Abstract 9876: RGX-104, a first-in-class immunotherapy targeting the liver-X receptor (LXR); Initial results from the Phase 1b RGX-104 plus Docetaxel combination dose escalation cohorts

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Emerson Lim: Disclosures

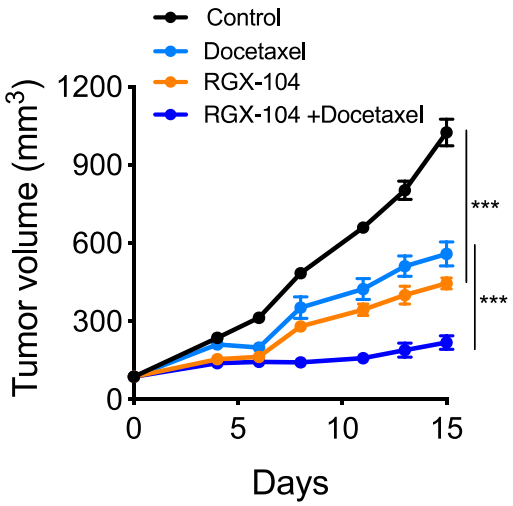
Travel Support: Bristol Myers Squibb

Stockholder: Pfizer

Background and Rationale

- RGX-104 is a first-in-class oral LXR agonist that depletes myeloid-derived suppressor cells (MDSCs) in tumors and circulation via induction of ApoE, resulting in activation of cytotoxic lymphocytes and clinical activity[1,2]
- Taxane therapy promotes the expansion of MDSCs by inducing expression of inflammatory cytokines such as CCL2, resulting in acquired taxane resistance[3,4,5,6,7]
- RGX-104 in combination with the taxane docetaxel is highly efficacious in a mouse tumor model known to activate CCL2 in response to docetaxel[7]
- Therefore, there is mechanistic rationale to combine RGX-104 with taxanes to counteract MDSC-associated taxane resistance, and thereby increase clinical efficacy
- Here we present preliminary safety, pharmacodynamic, and efficacy data from a Phase 1 dose escalation study of RGX-104 in combination with docetaxel in unselected patients with relapsed or refractory solid tumors or lymphoma
- For this dose escalation phase, the primary endpoint was to identify the maximum tolerated dose (MTD), or the maximum tested dose at which multiple dose-limiting toxicities (DLTs) are not observed

RGX-104 + Docetaxel
NSCLC tumor model



A549 tumor model
RGX-104 dose: 50mg/kg QD
***p <0.001

1. Tavazoie M et al. *Cell*. 2018 Feb 8;172(4):825-840
2. Mita M et al. *ASCO* 2018
3. White CM et al. *Cancer Immunol Immunother*. 1998 Apr;46(2):104-12
4. Qian DZ et al. *Prostate*. 2010 Mar 1;70(4):433-42
5. Loberg RD et al. *Cancer Res*. 2007 Oct 1;67(19):9417-24.
6. Volk-Draper L et al. *Cancer Res*. 2014 Oct 1;74(19):5421-34.
7. Wang T et al. *Oncol Lett*. 2018 Jul; 16(1): 1267–1274.

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Patient demographics and cohort dosing regimens

Patients were enrolled onto 3 dose escalation cohorts in a 3+3 design

Cohort 3
RGX-104: 100mg BID (5 days on/2 days off)
Docetaxel: 28mg/m^2 weekly x3
n = 3; melanoma (2), bladder

Cohort 2
RGX-104: 80mg BID (5 days on/2 days off)
Docetaxel: 28mg/m^2 weekly x3
n = 4; ovarian, HNSCC, adrenal, melanoma

Cohort 1
RGX-104: 80mg BID daily
Docetaxel: 35mg/m^2 weekly x3
n = 4; endometrial (2), bladder, neuroendocrine

Summary	
Total patients enrolled	11
Tumor types	
Melanoma(3), endometrial(2), bladder(2), adrenal(1), HNSCC(1) neuroendocrine(1), ovarian(1)	
Age range years, (median)	45-82 (66)
Male, n (%)	6 (54.5%)
Female, n (%)	5 (45.5%)
ECOG performance, n (%)	
0	4 (36,4%)
1	7 (63.6%)
Number of prior lines of therapy, n (%)	
1-2	4 (36,4%)
3-4	6 (54.5%)
5	1 (9.1%)
Prior anti-PD-1/L1 checkpoint inhibitor (CPI) therapy	54.5%
Prior cytotoxic chemotherapy	72.7%

