2024 ASCO® ANNUAL MEETING

First-in-human trial of the oral first-in-class Ubiquitin Specific Peptidase 1 (USP1) inhibitor RO7623066 (KSQ-4279), given as single agent and in combination with olaparib or carboplatin in patients with advanced solid tumors, enriched for deleterious homologous recombination repair (HRR) mutations

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Disclosures

Timothy A. Yap

I have the following relevant financial relationships to disclose:

Employee of: University of Texas MD Anderson Cancer Center, where I am Vice President, Head of Clinical Development in the Therapeutics Discovery Division, which has a commercial interest in DDR inhibitors (IACS30380/ART0380 was licensed to Artios).

Consultant for: 858 Therapeutics, AbbVie, Acrivon, Adagene, Aduro, Almac, Amgen Inc., Amphista, Artios, Astex, AstraZeneca, Athena, Atrin, Avenzo, Avoro, Axiom, Baptist Health Systems, Bayer, BeiGene, BioCity Pharma, Blueprint, Boxer, BridGene Biosciences, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Carrick Therapeutics, Circle Pharma, Clovis, Cybrexa, Daiichi Sankyo, Dark Blue Therapeutics, Debiopharm, Diffusion, Duke Street Bio, EcoR1 Capital, Ellipses Pharma, EMD Serono, Entos, FoRx Therapeutics AG, F-Star, Genesis Therapeutics, Genmab, GlaxoSmithKline, Glenmark, GLG, Globe Life Sciences, Grey Wolf Therapeutics, Guidepoint, Ideaya Biosciences, Idience, Ignyta, I-Mab, ImmuneSensor, Impact Therapeutics, Institut Gustave Roussy, Intellisphere, Janssen, Joint Scientific Committee for Phase I Trials in Hong Kong, Kyn, Kyowa Kirin, MEI pharma, Merck, Mereo, Merit, Monte Rosa Therapeutics, Natera, Nested Therapeutics, Nexys, Nimbus, Novocure, Odyssey Therapeutics, OHSU, OncoSec, Ono Pharma, Onxeo, PanAngium Therapeutics, Pegascy, PER, Pfizer, Piper-Sandler, Pliant Therapeutics, Prelude Therapeutics, Prolynx, Protai Bio, Radiopharma Theranostics, Repare, resTORbio, Roche, Ryvu Therapeutics, SAKK, Sanofi, Schrodinger, Servier, Synnovation, Synthis Therapeutics, Tango, TCG Crossover, TD2, Terremoto Biosciences, Tessellate Bio, Theragnostics, Terns Pharmaceuticals, Thryv Therapeutics, Tolremo, Tome, Trevarx Biomedical, Varian, Veeva, Versant, Vibliome, Voronoi Inc, Xinthera, Zai Labs and ZielBio.

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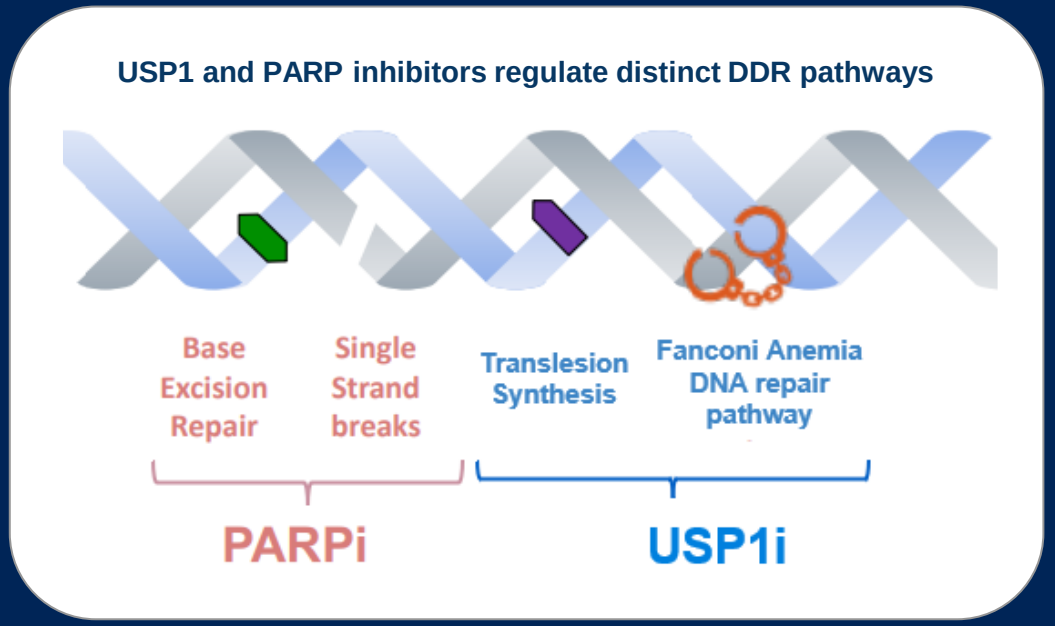
Key takeaways

- USP1 is a deubiquitinating enzyme that regulates the Translesion Synthesis and Fanconi Anemia DNA repair pathways.
- RO7623066 is a first-in-class inhibitor of USP1 that potentially synergizes with and overcomes resistance to PARP inhibitors.
- RO7623066 has a favorable safety profile as single agent.
- Anemia in combination with olaparib was manageable and reversible.
- Tumor PD data support the postulated mode of action of USP1 inhibition.
- Anti-tumor activity observed for the combination of RO7623066 with olaparib appears to be associated with *BRCA1* mutation status.

