2023 ESMO TAT

Targeted Anticancer Therapies

First-in-Class First-in-Human Phase 1 Trial of RBN-2397 in Patients with Advanced Solid Tumors Validates PARP7 as a Novel Anticancer Therapeutic Target

Timothy A. Yap[1], Andres Cervantes[2], Gerald S. Falchook[3], Manish R. Patel[4], Dejan Juric[5], Saiama N. Waqar[6], Erin L. Schenk[7], Geoffrey Shapiro[8], Valentina Boni[9], Cesar A. Perez[10], Barbara Burtness[11], Yana G. Najjar[12], Fabricio Racca[13], Katerin Rojas[14], Kristy Kuplast-Barr[15], Kristen McEachern[15], Manoj Samant[15], Viviana Bozón[15], Sudha Parasuraman[15], Melissa Johnson[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Hospital Clinico de Valencia, Biomedical Research Institute INCLIVA, Valencia, Spain; [3]Sarah Cannon Research Institute (SCRI) at HealthONE, Denver, CO; [4]SCRI, Florida Cancer Specialists, Sarasota, FL; [5]Massachusetts General Hospital, Boston, MA; [6]Washington University School of Medicine, St. Louis, MO; [7]University of Colorado, Anschutz Medical Center, Aurora, CO; [8]Dana Farber Cancer Institute, Boston MA; [9]NEXT Madrid, University Hospital QuirónSalud Madrid, Spain; [10]SCRI at Florida Cancer Specialists, Lake Nona, Orlando, FL; [11]Yale University School of Medicine, New Haven, CT; [12]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA; [13]Hospital Quirónsalud Barcelona – NEXT Barcelona, Barcelona, Spain; [14] Vall d'Hebron University Hospital, Barcelona, Spain; [15]Ribon Therapeutics, Cambridge, MA; [16]SCRI, Nashville, TN

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Declaration of Interests

Timothy A. Yap

Employment: University of Texas MD Anderson Cancer Center, where I am Medical Director of the Institute for Applied Cancer Science, which has a commercial interest in DDR and other inhibitors (IACS30380/ART0380 was licensed to Artios)

Grant/Research support (to Institution): Acrivon, Artios, AstraZeneca, Bayer, Beigene, BioNTech, Blueprint, BMS, Clovis, Constellation, Cyteir, Eli Lilly, EMD Serono, Forbius, F-Star, GlaxoSmithKline, Genentech, Haihe, ImmuneSensor, Ionis, Ipsen, Jounce, Karyopharm, KSQ, Kyowa, Merck, Mirati, Novartis, Pfizer, Ribon Therapeutics, Regeneron, Repare, Rubius, Sanofi, Scholar Rock, Seattle Genetics, Tesaro, Vivace and Zenith.

Consultancies: AbbVie, AstraZeneca, Acrivon, Adagene, Almac, Aduro, Amphista, Artios, Athena, Atrin, Avoro, Axiom, Baptist Health Systems, Bayer, Beigene, Boxer, Bristol Myers Squibb, C4 Therapeutics, Calithera, Cancer Research UK, Clovis, Cybrexa, Diffusion, EMD Serono, F-Star, Genmab, Glenmark, GLG, Globe Life Sciences, GSK, Guidepoint, Idience, Ignyta, I-Mab, ImmuneSensor, Institut Gustave Roussy, Intellisphere, Jansen, Kyn, MEI pharma, Mereo, Merck, Natera, Nexys, Novocure, OHSU, OncoSec, Ono Pharma, Pegascy, PER, Pfizer, Piper-Sandler, Prolynx, Repare, resTORbio, Roche, Schrodinger, Theragnostics, Varian, Versant, Vibliome, Xinthera, Zai Labs and ZielBio

