First-in-Class First-in-Human Phase 1 Trial and Translational Study of the Mono (ADP-Ribose) Polymerase-7 (PARP7) Inhibitor RBN-2397 in Patients With Selected Advanced Solid Tumors

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RBN-2397, a First-in-Class PARP7 Inhibitor, Reactivates Interferon Signaling and Antitumor Immunity

- PARP7 activity inhibits tumoral Type I interferon signaling and blocks antitumor immunity
- PARP7 gene is amplified and/or highly expressed in a subset of cancers
- RBN-2397 is an orally bioavailable, potent, selective, small molecule PARP7 inhibitor

RBN-2397-19-001 Is a First-in-Human Phase 1 Study of RBN-2397 in Patients With Advanced Solid Tumors

Dose Escalation: 3+3 Design Completed[1]

Adults with advanced or metastatic solid tumors

- Intermittent BID Dosing Schedule: 14 days on / 7 days off (n = 25)
- Continuous BID Dosing Schedule: 21 days on (n = 25)

→ MTD / RP2D

Dose Expansion: Ongoing

- Squamous Cell Carcinoma of Lung (SCCL, n = 22)
- Head & Neck Squamous Cell Carcinoma (HNSCC, n = 17)
- Hormone Receptor Positive Breast Cancer (HR+ BC, n = 14)
- PARP7 Amplified Tumors (n = 0)

- 50 patients received doses from 25 to 500 mg BID
- RP2D was 200 mg BID on a continuous schedule with micronized tablets
- RBN-2397 was well tolerated with majority of AEs being mild to moderate
- Preliminary antitumor activity observed including 1 PR and 13 SD with clinical benefit > 4 months
- Proof of mechanism demonstrated by increasing tumoral Type I IFN response and immune cell infiltration after treatment with RBN-2397 at doses ≥ 25 mg BID

- Includes cancers of squamous histology and selected other tumor types predicted to respond to RBN-2397 based on findings from the Dose Escalation phase
- Objectives: Assess safety, PK, PD, and preliminary antitumor activity of RBN-2397 at the RP2D
- Prospective enrollment of PARP7 amplified patients using FoundationOne CDx (defined as >6 copies) was implemented but unsuccessful
- Data cutoff: January 31, 2023

[1]Falchook, ASCO 2021; Kuplast-Barr, AACR 2022.

Patient Demographics and Disposition (Expansion Phase)

	SCCL (N=22)	HNSCC (N=17)	HR+ BC (N=14)	Total (N=53)
Age (years), median (range)	68 (22; 83)	64 (50; 77)	59 (43; 77)	64 (22; 83)
Prior Lines of Therapy, median (range)	2 (1; 5)	3 (2; 7)	5 (1; 8)	3 (1; 8)
Prior Immunotherapy, n (%)				
Yes	18 (81.8)	11 (64.7)	4 (28.6)	33 (62.3)
No	4 (18.2)	6 (35.3)	10 (71.4)	20 (37.7)
Cycles of Treatment Received, median (range)	2 (1; 8)	2 (1; 24)	2 (1; 8)	2 (1; 24)
Treatment Ongoing at Cutoff Date, n (%)	1 (4.5)	2 (11.8)	2 (14.3)	5 (9.4)
Discontinued, n (%)	21 (95.5)	15 (88.2)	12 (85.7)	48 (90.6)
Reason for Discontinuation, n (%)				
Progressive Disease	14 (63.6)	8 (47.1)	10 (71.4)	32 (60.4)
Physician Decision / Withdrawal of Consent	2 (9.1)	4 (23.5)	2 (14.3)	8 (15.1)
AE, non-DLT	1 (4.5)	1 (5.9)	0	2 (3.8)
Other	4 (18.2)	2 (11.8)	0	6 (11.3)