RO7623066 is a first-in-class USP1 inhibitor

- USP1 regulates the DNA Translesion Synthesis and Fanconi Anemia repair pathways, by removing ubiquitin from a variety of substrates (incl. PCNA, FANCI, FANCD2, *etc.*) that are crucially involved in DNA damage response (DDR) [1,2]
- RO7623066 (formerly KSQ-4279) is a novel first-in-class small molecule, allosteric inhibitor of USP1 (USP1i) with excellent selectivity [3]
- USP1i combination strategies are expected to synergize with and overcome resistance to PARPi and other DDR agents in HRR deficient tumors



USP1 = Ubiquitin Specific Peptidase 1; HRR = Homologous recombination repair

1 Nijman *et al.*, *Mol Cell, 2005*; 2 Lim *et al.*, *Mol Cell 2018*; 3 Cazdow *et al.*, *EJC abstract 184 (2020)*

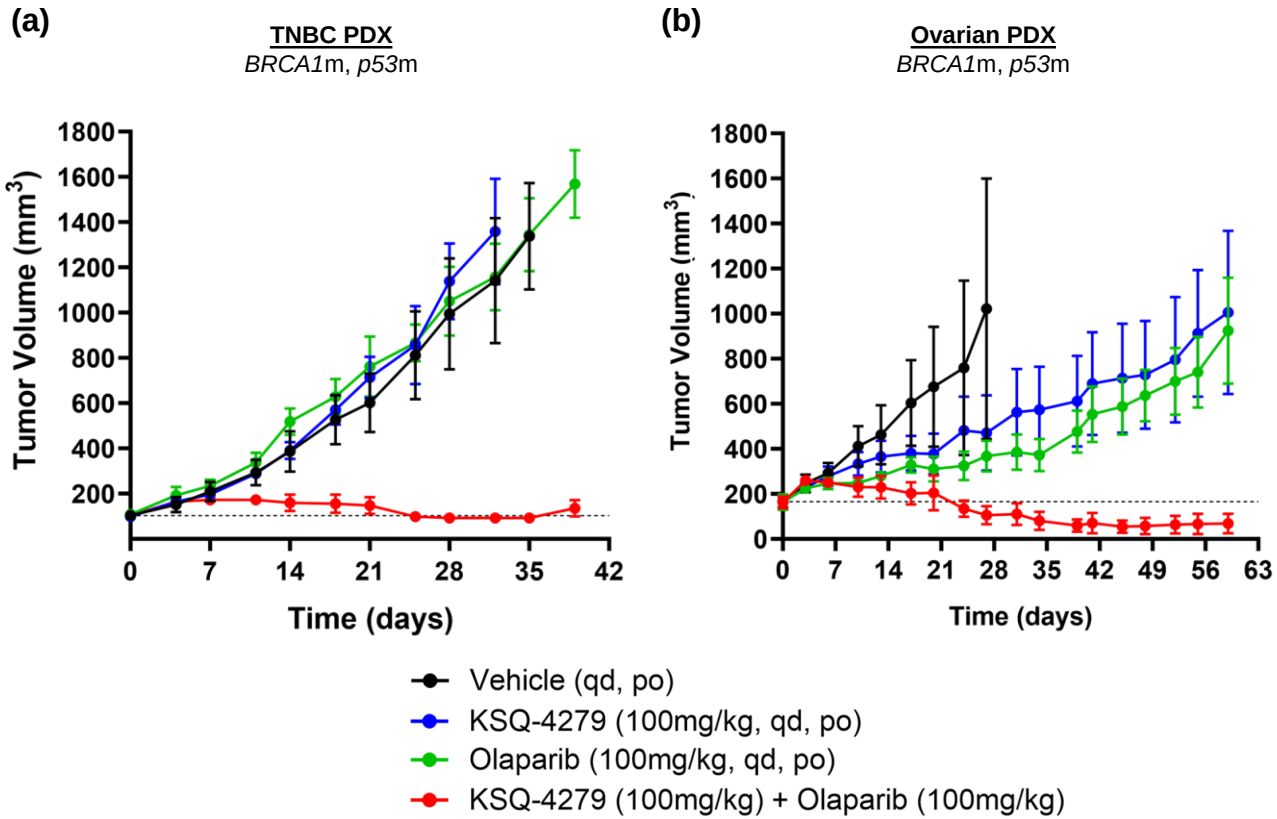
RO7623066 shows strong synergistic activity with PARPi and cisplatin in *BRCA1*m PDX models