Stockholder in: Seagen

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

PARP7 is a stress-induced monoART* not typically expressed in normal tissues

PARP7 expression blocks antitumor immunity

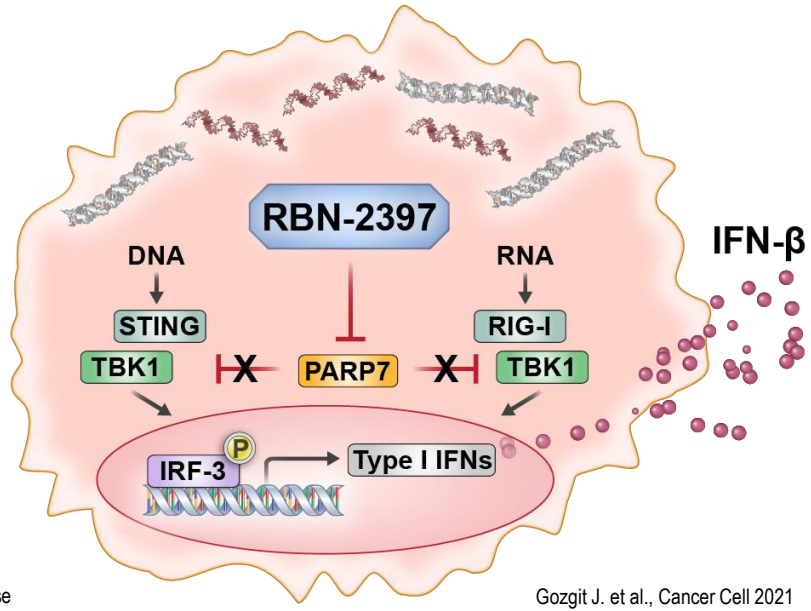
- Inhibits tumoral Type I interferon signaling

PARP7 gene is amplified and/or highly expressed in a subset of cancers

RBN-2397: orally bioavailable, potent, selective, small molecule PARP7 inhibitor

- Complete tumor regressions in preclinical models as single agent and in combination with anti-PD-1 therapy
- Tumor-produced Type I IFN and CD8 T cells are essential for antitumor immunity

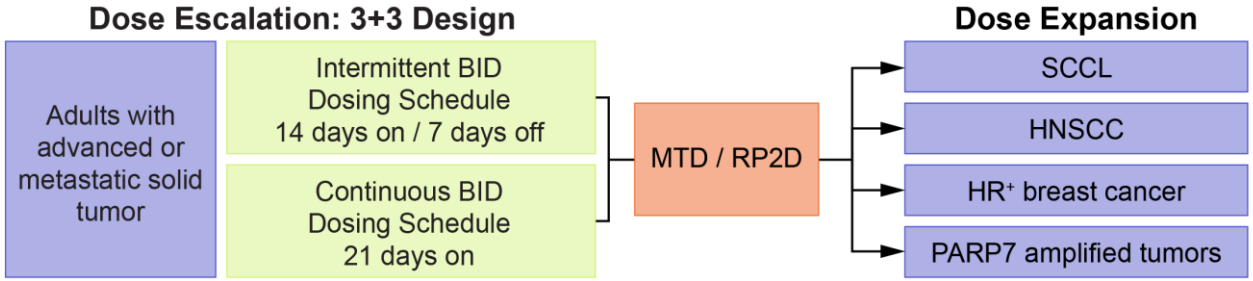
RBN-2397 "releases the brake" and induces Type I IFNs



*Mono-ADP-ribosyltransferase

Gozgit J. et al., Cancer Cell 2021

Study RBN-2397-19-001: First-in-Human Phase 1 Trial of RBN-2397 in Patients with Advanced Solid Tumors



Dose Escalation

- 50 patients enrolled; doses from 25 mg to 500 mg BID tested across both dosing schedules and relative bioavailability assessment
- Most common tumor types were breast (n=8), lung (n=7), and colon (n=5)

RP2D was 200 mg BID on a continuous dosing schedule with micronized tablets

Dose Expansion

- 53 patients enrolled; SCCL (n=22), HNSCC (n=17), and HR+ breast (n=14)
- RBN-2397 was well tolerated at the RP2D with biological and anti-tumor activity at observed exposures