Summary of Treatment-Related Adverse Events

Treatment-Related AEs in ≥ 5% of Patients*

Preferred Term	Expansion Only (N = 53), n (%)		Escalation and Expansion (N = 103), n (%)		
	All Grades**	Grade 3***	All Grades	Grade 3****	Grade 4
Any Related TEAE	39 (73.6)	8 (15.1)	78 (75.7)	16 (15.5)	1 (1.0)
Dysgeusia	20 (37.7)	0	39 (37.9)	0	0
Fatigue	12 (22.6)	1 (1.9)	21 (20.4)	2 (1.9)	0
Nausea	10 (18.9)	1 (1.9)	18 (17.5)	1 (1.0)	0
Decreased Appetite	6 (11.3)	0	14 (13.6)	0	0
Diarrhoea	5 (9.4)	0	10 (9.7)	2 (1.9)	0
Weight Decreased	3 (5.7)	0	8 (7.8)	0	0
AST Increased	5 (9.4)	2 (3.8)	8 (7.8)	3 (2.9)	1 (1.0)
ALT Increased	5 (9.4)	2 (3.8)	7 (6.8)	2 (1.9)	1 (1.0)
Anaemia	1 (1.9)	1 (1.9)	6 (5.8)	3 (2.9)	0
Constipation	0	0	5 (4.9)	0	0
Pruritus	3 (5.7)	0	5 (4.9)	0	0

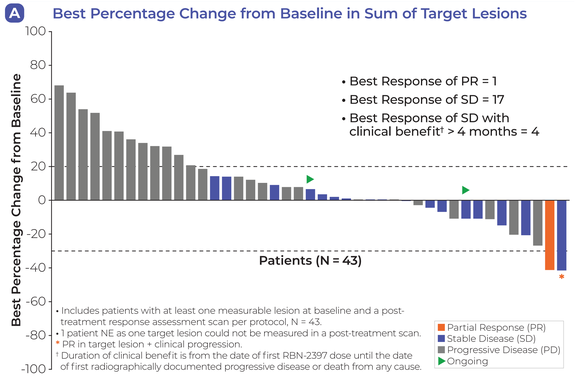
*Table cutoff of ≥ 5% is based on All Grades column for combined escalation and expansion phase (N=103). **No Gr4 AEs were reported in the expansion phase. ***Other Gr3 AEs reported in the expansion phase not presented in the Table (each n=1): Pleural infection; pneumonitis. ****Other Gr3 AEs reported in the escalation phase not presented in the Table (each n=1): Bilirubin increase; febrile neutropenia, neutropenia; thrombocytopenia.

In the Expansion Phase:

- Treatment-related SAEs occurred in 3 patients (5.7%): Gr2 pneumonitis, Gr3 pleural infection and Gr1 post-obstructive pneumonia, Gr3 pneumonitis
- Treatment interruptions due to AEs occurred in 15 patients (28.3%) and discontinuations due to AEs occurred in 6 patients (11.3%)
- No immune-related AEs reported
- Lower frequency of hematologic toxicities compared to approved PARP1/2 inhibitors

Clinical Response

A Best Percentage Change from Baseline in Sum of Target Lesions



B Duration on Study Treatment

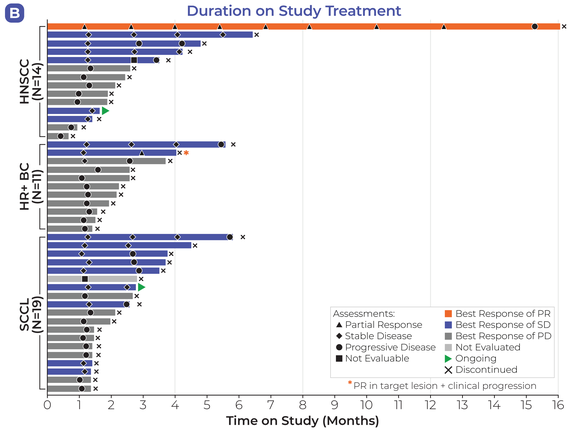
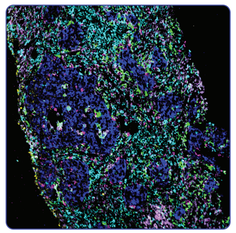


