2021 ASCO® ANNUAL MEETING

A FIRST-IN-HUMAN PHASE 1 STUDY OF A NOVEL PARP7 INHIBITOR RBN-2397 IN PATIENTS WITH ADVANCED SOLID TUMORS

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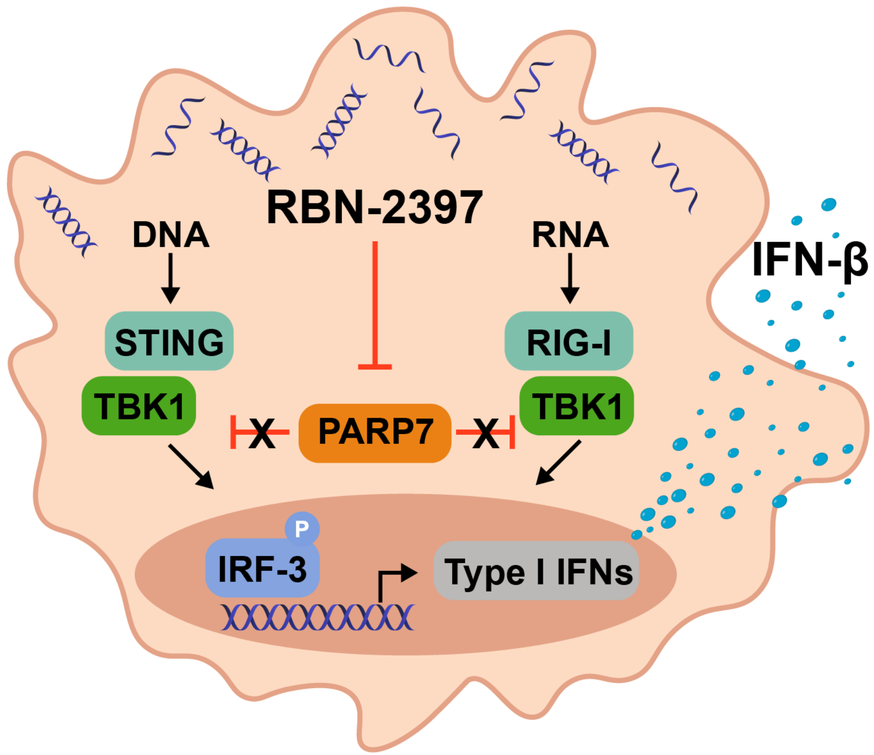
Cancers Express PARP7 in Response to Cellular Stress

- **Targeting Type I IFN response is an emerging therapeutic strategy in oncology**
- **PARP7 expressed in cancer cells blocks intratumoral Type I IFN expression and antitumor immunity**
- **PARP7 is expressed in cancer but not normal tissue**
  - > 90% of NSCLC tumors are PARP7+[1]
- **Frequency of PARP7 amplification[1,2]:**
  - Squamous NSCLC (SCCL): 15-29%
  - HNSCC: 6-14%
  - Cervical cancer: 4-10%
  - Ovarian cancer (all subtypes): 3-15%
- **RBN-2397 is a potent, selective, orally bioavailable inhibitor of PARP7**

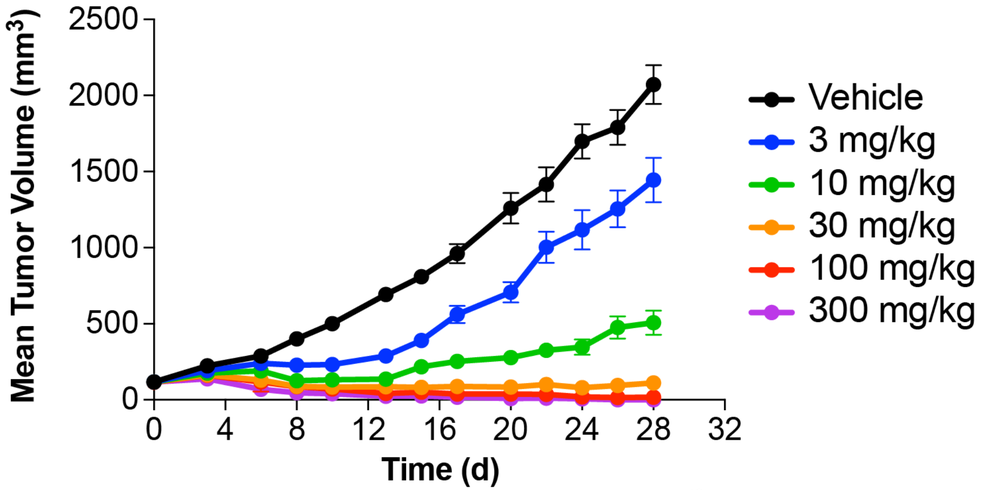
PARP7 inhibition "releases the brake" and induces Type I IFNs