NCT: 04053673

Patient Demographics and Disposition

Demographics	Dose Escalation N=50	Dose Expansion N=53
Age (Years)		
Mean (SD)	63.1 (11.3)	63.7 (10.8)
Median (range)	67 (33; 81)	64 (22; 83)
Prior Lines of Therapy		
Mean (SD)	4.2 (2.0)	3.6 (1.9)
Median (range)	4 (2; 10)	3 (1; 8)
Gender - N (%)		
Female	28 (56)	18 (34)
Male	22 (44)	35 (66)

Disposition	Dose Escalation N=50	Dose Expansion N=53
Cycles of Treatment Received		
Mean (SD)	4.4 (5.3)	3.3 (3.5)
Median	2.0	2.0
Treatment Ongoing at Cutoff Date - N (%)	0 (0)	5 (9.4)
Discontinued - N (%)	50 (100)	48 (90.6)
Reason for Discontinuation - N (%)		
Progressive Disease	27 (54.0)	32 (60.4)
Physician Decision or Withdrawal of Consent	10 (20.0)	8 (15.1)
AE, non-DLT	2 (4.0)	2 (3.7)
Other	11 (22.0)	6 (11.3)

Data cutoff date: 31 Jan 2023

Single Agent RBN-2397 has a Favorable Safety and Tolerability Profile

Treatment-related AEs in ≥ 5% of Total Treated Study Population

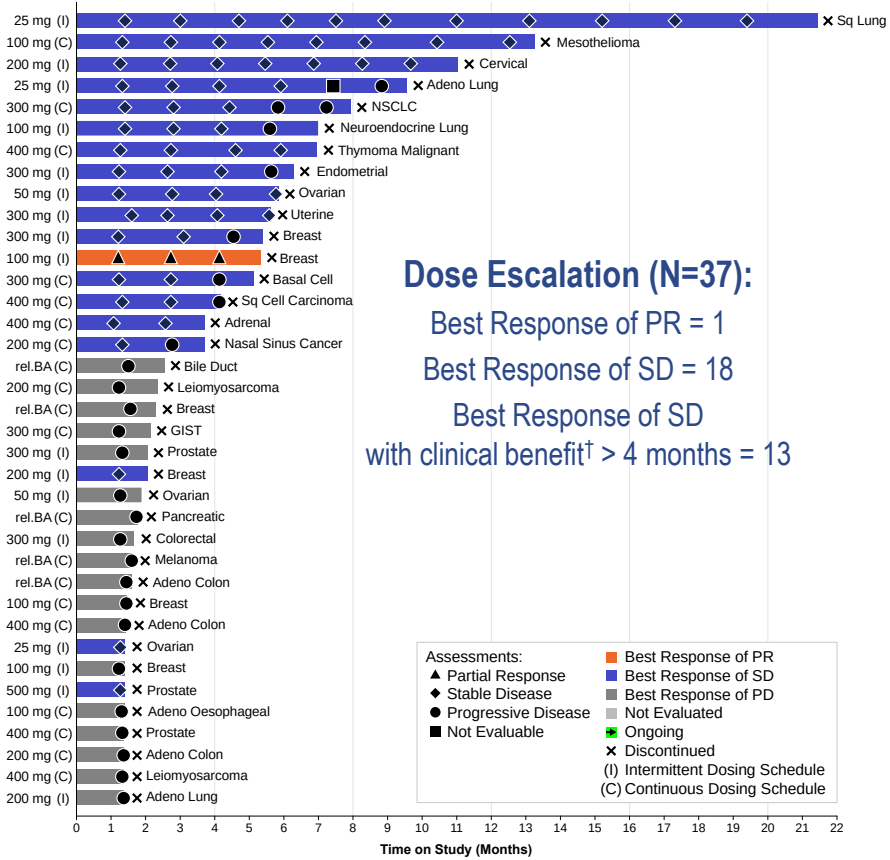
Treatment-related AEs in ≥ 5%	Total		
Preferred Term	N=103 n (%)		
	All Gr	G3*	Gr 4
Any Related TEAE	78 (75.7)	16 (15.5)	1 (1.0)
Dysgeusia	39 (37.9)	0	0
Fatigue	21 (20.4)	2 (1.9)	0
Nausea	18 (17.5)	1 (1.0)	0
Decreased Appetite	14 (13.6)	0	0
Diarrhoea	10 (9.7)	2 (1.9)	0
Weight Decreased	8 (7.8)	0	0
Aspartate Aminotransferase Increased	8 (7.8)	3 (2.9)	1 (1.0)
Alanine Aminotransferase Increased	7 (6.8)	2 (1.9)	1 (1.0)
Anaemia	6 (5.8)	3 (2.9)	0
Constipation	5 (4.9)	0	0
Pruritus	5 (4.9)	0	0