RO7623066 in combination with:

(a) olaparib leads to durable tumor control in PARPi resistant TNBC PDX model

(b) olaparib leads to durable tumor regression in ovarian PDX model

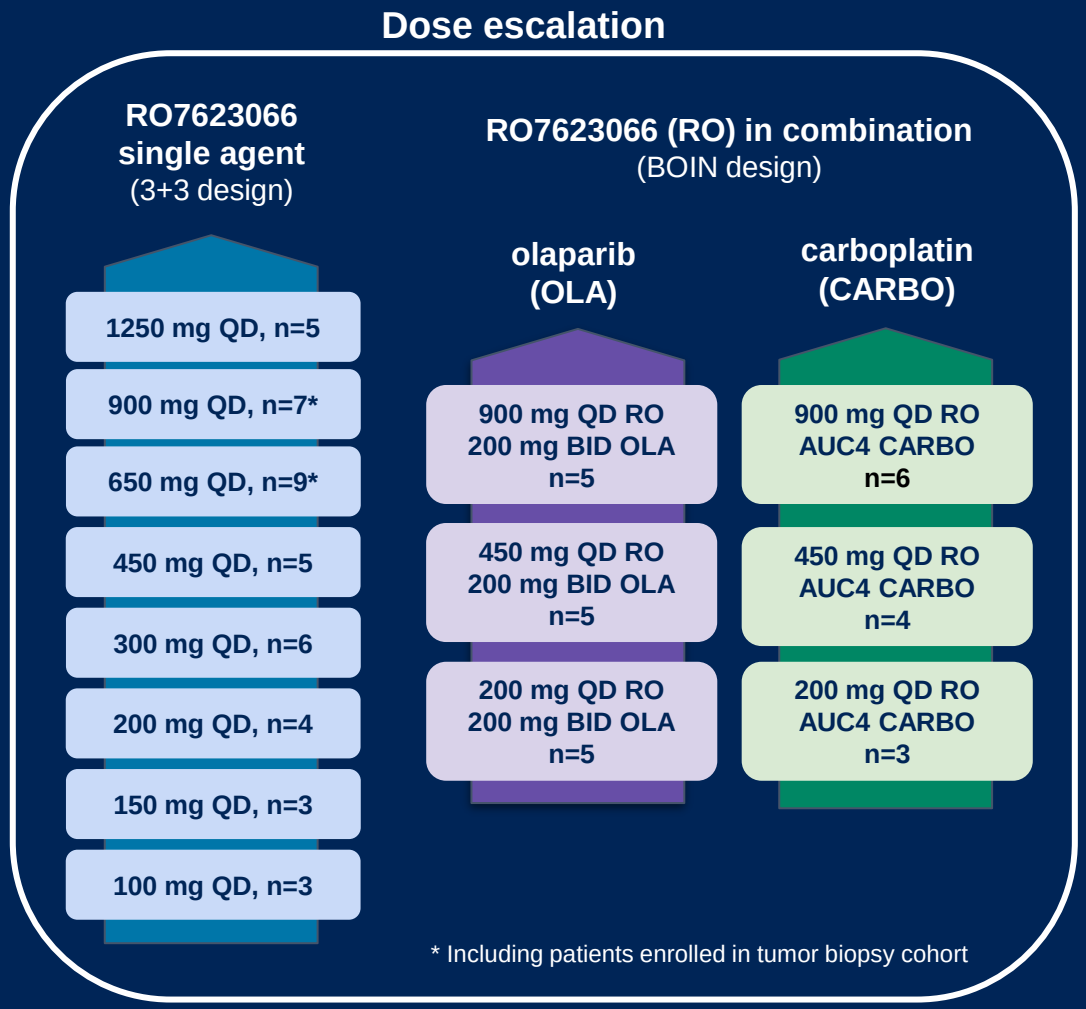
(c) cisplatin leads to improved durability of anti-tumor response in cisplatin sensitive TNBC PDX model (data not shown)



PDX = Patient Derived Xenograft; TNBC = Triple Negative Breast Cancer

RO7623066 = KSQ-4279; adapted from AACR Annual Meeting 2022 presented by Andrew Wylie, KSQ Therapeutics

First-in-human study - A Phase 1/1b modular study



Key inclusion criteria

- Pts ≥ 18 years with progressive advanced/ metastatic solid tumors
- For single agent tumor biopsy and combination cohorts: Deleterious mutation in 1 of the following genes: *BRCA1/2, PALB2, RAD51, RAD51B/C/D, BARD1, BRIP1, FANCA, NBN*
- Prior platinum-based chemo and PARP inhibitors allowed
- ECOG PS 0-1
- **Hgb ≥ 9.0 g/dL**, platelets ≥ 100 × 10^9/L, ANC ≥ 1.5 × 10^9/L