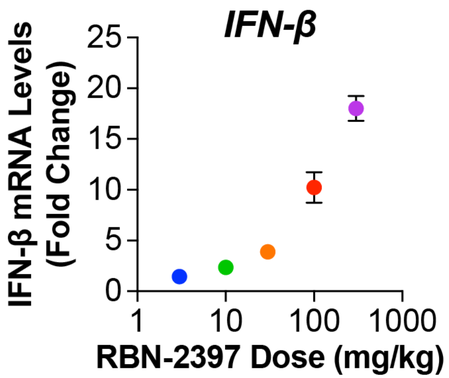


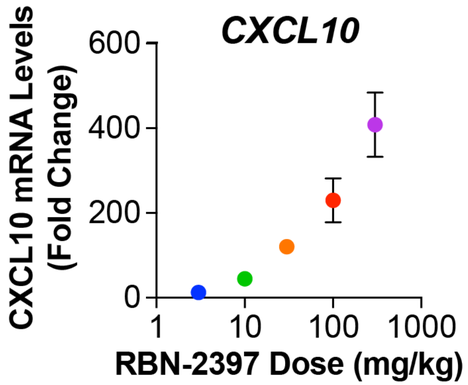
[1] Wong J et al., AACR 2021
[2] TCGA and Foundation Medicine INSIGHTS database

RBN-2397 Restores Tumor-Derived Type I IFN Response Resulting in Antitumor Immunity in Mouse Models

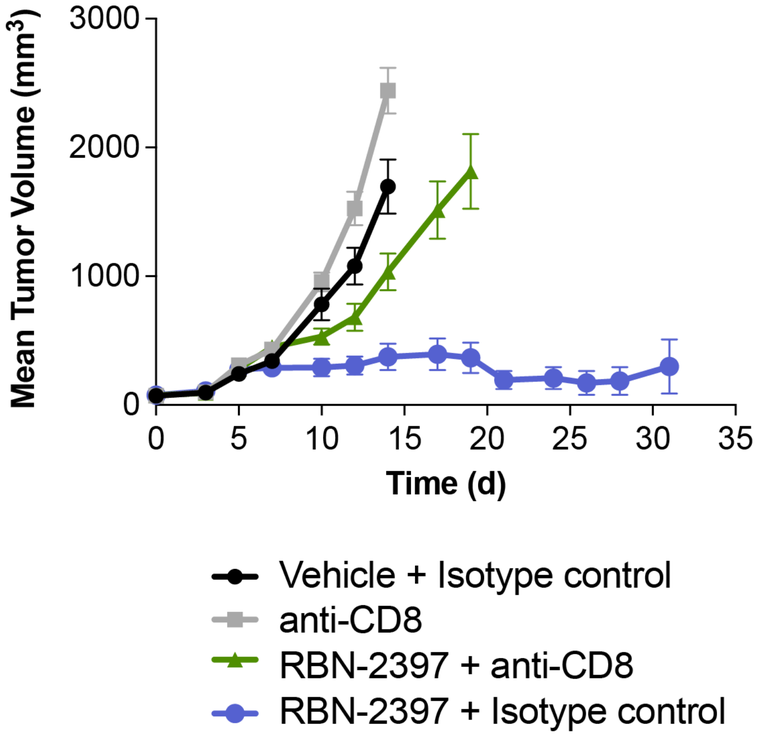
Dose-Dependent, Complete Regressions in an *NCI-H1373* Xenograft Model With Increased ISG Expression





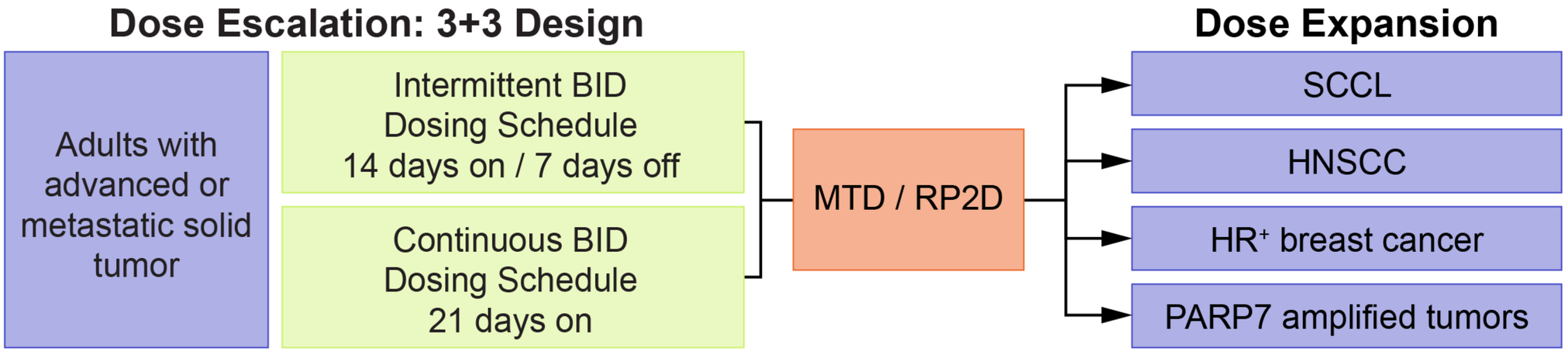


Complete Regressions in a *CT26* Syngeneic Model Dependent on CD8 T Cells



Gozgit J et al., AACR 2020

Study RBN-2397-19-001: Design and Objectives



Primary Objective:

- Determine DLTs, MTD, and establish the RP2D

Key Secondary Objectives:

- Characterize the safety profile
- Examine PK parameters, including the relative bioavailability of a micronized tablet
- Identify preliminary antitumor activity based on RECIST v1.1

Exploratory Objective:

- Examine pharmacodynamic activity and correlate biomarkers with clinical responses

NCT: 04053673

Patient Demographics and Disposition

Patient Demographics	N = 50
Number of pts on intermittent schedule[1]	25
Number of pts on continuous schedule [2]	25
Age (Years)	
Median age (range)	66.5 (33; 81)
Number of Prior Lines of Systemic Therapy	
Median (range)	4.0 (1; 10)
Most Common Cancer Type - N (%)	
Breast	8 (16)
Lung	7 (14)
Endometrial	4 (8)
Colon	4 (8)
Pancreas	4 (8)
Other	23 (46)