*Other Gr3 AEs reported that are not presented in the Table (each n=1): Bilirubin increase; febrile neutropenia, neutropenia; thrombocytopenia; pleural infection; pneumonitis. No other Gr4 AEs were reported.

- Treatment-related SAEs occurred in 5 (4.9%):
  - 2 in escalation (also DLTs)
    - Gr4 increase in ALT and AST (500 mg BID, intermittent)
    - Gr3 febrile neutropenia (400 mg BID, continuous)
  - 3 in expansion (200 mg BID, continuous)
    - Gr2 pneumonitis
    - Gr3 pleural infection and Gr1 post-obstructive pneumonia
    - Gr3 pneumonitis
- Treatment interruptions due to AEs occurred in 28 (27.2%):
  - Escalation 13 (26.0%)
  - Expansion 15 (28.3%)
- Treatment discontinuation due to AEs occurred in 12 (11.7%) including 6 (12.0%) in escalation and 6 (11.3%) in expansion
- Lower frequency of hematologic toxicities compared to approved PARP1/2 inhibitors

Data cutoff date: 31 Jan 2023

Preliminary Antitumor Activity Observed in Multiple Tumor Types

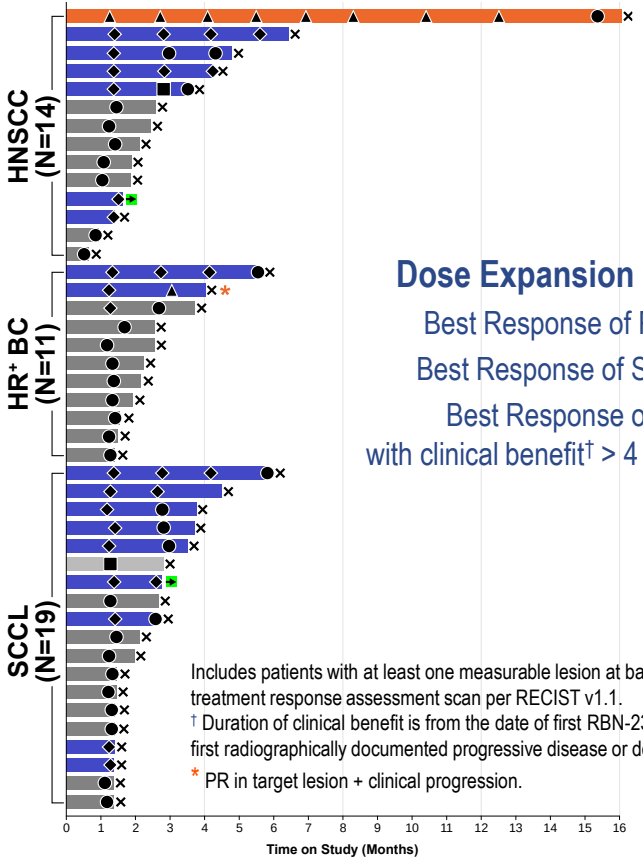


Dose Escalation (N=37):