Primary and secondary objectives

- MTD and RDE/RP2D
- Safety and tolerability
- Pharmacokinetics (PK)
- Preliminary antitumor activity

Exploratory objectives

- Pharmacodynamics (PD) in tumor tissue and blood

First presentation of clinical data from dose escalation part 1 of this ongoing study

- Study identifiers: NCT05240898, WP45169
- First patient in: August 2021
- Data cut-off date: 28 March 2024

MTD = maximum tolerated dose; RDE = recommended dose for expansion; RP2D = recommended phase 2 dose; ANC = absolute neutrophil count; ECOG PS = Eastern Cooperative Group performance status; Hgb = hemoglobin

Patient demographics and disease characteristics

Treatment	RO7623066 (n=42)	RO7623066 + OLA (n=15)	RO7623066 + CARBO (n=13)
Median age, years (range)	63 (38-84)	64 (40-84)	65 (49-71)
Female/male, n (%)	31 (74) / 11 (26)	9 (60) / 6 (40)	9 (69) /4 (31)
ECOG, 0/1 n (%)	8 (19) / 34 (81)	3 (20) / 12 (80)	3 (23) / 10 (77)
Primary Tumor type, n (%)			
Ovarian	4 (10)	6 (40)	4 (31)
Pt sensitive	-	1 (7)	3 (23)
Pt resistant/refractory	4 (10)	4 (27)	1 (8)
unknown	-	1 (7)	-
Pancreatic	5 (12)	3 (20)	3 (23)
Colorectal	6 (14)	1 (7)	1 (8)
Breast	5 (12)	-	2 (15)
Prostate	1 (2)	4 (27)	-
NSCLC	2 (5)	-	-
Appendiceal	-	1 (7)	-
Endometrial	1 (2)	-	1 (8)
Bile duct	-	-	1 (8)
Bladder	-	-	1 (8)
Others*	18 (43)	-	-

Treatment	RO7623066 (n=42)	RO7623066 + OLA (n=15)	RO7623066 + CARBO (n=13)
Mutational analysis, n (%)	NA[$]	15 (100)	13 (100)
BRCA1	6 (14)	7 (47)	2 (15)
BRCA2	6 (14)	8 (53)	7 (54)
PALB2	1 (2)	-	-
RAD51	1 (2)	-	-
RAD51B	-	-	-
RAD51C	-	1 (7)	1 (8)
RAD51D	-	1 (7)	-
BARD1	-	-	-
BRIP1	-	-	1 (8)
FANCA	1 (2)	1 (7)	-
NBN	-	-	2 (15)
Median number of prior therapies, range	5, 1-14	4, 2-10	3, 1-7
Prior PARPi	13 (31)	9 (60)	6 (46)
Prior Pt therapy	30 (71)	12 (80)	11 (85)

[$] enrollment not restricted to HRR mutation

* Others include: Soft tissue sarcoma, primary peritoneal, adrenal, cervical, fallopian tube, and gastric cancer

Pt = Platinum

Treatment-emergent AEs regardless of causality

Adverse Event *All TEAEs in > 20% for single agent and in > 30% for combination*	**Single agent (n=42)**		**RO7623066 + OLA* (n=15)**		**RO7623066 + CARBO (n=13)**	
	All Grades	**Grade ≥3**	**All Grades**	**Grade ≥3**	**All Grades**	**Grade ≥3**
Anemia	**35.7%**	**4.8%**	**86.7%**	**73.3%**	**69.2%**	**30.8%**
Blood creatinine increased	33.3%	0	33.3%	0	30.8%	0
Hyponatremia	28.6%	11.9%	-	-	61.5%	7.7%
GGT increased	26.2%	9.5%	40.0%	13.3%	38.5%	15.4%
Constipation	21.4%	0	-	-	38.5%	0
Cough	21.4%	0	-	-	-	-
Platelet count decreased	-	-	-	-	53.8%	15.4%
Fatigue	-	-	46.7%	0	46.2%	7.7%
ANC decreased	-	-	33.3%	13.3%	46.2%	30.8%
Nausea	-	-	33.3%	0	-	-
AST increased	-	-	-	-	38.5%	7.7%
Blood ALP increased	-	-	-	-	30.8%	0
Dizziness	-	-	-	-	30.8%	0

***Anemia adverse events were reversible and manageable:**

- No adverse events > G3
- No event led to study treatment discontinuation; only one led to RO7623066 dose reduction
- Safety/PK-analysis suggests that G3 anemia is mainly driven by exposure of olaparib, not RO7623066
- Patient were eligible with Hgb ≥ 9 g/dL, prior transfusions > 2 weeks
- 5/11 patients (45%) with anemia G3 had Hgb <10 g/dL at baseline
- Number of prior therapies: 4 (median); range 2-10
- Prior platinum: 80%; prior PARPi: 60%

