -	0 -	0 -	4 (28.6%)	0 -	6 (14.6%)	0 -
RASH	1 (7.7%)	1 (7.7%)	2 (14.3%)	0 -	2 (14.3%)	0 -	5 (12.2%)	1 (2.4%)

Table 2: All treatment-related AEs observed in more than 10% of pts

	DOSE ESCALATION PART All N=13	EXTENSION PART CRC N=14	EXTENSION PART PDAC N=14	EXTENSION PART All N=28	ALL N=41
EOSINOPHILIA	1 (7.7%)	1 (7.1%)	1 (7.1%)	2 (7.1%)	3 (7.3%)
MYOCARDITIS	1 (7.7%)	0	0	0	1 (2.4%)
HYPERTHYROIDISM	1 (7.7%)	1 (7.1%)	1 (7.1%)	2 (7.1%)	3 (7.3%)
ADRENOCORTICOTROPIC HORMONE DEFICIENCY	0	1 (7.1%)	1 (7.1%)	2 (7.1%)	2 (4.9%)
HYPOTHYROIDISM	0	0	2 (14.3%)	2 (7.1%)	2 (4.9%)
THYROIDITIS	1 (7.7%)	0	0	0	1 (2.4%)
STOMATITIS	0	0	1 (7.1%)	1 (3.6%)	1 (2.4%)
CONJUNCTIVITIS	1 (7.7%)	0	0	0	1 (2.4%)
RASH	2 (15.4%)	2 (14.3%)	2 (14.3%)	4 (14.3%)	6 (14.6%)
PRURITUS	1 (7.7%)	0	2 (14.3%)	2 (7.1%)	3 (7.3%)

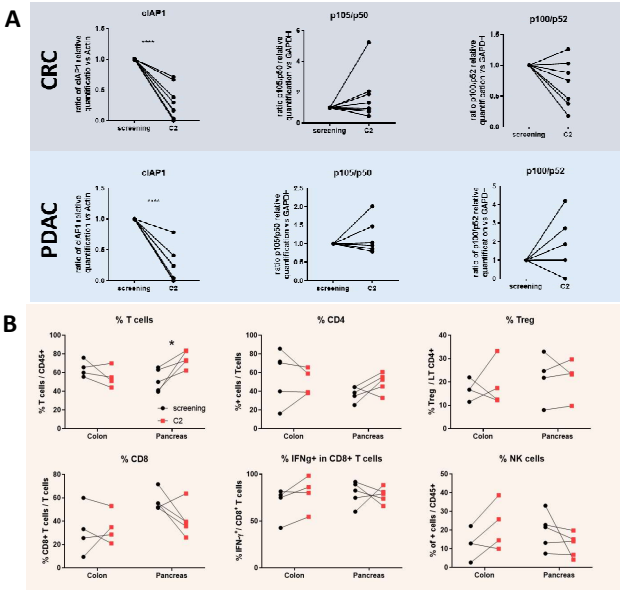
Table 3: Immune-related AEs

EFFICACY DATA



Of 40 patients (escalation+expansion) with RECIST-evaluable disease, one patient with PDAC acheived a confirmed PR (in expansion), 4 patients had SD, while 35 patients had PD as their best response.

PHARMACODYNAMIC DATA



Target modulation in paired tumor samples: cIAP1 down-modulation (assessed using western blotting) was seen in all cases, but NF-κB modulation (also WB) was variable (panel A). Changes in immune cell types assessed by flow cytometry on fresh tumor samples were also variable although an increasein CD4 T cells was observed in PDAC (panel B). (biopsies were performed during screening and at cycle 2, day 8 (C2)). **Pharmacokinetic analysis is on-going**.

CONCLUSION

The combination of xevinapant 200 mg qd 14 days on/7 days off and pembrolizumab 200 mg IV q3wk was overall well tolerated with no safety signal. The overall anti-tumor activity was low. Biomarker analyses are on-going.

Acknowledgements : We would like to thank the patients and their families, all the study staff from Centre Léon Bérard. This trial was sponsored by Centre Léon Bérard, supported by funding from MSD. Study treatments were provided by MSD and Debiopharm.. ✉ : philippe.cassier@lyon.unicancer.fr