Best Response of PR = 1

Best Response of SD = 18

Best Response of SD with clinical benefit† > 4 months = 13



Dose Expansion (N=44):

Best Response of PR = 1

Best Response of SD = 17

Best Response of SD with clinical benefit† > 4 months = 4

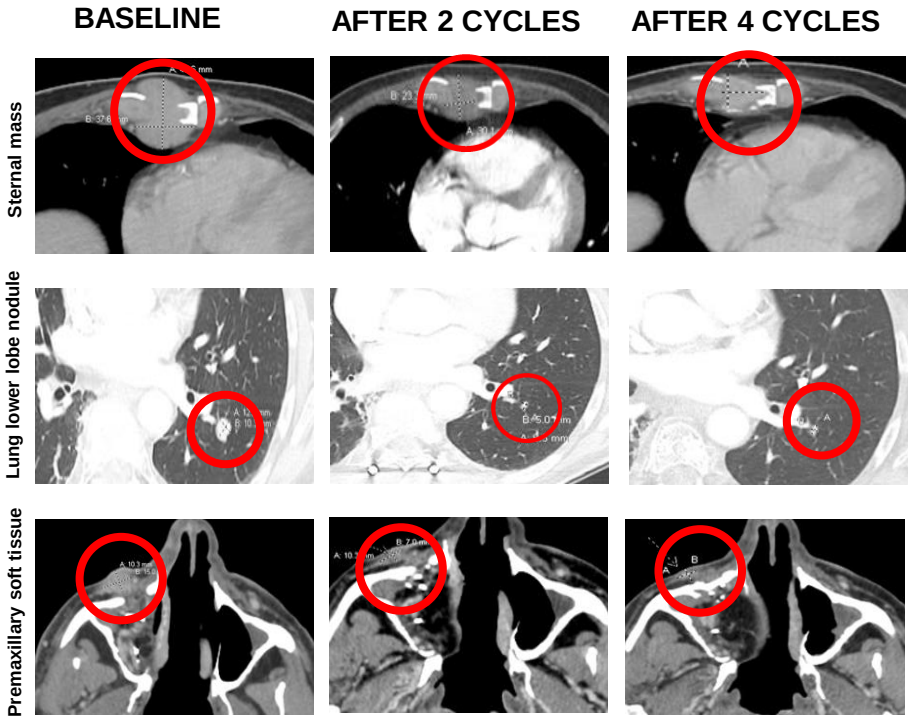
Includes patients with at least one measurable lesion at baseline and a post-treatment response assessment scan per RECIST v1.1.

† Duration of clinical benefit is from the date of first RBN-2397 dose until the date of first radiographically documented progressive disease or death from any cause.

* PR in target lesion + clinical progression.