TEAE = Treatment-Emergent Adverse Event; Hgb = Hemoglobin

Overall safety summary

Single agent dose level	100mg (n=3)	150mg (n=3)	200mg (n=4)	300mg (n=6)	450mg (n=5)	650mg (n=9)	900mg (n=7)	1250mg (n=5)	Total (n=42)
RO7623066-related TEAEs	2 (66.7%)	1 (33.3%)	2 (50%)	4 (66.7%)	3 (60%)	6 (66.7%)	6 (85.7%)	4 (80%)	28 (66.7%)
Related Grade ≥3 AEs	0	0	0	0	1 (20)	3 (33.3%)	1 (14.3%)	1 (20%)*	6 (14.3%)
Dose reduction (all)	0	0	0	0	0	0	0	0	0
Discontinuation (all)	0	0	0	0	1 (20%)**	0	0	0	1 (2.4%)

* One DLT: G3 Maculopapular rash at 1250mg QD; ** G3 Hyponatremia at 450mg QD - possibly related to RO7623066

Combination dose level	200mg + OLA (n=5)	450mg + OLA (n=5)	900mg + OLA (n=5)	Total (n=15)	200mg + CARBO (n=3)	450mg + CARBO (n=4)	900mg + CARBO (n=6)	Total (n=13)
RO7623066-related TEAEs	5 (100%)	5 (100%)	4 (80%)	14 (93.3%)	3 (100%)	4 (100%)	6 (100%)	13 (100%)
Related Grade ≥3 AEs	2 (40%)[#]	3 (60%)[#]	3 (60%)	8 (53.3%)	2 (66.7%)	4 (100%)	4 (66.7%)[§]	10 (76.9%)
RO7623066 dose reduction (all)	0	0	1 (20%)	1 (6.7%)	0	0	0	0
RO7623066 discontinuation (all)	0	0	0	0	0	0	0	0
OLA or CARBO dose reduction (all)	1 (20%)	2 (40%)	1 (20%)	4 (26.7%)	0	0	1 (16.7%)	1 (7.7%)
OLA or CARBO discontinuation (all)	1 (20%)	2 (40%)	0	3 (20%)	0	0	1 (16.7%)	1 (7.7%)

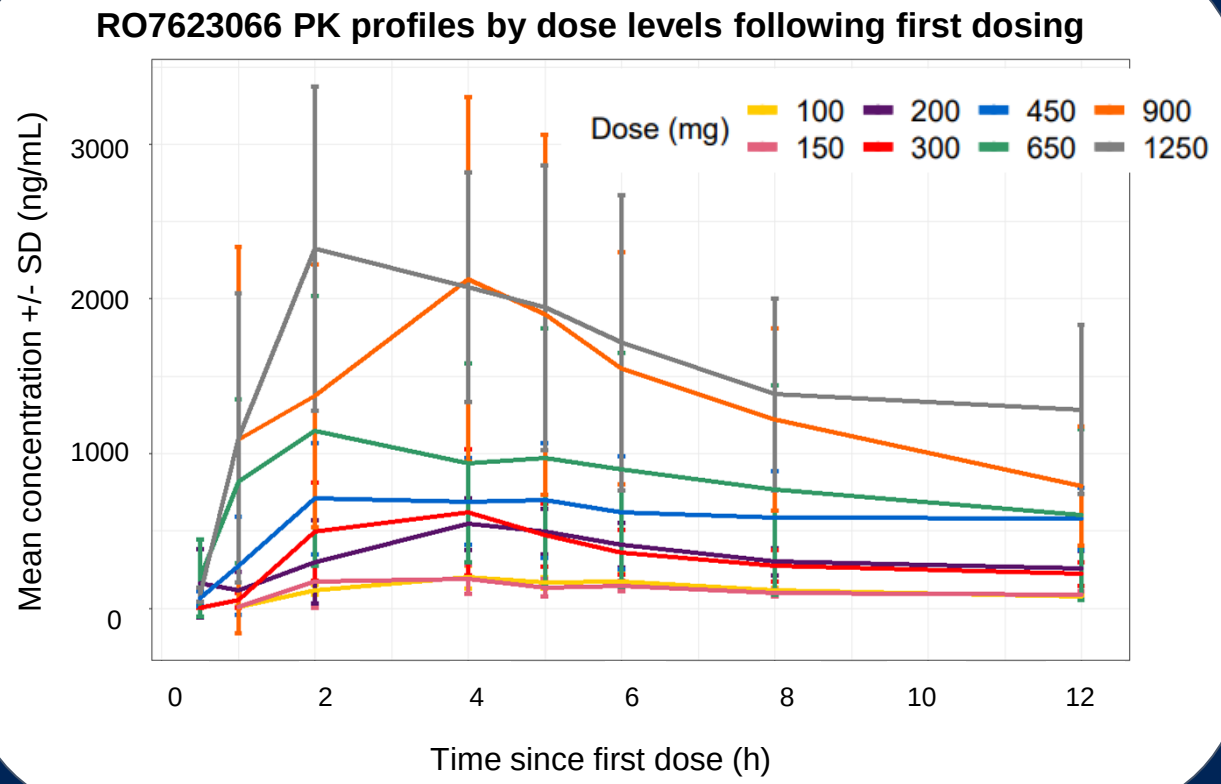
[#] Two DLTs: G3 WBC decreased at 200mg QD; anemia G3 at 450mg QD