Patient Disposition	N = 50
Number of cycles of treatment received	
Mean (SD)	3.9 (4.7)
Median	2
Treatment ongoing at cutoff date - N (%)	6 (12)
Discontinued - N (%)	44 (88)
Reason for discontinuation - N (%)	
Progressive Disease	32 (64)
Physician Decision	4 (8)
Other	5 (10)
AE or DLT	2 (4)
Withdrawal of consent	1 (2)

[1] **Doses tested in intermittent dosing schedule: 25, 50, 100, 200, 300, 500 mg BID**

[2] **Doses tested in continuous dosing schedule: 100, 200, 300, 400 mg BID; relative BA assessment**

Data cutoff date: 01 April 2021

Treatment-Related Adverse Events

Preferred Term (≥ 2 patients)	Intermittent Schedule N = 25 N (%)		Continuous Schedule N = 25 N (%)		Total N = 50 N (%)	
Any treatment-related AE	**All Gr 18 (72)**	**≥ Gr3 5 (20)**	**All Gr 21 (84)**	**≥ Gr3 3 (12)**	**All Gr 39 (78)**	**≥ Gr3 8 (16)**
Dysgeusia/Taste disorder	10 (40)	0	8 (32)	0	18 (36)	0
Decreased appetite	3 (12)	0	5 (20)	0	8 (16)	0
Fatigue	2 (8)	1 (4)	5 (20)	0	7 (14)	1 (2)
Nausea	2 (8)	0	4 (16)	0	6 (12)	0
Anemia	1 (4)	0	4 (16)	2 (8)	5 (10)	2 (4)
Constipation	4 (16)	0	1 (4)	0	5 (10)	0
Diarrhea	4 (16)	2 (8)	1 (4)	0	5 (10)	2 (4)
Weight decreased	4 (16)	0	1 (4)	0	5 (10)	0
Dehydration	1 (4)	0	2 (8)	0	3 (6)	0
Alopecia	1 (4)	0	1 (4)	0	2 (4)	0
AST increased	1 (4)	1 (4)	1 (4)	0	2 (4)	1 (2)
Insomnia	1 (4)	0	1 (4)	0	2 (4)	0
Myalgia	1 (4)	0	1 (4)	0	2 (4)	0
Neutropenia	0	0	2 (8)	1 (4)	2 (4)	1 (2)
Pruritus	1 (4)	0	1 (4)	0	2 (4)	0
Rash maculo-papular	0	0	2 (8)	0	2 (4)	0
Thrombocytopenia	1 (4)	1 (4)	1 (4)	0	2 (4)	1 (2)

Treatment-Related AEs ≥ Gr3 ; N = 8 patients			
AE	**Grade**	**n/N**	**Dose/Schedule**
Anemia	Gr3	1/3	100 mg /continuous
Diarrhea	Gr3	1/3	200 mg /intermittent
Fatigue	Gr3	1/6	300 mg /intermittent
Thrombocytopenia	Gr3	1/6	300 mg /intermittent
Febrile neutropenia Neutropenia	Gr3 Gr3	1/6	400 mg /continuous
Anemia	Gr3	1/6	400 mg /continuous
Diarrhea	Gr3	1/4	500 mg /intermittent
Bilirubin increase ALT/AST increase	Gr3 Gr4	1/4	500 mg /intermittent

Data cutoff date: 01 April 2021

Safety, Tolerability, and DLTs

Dose-Limiting Toxicities, N = 2					
Dose/schedule	**n/N***	**AE**	**Grade**	**Other contributing factors**	**Outcome**
500 mg / intermittent	1/3	ALT/AST increase	Gr4	Underlying liver metastases and fatty liver	Partial resolution of AE at time of study discontinuation in the setting of PD
400 mg / continuous	1/6	Febrile neutropenia	Gr3	Concurrent urinary tract infection and Covid-19 infection	Complete resolution of AE at time of study discontinuation

** Number of patients who completed cycle 1 and evaluable for DLT assessment*

- **500 mg BID (intermittent): deemed a non-tolerated dose**
- **400 mg BID (continuous): deemed tolerated**
- **Two treatment-related SAEs on study corresponding to the DLTs**
- **Six patients had dose reductions**
  - 4 due to Gr2 or Gr3 AEs during Cycles 2 or 3 at doses of 100, 200, 300, 500 mg (1 each)
  - 2 patients (both at 400 mg continuous) as a precautionary measure following DLT (increased ALT/AST) observed in another patient
- **Two patients discontinued study due to treatment-related AEs at 400 mg continuous and 500 mg intermittent dose levels**