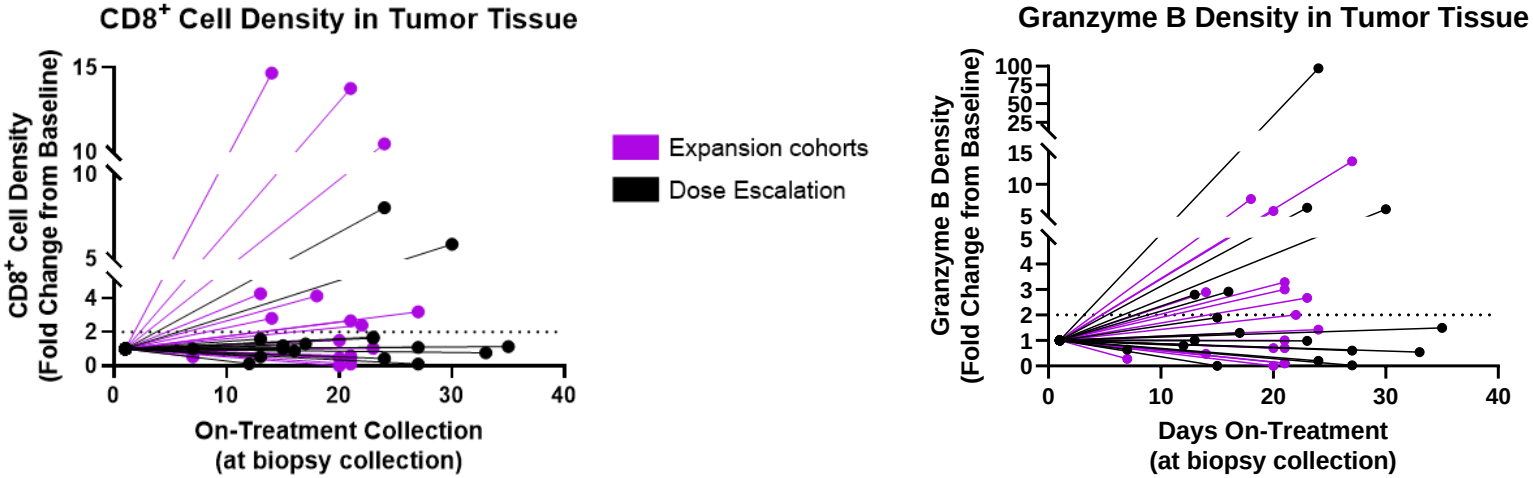
Durable Partial Response in Patient with HNSCC

- 50-year-old WM with paranasal sinus carcinoma; Non-smoker; HPV negative (by CISH)
- Five prior lines of systemic treatment
  - Neo-adjuvant: carboplatin and paclitaxel
  - Adjuvant: cisplatin and pembrolizumab
  - Metastatic (1): pembrolizumab
  - Metastatic (2): cetuximab
  - Metastatic (3): pembrolizumab and investigational STING agonist
- Biomarkers in baseline biopsy
  - High CD8 and Granzyme B density (744 and 167 respectively)
  - FMI: TMB = 2.5 muts/Mb; SMARCB1 deletion; MSS
- Was on study for ~16 months



Timothy A. Yap

CD8+ T Cells and Granzyme B Expression Increased in On-Treatment Biopsies of Patients Treated with RBN-2397