Figure 1: Clinical response assessed from 43 evaluable patients, per RECIST v1.1

- One durable PR in HNSCC patient with 41% tumor reduction; was on study for ~16 months and now off study
- One HR+ BC pt with SD after 2 cycles, then 41% tumor reduction in target lesion along with clinical progression (rising CEA, increasing SUV on PET/CT) after 4 cycles; now off study
- 17 patients had SD, out of which 4 had clinical benefit > 4 months

Durable Partial Response in Patient With HNSCC



50-year-old white male with paranasal sinus carcinoma; non-smoker; HPV negative

- Five prior lines of systemic therapy
- Documented disease progression on immediate prior line of therapy (pembrolizumab and investigational STING agonist)
- Baseline biopsy showed:
  - High CD8 and Granzyme B density (744 and 167 objects/mm², respectively)
  - TMB = 2.5 muts/Mb; SMARCB1 deletion; MSS
- On-treatment sample was not evaluable
- Patient was on study for ~16 months

Figure 2: MIBI-TOF data illustrating the presence of multiple immune cell populations in the baseline pelvic mass biopsy. Image is representative of three regions of interest.

Abbreviations: CEA = carcinoembryonic antigen; CN = copy number; DLT = dose-limiting toxicity; MIBI-TOF = multiplexed ion beam imaging by time of flight; MSS = microsatellite stable; MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose; SUV = standardized uptake value; TMB = tumor mutational burden.

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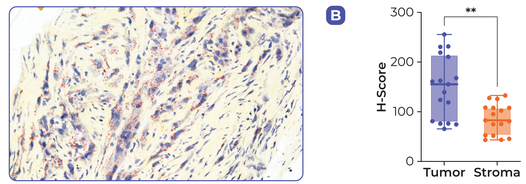
PARP7 Is Expressed in All Baseline Patient Biopsies

PARP7 mRNA Expression in Baseline Biopsies Is Higher in Tumor Cells than Stroma



C PARP7 Copy Number is Increased in Many Baseline Biopsies

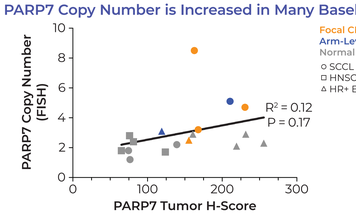


Figure 3: A) Representative RNA ISH image from the baseline chest wall biopsy of an SCCL patient (40x magnification). Tumor and stroma H-scores were calculated by image analysis (HALO) to be 210 and 75, respectively. Pink dots represent individual copies of PARP7 mRNA; the slide was counterstained with hematoxylin. **B)** Comparison of PARP7 RNA ISH tumor and stroma H-scores for 17 baseline biopsies, illustrating the significantly higher mRNA expression seen in tumor cells compared to surrounding stroma (Tumor H-scores range 66-256; Stroma H-scores range 43-133; P = 0.0026). **C)** Comparison of PARP7 copy number (CN; FISH) and PARP7 mRNA expression (RNA ISH Tumor H-score) on 17 baseline biopsies. Focal CN gains have a ratio of PARP7:Chromosome 3 > 2. Arm-level CN gains have ≥ 3 copies of PARP7, with concomitant gains in chromosome 3.