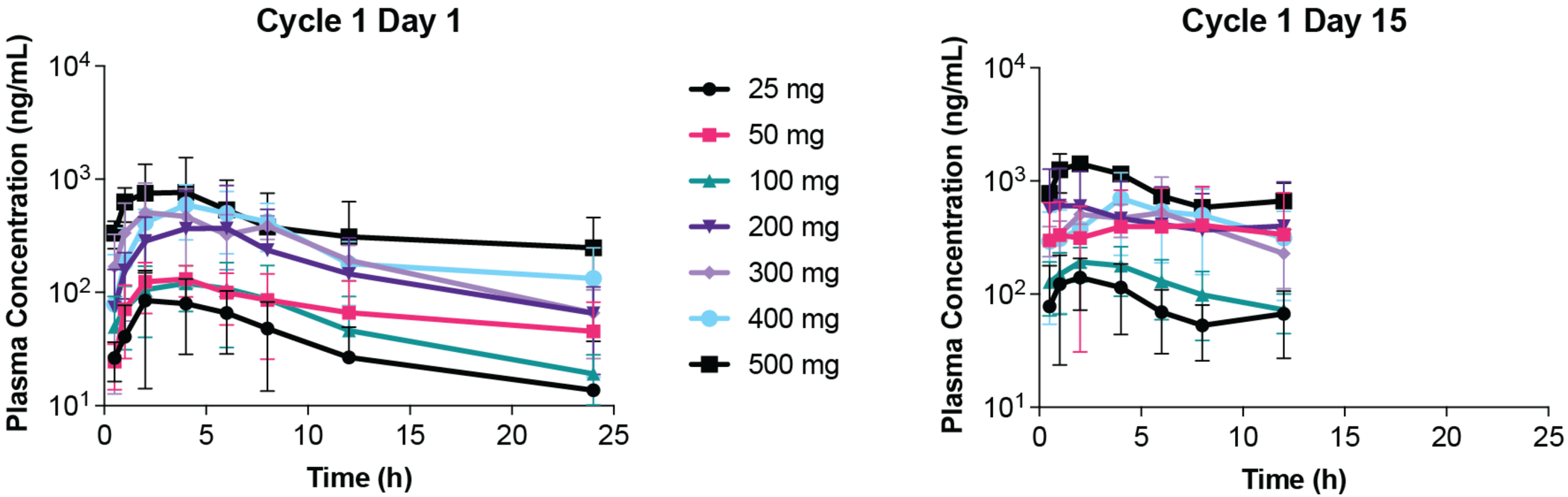
Data cutoff date: 01 April 2021

MTD and RP2D Declaration

- **MTD: 400 mg BID on a continuous dosing schedule**
- **RP2D #1: 300 mg BID on a continuous dosing schedule**
- **Relative bioavailability (BA) of micronized vs unmicronized tablets was evaluated**
  - Micronized RBN-2397 tablets produced to ensure homogenous particle size for better BA
  - Single, fixed-sequence, crossover design; 7 patients treated with 100 mg tablet strength
  - Micronization of RBN-2397 increased exposure as expected
    - 1.5-fold increase in AUC
    - 2.4-fold increase in Cmax
  - Relative BA data compared to PK data from all escalation cohorts using unmicronized tablets
  - Dose of 200 mg BID with micronized tablets determined to provide exposure corresponding to that with RP2D with unmicronized tablets
- **RP2D #2 (with micronized tablets): 200 mg BID on a continuous dosing schedule**

Dose-dependent Pharmacokinetics

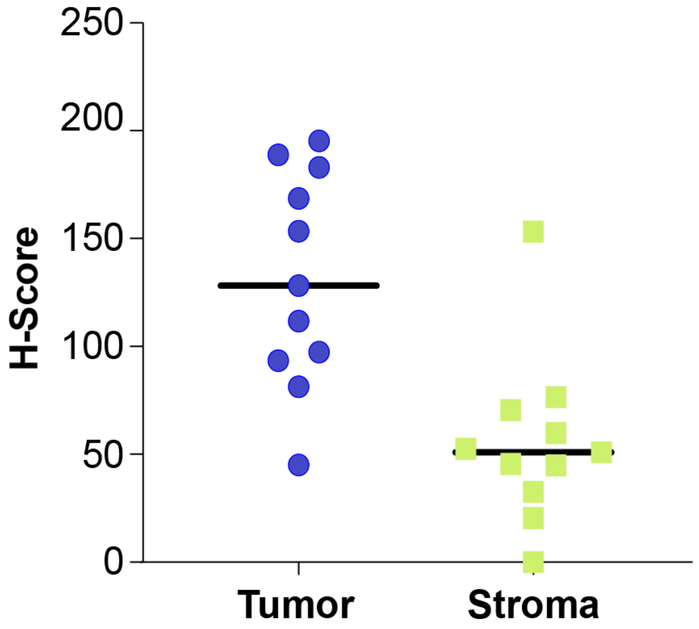
Mean Plasma Concentration-Time Profile



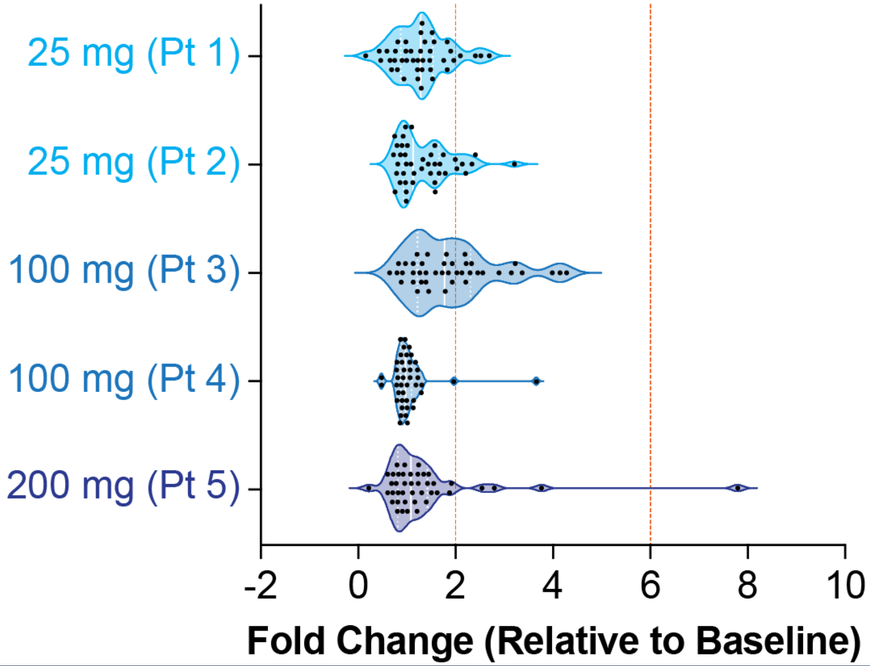
- Dose range of 100-500 mg showed linear exposure
- Steady-state reached between Days 8-15
- Mean half-life approximately 7 hours, supporting BID dosing
- Majority of patient exposures within projected efficacious range based on animal studies