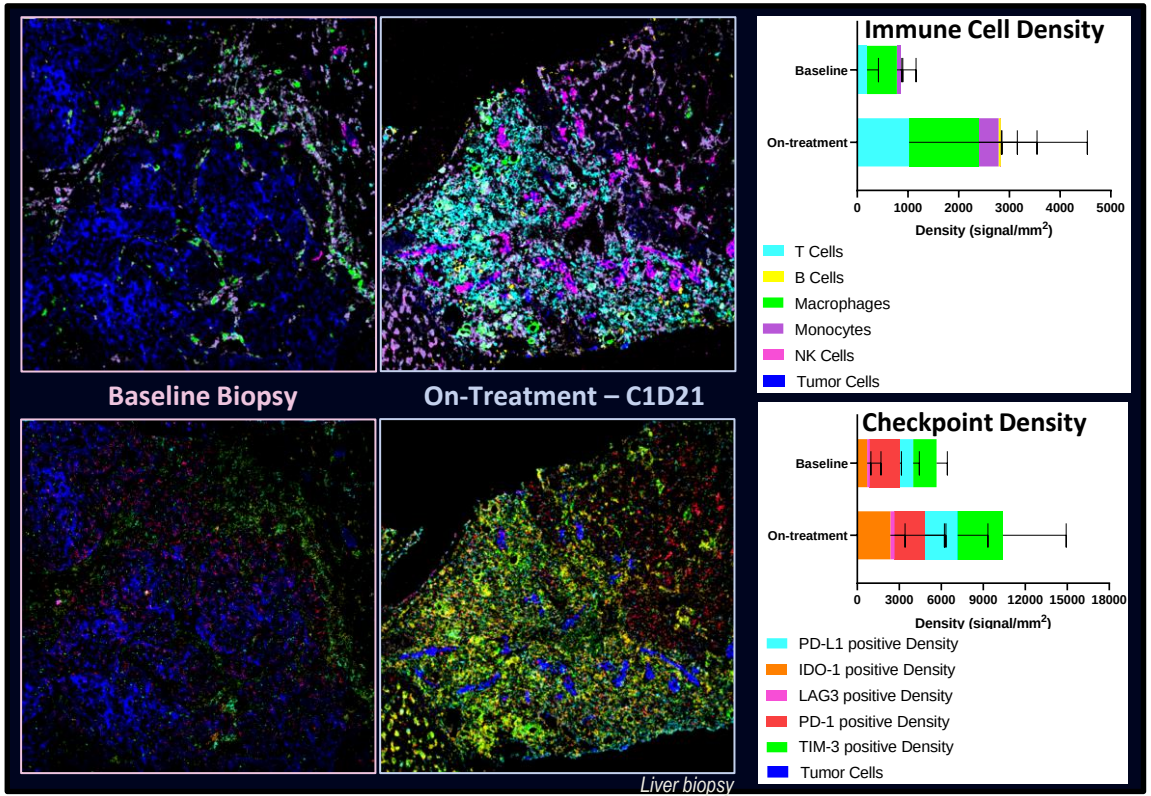


- All baseline biopsies had detectable levels of PARP7 expression by RNA ISH with more expression observed in tumor than in stroma
- Majority of patients in expansion cohorts exhibited increases in CD8+ T cells and/or Granzyme B in on-treatment biopsies, independent of clinical response and cancer types

Proof of Mechanism Demonstrated in SCCL Patient

Increases in T Cells and Macrophages On-Treatment is Evidence of Immune Activation

- Prior lines of systemic therapy
  - Adjuvant: Carboplatin/Taxol
  - Metastatic: Nivolumab
- Best response on RBN-2397: PD in Cycle 3
- Baseline molecular characteristics
  - High PARP7 mRNA expression by RNA ISH (RNAscope) Tumor H-Score = 230
  - PARP7 amplification identified by FOneCDx, confirmed by FISH
- Changes in on-treatment biopsy (by MIBI-TOF)
  - Increases in multiple immune cell populations such as $CD8^+$ T cells, monocytes, and macrophages
  - Increases in expression for multiple checkpoint proteins
    - PD-1 increases on T cells
    - PD-L1 increases on tumor cells



RBN-2397 is a Biologically Active Agent with a Favorable Safety Profile

- **RBN-2397 was well tolerated with majority of AEs being mild to moderate**
  - No significant chronic or immune-related toxicities observed
- **Preliminary anti-tumor activity observed in both dose escalation and expansion cohorts**
  - Dose escalation: 1 PR in HR+ breast cancer and 13 SD with clinical benefit > 4 months
  - Dose expansion: 1 PR in HNSCC and 4 SD with clinical benefit > 4 months
- **PARP7 expression seen in all evaluated baseline biopsies with higher expression in tumor cells compared to stroma**
- **Induction of adaptive immunity following RBN-2397 treatment evidenced by increases in $CD8^+$ T cells and/or Granzyme B expression in most expansion cohort patients across tumor types**
  - Increased expression of various checkpoint proteins including PD-1 on T cells and PD-L1 on tumor cells also noted in a subset of samples which underwent MIBI-TOF analysis
- **These data validate PARP7 as a novel anticancer therapeutic target and confirm proof of RBN-2397 mechanism**
  - Support ongoing trials of RBN-2397 in combination with pembrolizumab (NCT05127590) and nivolumab (jRCT2031210373)

2023 ESMO TAT

Targeted Anticancer Therapies

The authors would like to thank the patients, their families and caregivers, and the clinical staff at each site participating in the study

This study was funded by Ribon Therapeutics

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org