Paired Tumor Biopsies Show Evidence of Immune Activation

Increases in CD8 and/or Granzyme B Expression in 12/20 On-Treatment Biopsies

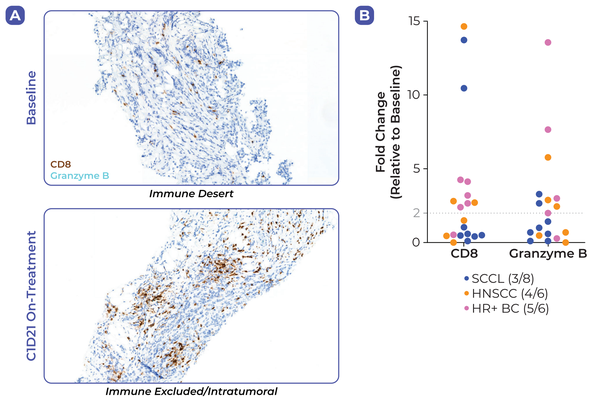
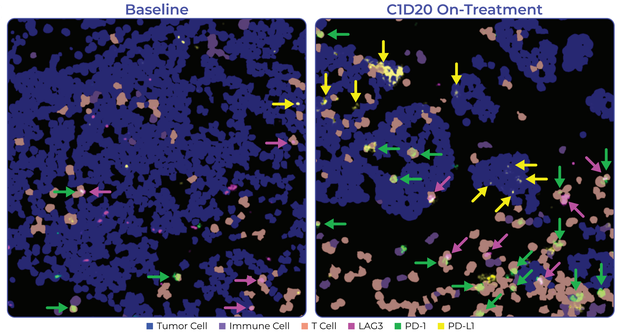


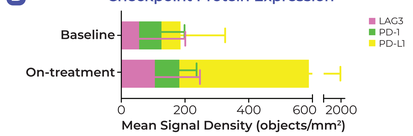
Figure 4: A) Representative 20x images from the baseline and on-treatment lymph node biopsies of a patient with HR+ BC who exhibited a mixed response: 41% reduction in their target lesion, accompanied by clinical progression. Image analysis identified a 2.7-fold increase in CD8 density and a 3-fold increase in Granzyme B density in the on-treatment sample. **B)** CD8 and Granzyme B expression were assessed by IHC in paired biopsies from 20 patients. Positivity for each marker was quantified by image analysis (HALO), and fold change over baseline was plotted for the on-treatment samples. CD8⁺ T cells were increased ≥ 2-fold in 10/20 samples, while Granzyme B expression increased by ≥ 2-fold in 9/19 samples.

Increases in Immune Checkpoint Expression Indicate Potential of RBN-2397 to Prime Tumors for Immune Checkpoint Inhibitor Therapy

A



B Checkpoint Protein Expression



C Increased Checkpoint Expression Observed in On-Treatment Biopsies

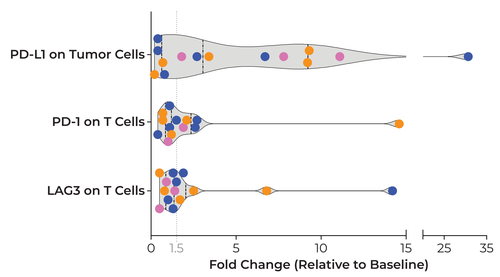


Figure 5: A) MIBI-TOF cell classification images illustrate increased expression of multiple checkpoint proteins in the on-treatment lung biopsy of an HNSCC patient. Images are representative of 12 (baseline) and 7 (on-treatment) regions of interest. **B)** Quantification of total signal density for the proteins of interest for the patient shown in panel **A**. **C)** Checkpoint expression increases observed in the three cohorts for PD-1 and LAG3 on T cells and PD-L1 on tumor cells across all biopsies via MIBI-TOF analysis (n = 14).

Conclusions

- Single-agent RBN-2397 at 200 mg BID was well tolerated, with majority of AEs being mild to moderate
- Preliminary antitumor activity observed in tumor types predicted to respond to RBN-2397
- PARP7 expression seen in all baseline biopsies with higher expression in tumor cells compared to stroma
- PARP7 copy number gains identified in baseline biopsies that trend toward higher mRNA expression
- Demonstration of increase in CD8⁺ T cells and/or Granzyme B expression, as well as increases in checkpoint proteins across tumor types in majority of on-treatment biopsies
- No clear correlation between PARP7 mRNA expression, biological activity, and clinical activity
- Translational data demonstrate immunomodulatory mechanism of RBN-2397 and support ongoing trials of RBN-2397 in combination with pembrolizumab (NCT05127590) and nivolumab (jRCT2031210373)

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