Baseline PARP7 Expression and On-Treatment Induction of Type I IFN and Adaptive Immunity Evident in Patient Biopsies

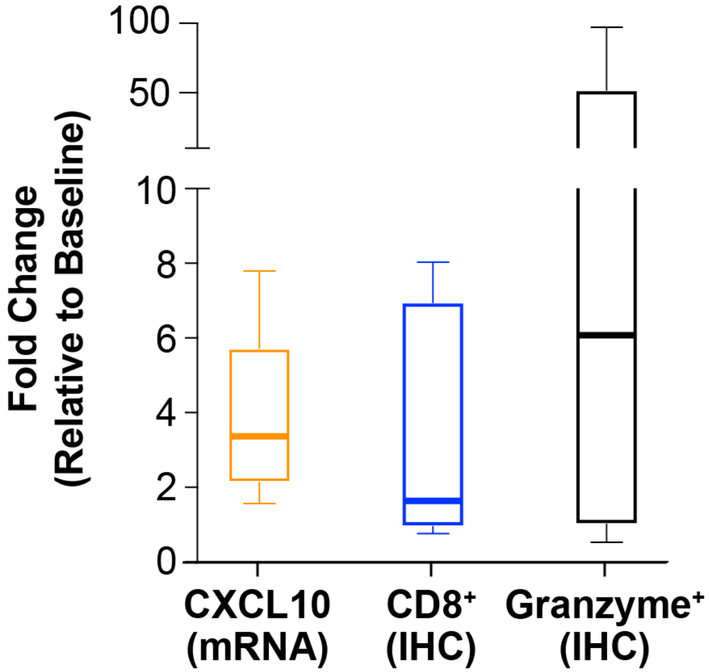
PARP7 Expression in Baseline Biopsies



Induction of ISG Expression in On-Treatment Biopsies



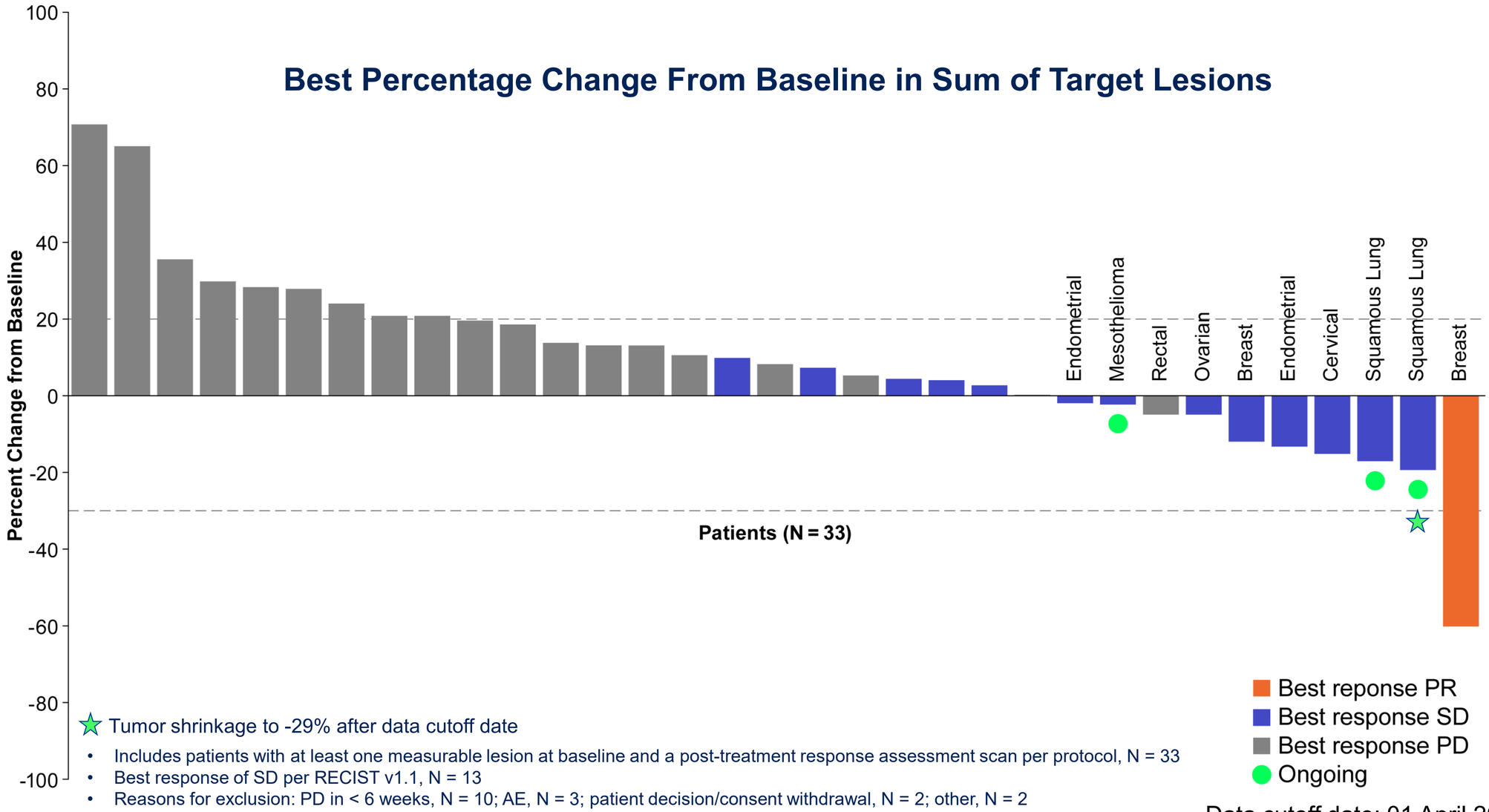
Increase in CXCL10, CD8⁺ T cells, Granzyme B⁺ Cells in On-Treatment Biopsies