[§] One DLT: G4 thrombocytopenia at 900mg QD

TEAE = Treatment-Emergent Adverse Event; DLT = Dose Limiting Toxicity; WBC = White Blood Cell

RO7623066 clinical PK observations

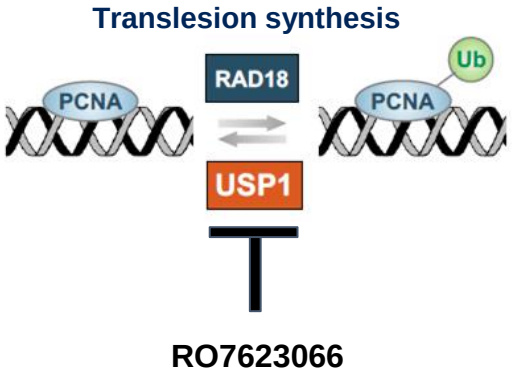
- RO7623066 single agent PK was evaluated within a wide range of doses between 100 mg and 1250 mg QD
- RO7623066 PK is almost dose proportional for doses up to 650 mg
- RO7623066 absorption starts to saturate at higher doses tested, thereby supporting BID dosing
- RO7623066 does not impair olaparib exposure (data not shown)



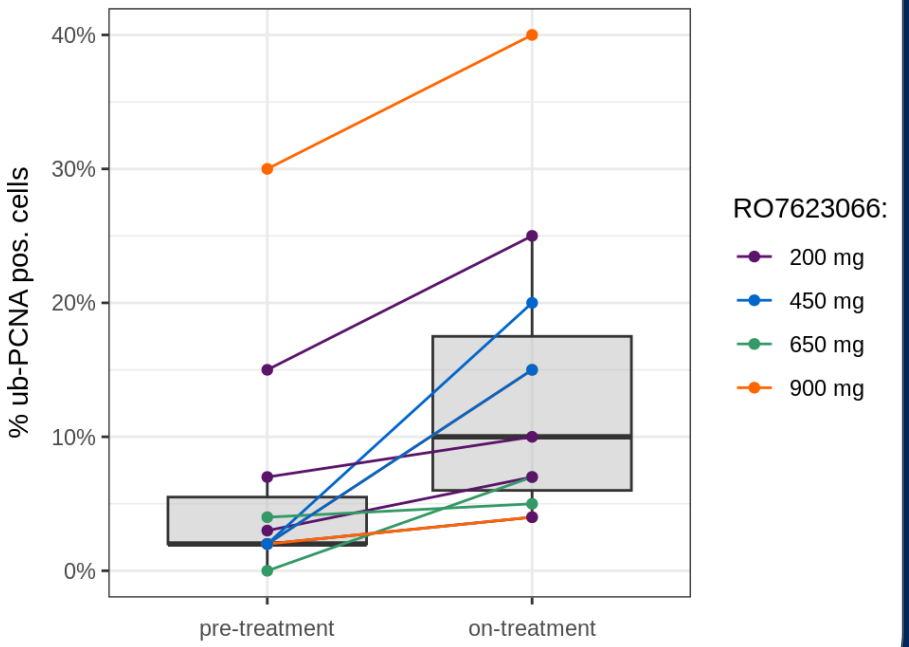
Observed PK data (mean +/- standard deviation) from 42 patients treated with RO7623066 as single agent are shown following first single oral administration on C1D1

Pharmacodynamic (PD) data support the postulated mode of action of USP1 inhibition

- Ubiquitinated PCNA (ub-PCNA) IHC data from paired tumor biopsies across all dose groups and treatment arms (n=11)
- A trend for ub-PCNA induction was observed in tumor biopsies from patients receiving RO7623066 supportive of intratumoral USP1- inhibition