Evaluable baseline biopsies, N = 11

On-treatment biopsies collected C2D1-C2D14; evaluable paired biopsies, N = 5

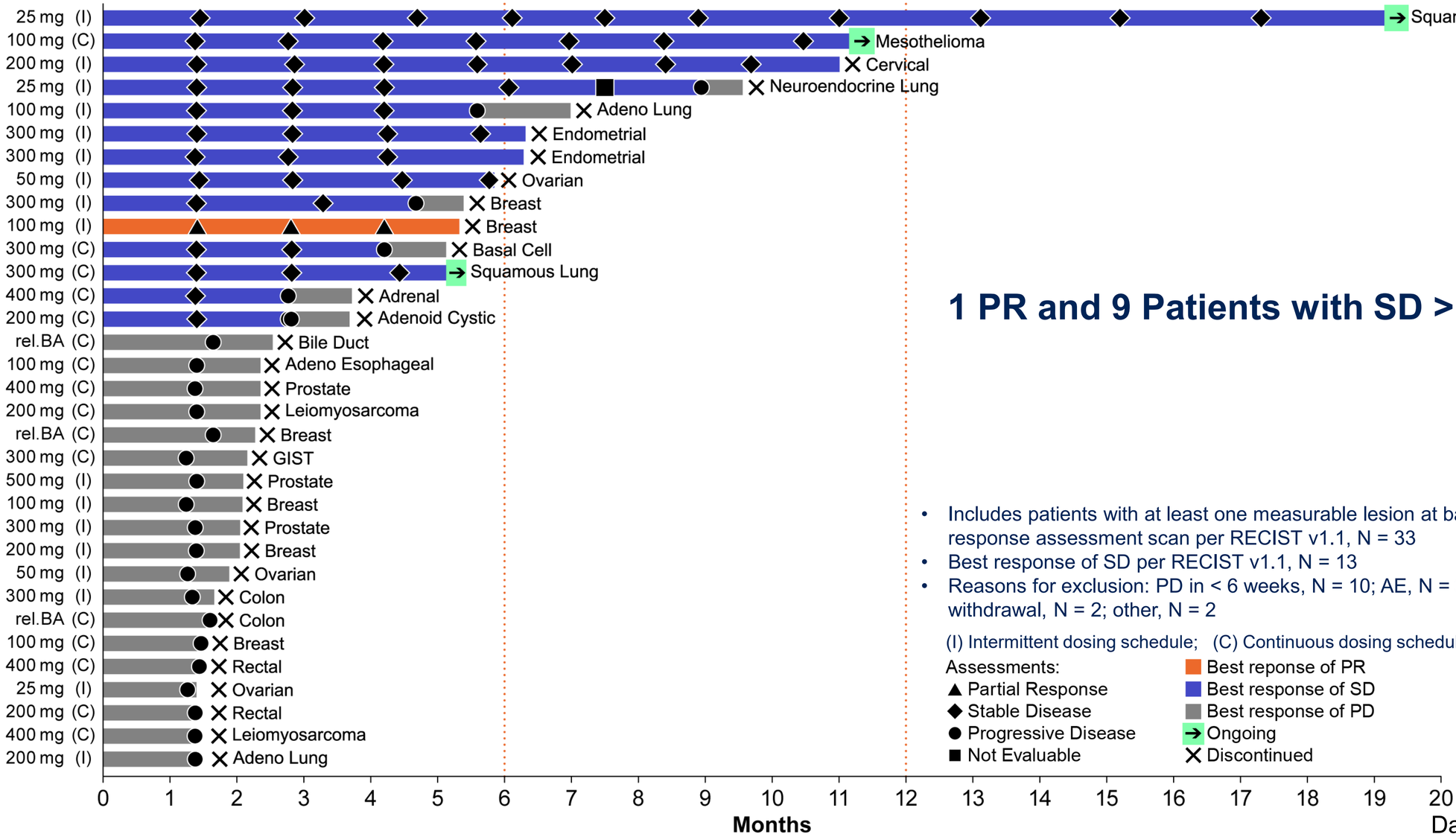
Best Clinical Response



- Includes patients with at least one measurable lesion at baseline and a post-treatment response assessment scan per protocol, N = 33
- Best response of SD per RECIST v1.1, N = 13
- Reasons for exclusion: PD in < 6 weeks, N = 10; AE, N = 3; patient decision/consent withdrawal, N = 2; other, N = 2