Inhibition of USP1 by RO7623066 leads to accumulation of ub-PCNA



PCNA = Proliferating Cell Nuclear Antigen; IHC = Immunohistochemistry

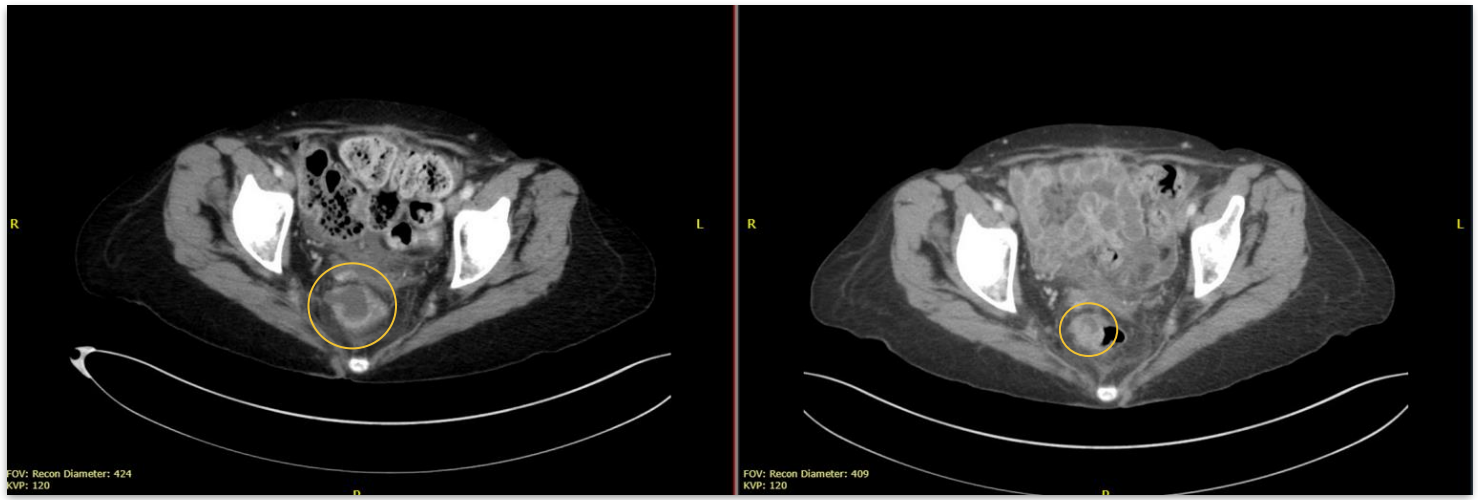
PD analyses were carried out on paired tumor tissue samples to measure USP1 inhibition by the increase of ub-PCNA signal

Limited single agent activity of RO7623066

- 1 (3%) patient had a RECIST v1.1 PR at 100 mg QD lasting for 10 weeks
- 7/29* (24%) had RECIST v1.1 SD as best response, 5/29 (17%) had SD for >16 weeks

Case report of patient with PR by RECIST v1.1

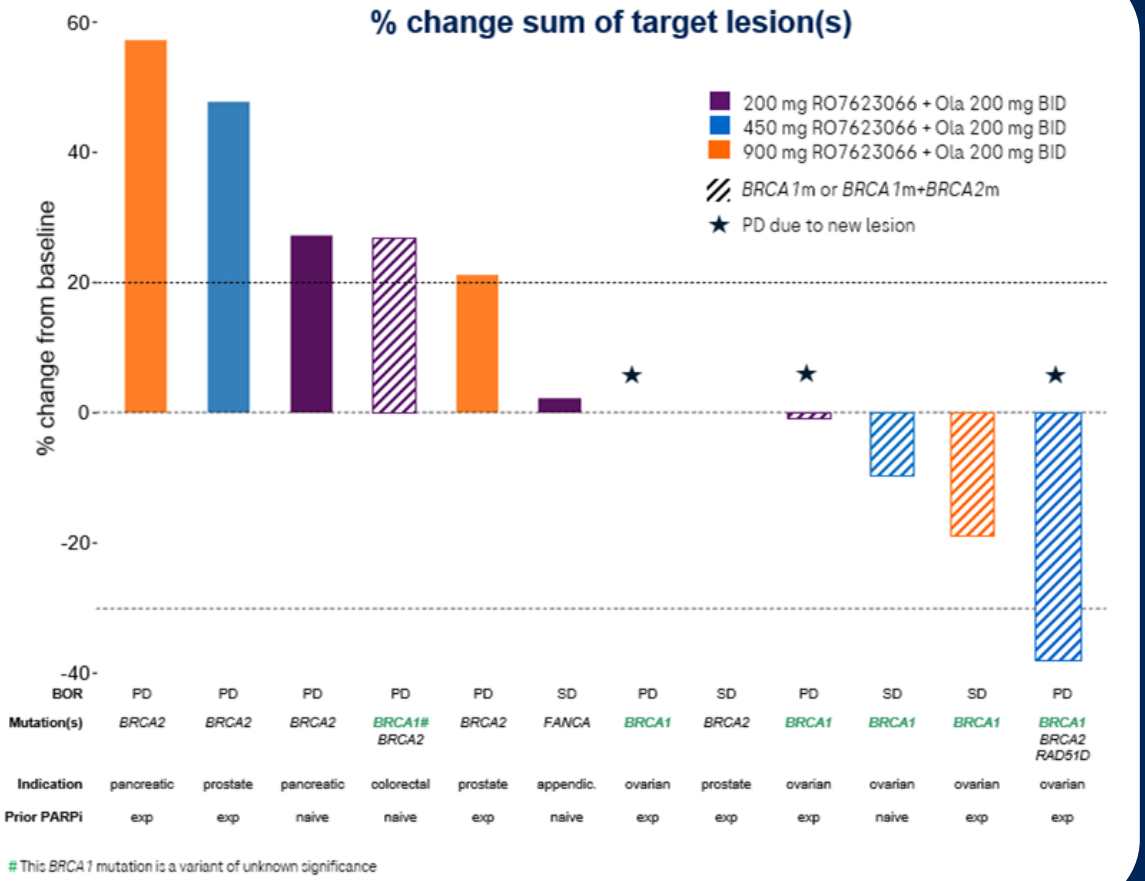
- 74 yr old
- Initial diagnosis Dec 2017
- Advanced fallopian tube cancer with metastases to rectum, lung, peritoneum, lymph nodes
- No HRR mutations
- 5 prior lines of therapy
  - carboplatin/paclitaxel + bevacizumab followed by bevacizumab maintenance
  - doxorubicin
  - carboplatin/gemcitabine
  - PY159 (anti-Trem 1)
  - AB122 (anti-PD-1)/AB308 (anti-TIGIT) until Jul 21
- Start RO7623066: Aug 2021

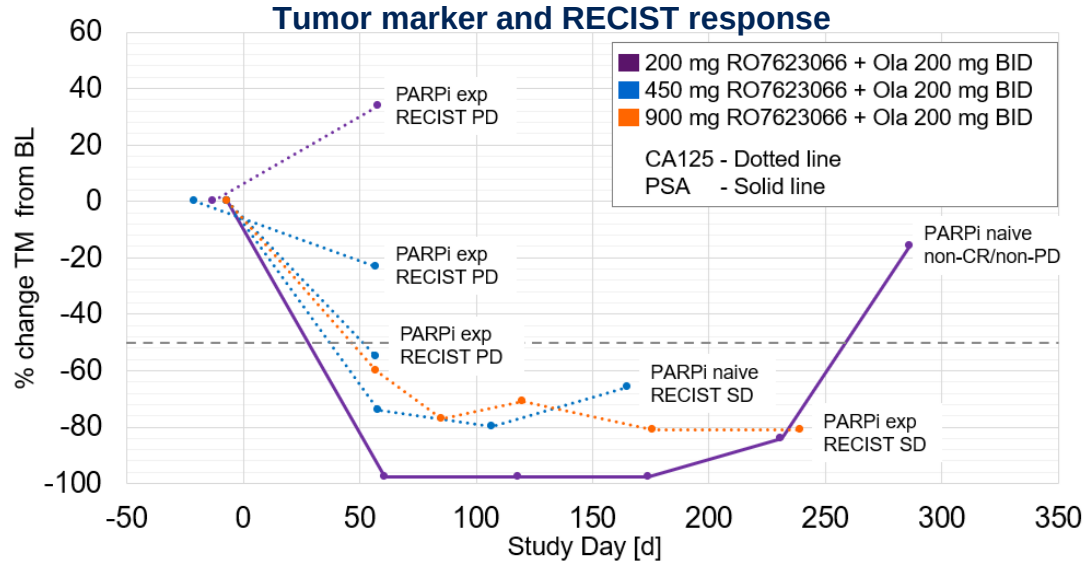


* 5/34 had non-measurable disease, 8/42 patients did not have a tumor re-assessment

PR = Partial Response; SD = Stable Disease

Preliminary anti-tumor activity of RO7623066 + olaparib





- 7/14* (50%) had *BRCA1* or *BRCA1+BRCA2* mutations
- 4/12 (33%) showed BOR of SD per RECIST v1.1
- 3 pts (2 *BRCA1*m ovarian cancer, 1 *BRCA2*m prostate cancer) had tumor marker response (greater than -50%)

*2/14 had non-measurable disease, 1/15 patient did not have a tumor re-assessment

BOR = Best Overall Response; SD = Stable Disease; TM = Tumor Marker

Conclusions and next steps

- RO7623066 is a first-in-class inhibitor of USP1 that potentially synergizes with and overcomes resistance to PARP inhibitors.
- RO7623066 has a favorable safety profile as single agent. In combination with olaparib, the safety profile was manageable despite the rate of anemia. An MTD was not reached.
- PK is almost dose proportional up to 650 mg QD. BID dosing will be pursued due to an absorption limit at higher dose levels.
- Tumor PD data support the postulated mode of action of USP1 inhibition.
- Consistent with preclinical data, preliminary clinical anti-tumor activity of the combination with olaparib appears to be associated with *BRCA1* mutation status.
- Further evaluation of RO7623066 + olaparib in backfill cohorts to determine the RDE/RP2D is ongoing. To address hematologic toxicity, eligibility criteria/ anemia management guidelines have been updated (*e.g.*, Hgb ≥ 10g/dL at baseline).

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