Data cutoff date: 01 April 2021

Duration on Study Treatment



1 PR and 9 Patients with SD > 4 Months

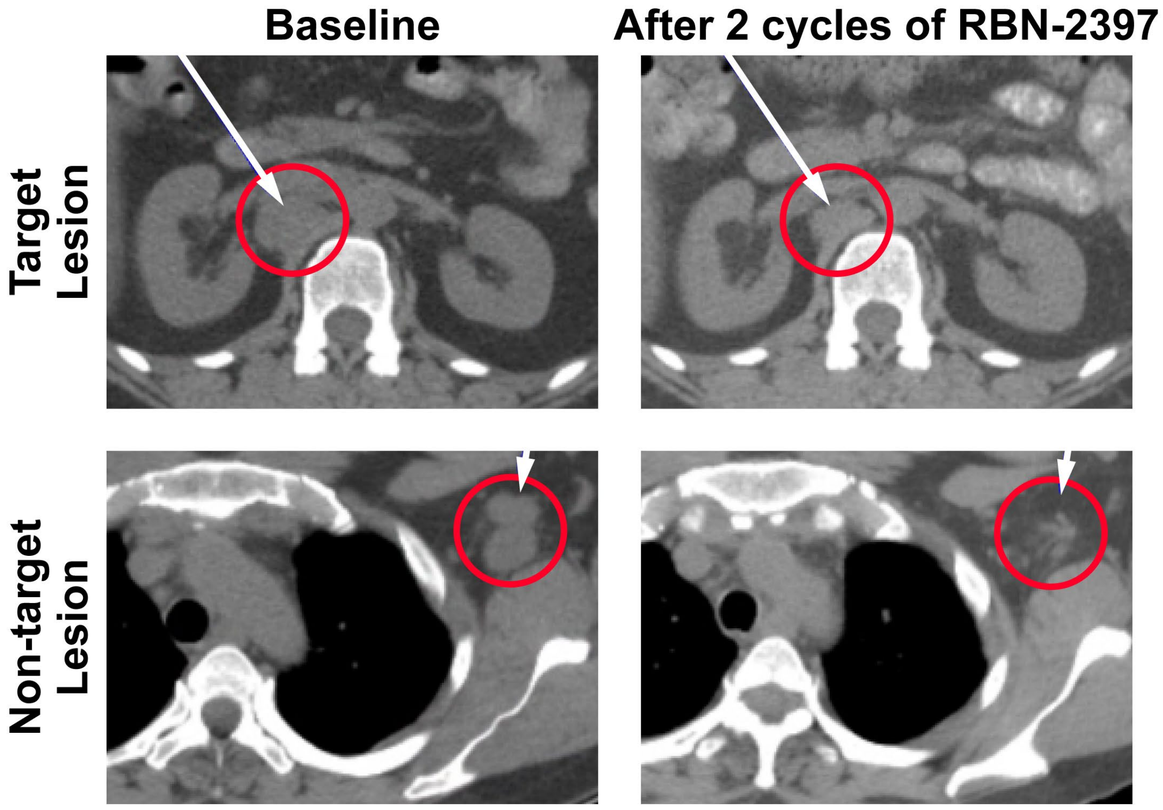
- Includes patients with at least one measurable lesion at baseline and a post-treatment response assessment scan per RECIST v1.1, N = 33
- Best response of SD per RECIST v1.1, N = 13
- Reasons for exclusion: PD in < 6 weeks, N = 10; AE, N = 3; patient decision/consent withdrawal, N = 2; other, N = 2

(I) Intermittent dosing schedule; (C) Continuous dosing schedule

Data cutoff date: 01 April 2021

Confirmed Partial Response in a Breast Cancer Patient

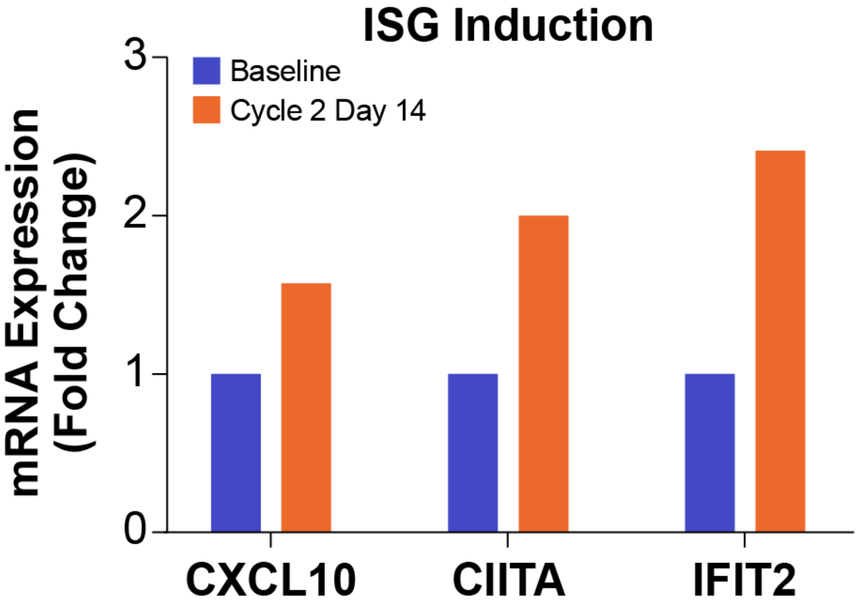
- **52-yr-old with metastatic ductal breast cancer**
  - HR+/HER2- ; BRCA 1/2 wild type
- **6 prior lines of systemic therapy**
  - 1st line: Taxotere, Adriamycin, and cytoxan
  - 2nd line: Triptorelin, tamoxifen
  - 3rd line: Adjuvant tamoxifen
  - 4th line: Palbociclib and letrozole
  - 5th line: Investigational ER alpha antagonist
  - 6th line: Everolimus and exemestane
- **Documented PD prior to study entry**
- **Confirmed PR after 4 cycles of treatment**
  - 60% decrease in target lesion
- **Clinical progression after 6 cycles of treatment**

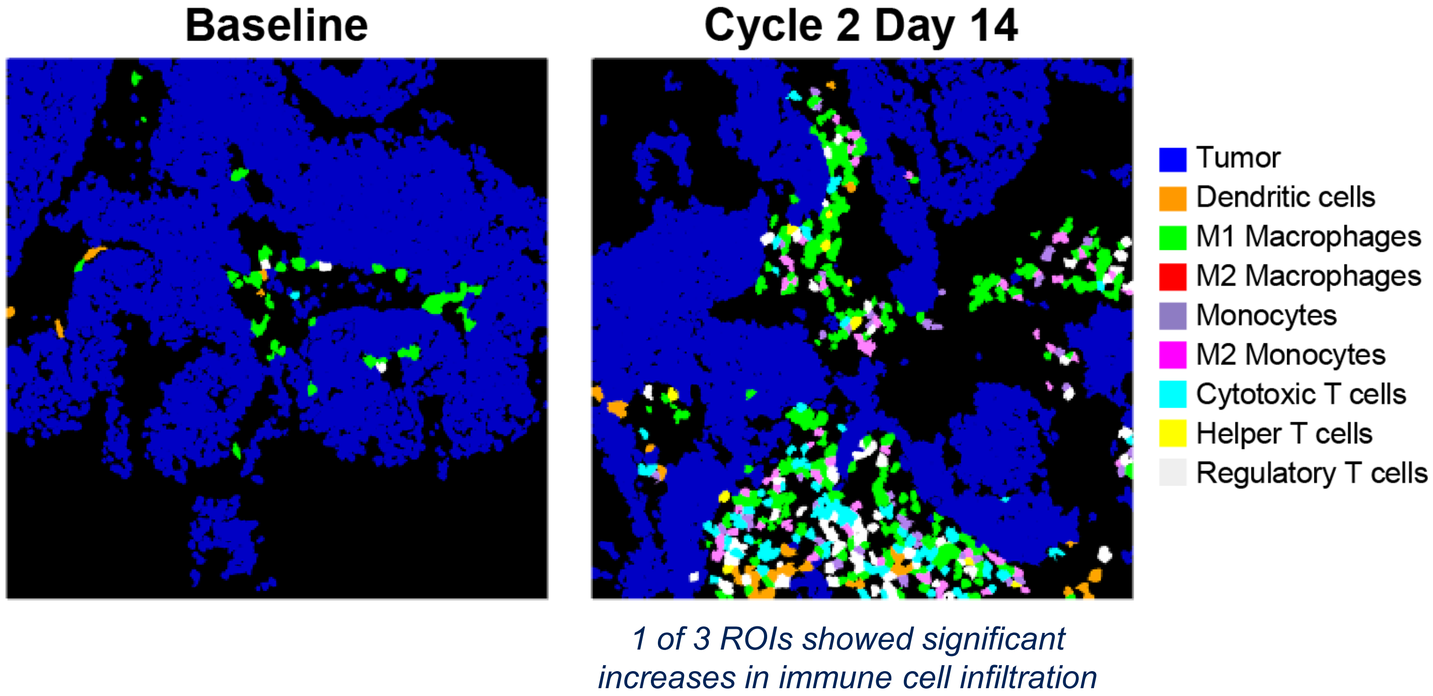


Courtesy: Dr. Manish Patel

Evidence for Adaptive Immune Response in SCCL Patient with Stable Disease for 17+ months

On-Treatment Increase in ISGs, CD8+ T Cells, and M1 Macrophages by MIBI-TOF





1 of 3 ROIs showed significant increases in immune cell infiltration

- 72-year-old with 3 prior lines of therapy; baseline PARP7 tumor H score: 112
- Starting dose: 25 mg BID (intermittent); subsequent escalation to 200 mg (Cycle 14) and then 300 mg BID (Cycle 24)

Conclusions and Next Steps

- Single-agent RBN-2397 was well-tolerated with majority of AEs being mild to moderate
- RP2D was 200 mg BID on a continuous dosing schedule with micronized tablets
- Preliminary antitumor activity observed in tumor types predicted to respond to RBN-2397
    - 1 PR and 9 patients with SD > 4 months
- Proof of mechanism demonstrated by increase in tumoral Type I IFN response and immune cells after treatment with RBN-2397
- Expansion phase currently enrolling patients with SCCL (sq-NSCLC), HNSCC, HR+ breast cancer, and PARP7-amplified tumors
- Phase 1b/2 combination study of RBN-2397 and pembrolizumab in SCCL planned for 2H 2021

Acknowledgements

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