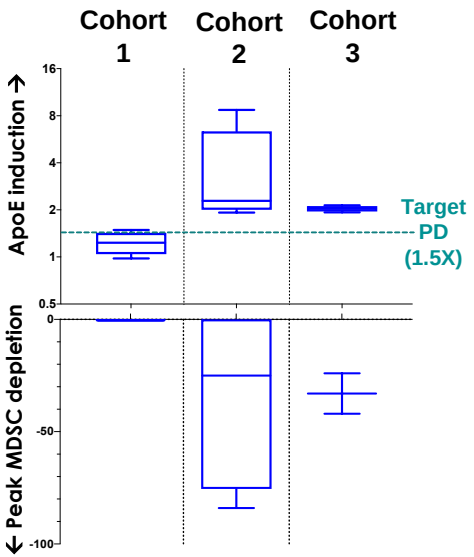
Safety & Pharmacodynamics

Safety

- Drug-related AEs were consistent with the individual toxicity profiles of docetaxel and RGX-104, with neutropenia being the most common AE and dose-limiting in cohort 1 (80mg BID daily of RGX-104 + 35mg/m^2 weekly x3 of docetaxel)
- AEs of neutropenia/leukopenia markedly reduced on the 5 days-on/2 days-off (5/2) regimen of RGX-104 (cohorts 2 and 3)
  - No DLTs were observed in cohorts 2 or 3
- MTD not reached at 100mg BID (5/2) RGX-104 + docetaxel 28mg^2 weekly x3

Pharmacodynamics

- ApoE gene induction in peripheral immune cells is a direct pharmacodynamic marker of LXR agonist (RGX-104) activity
- ApoE gene induction at steady-state (day 15) in cohorts 2 and 3 exceeded target (>1.5X), resulting in robust depletion of peripheral CD33$^+$CD15$^+$ MDSCs (measured in cycle 2)



RGX-104 Treatment Related AEs > Grade 1

Cohorts	All Cohorts (n=11)	Cohort 1 (n=4)			Cohort 2 (n=4)			Cohort 3 (n=3)		
Number of Cycles*		8			20			7		
Preferred TERM/GRADES	Grade >1	2	3	4	2	3	4	2	3	4
Neutropenia	3	1		1		1				
Anaemia	2				2					
Diarrhoea	2	1	1							
Fatigue	2	1			1					
Stomatitis	2	1	1							
Alopecia	1				1					
AST increased	1				1					
ALT increased	1				1					
Decreased appetite	1				1					
Dehydration	1	1								
Dry eye	1				1					
Leukopenia	1		1							
Lymphocyte count decreased	1		1							
Nausea	1				1					
Phlebitis	1				1					
Pruritus	1				1					
Rash maculo-papular	1				1					
Tooth infection	1					1				
Grand Total	**24**	**5**	**4**	**1**	**12**	**2**	**0**	**0**	**0**	**0**

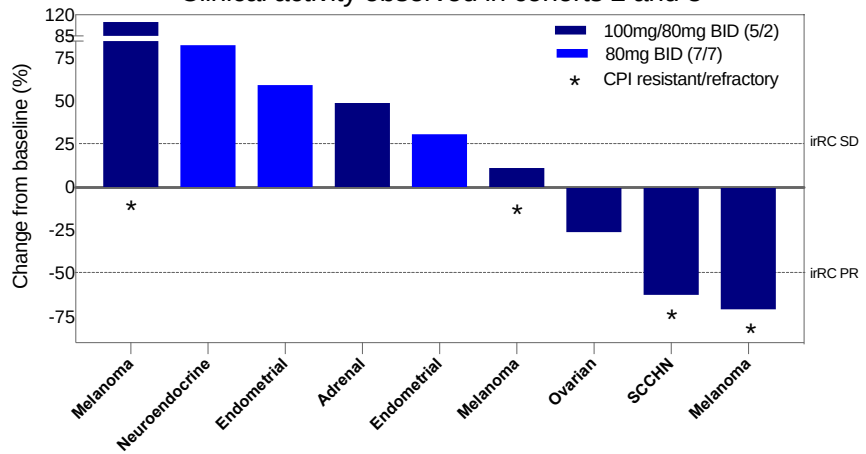
*One cycle = 28 days of treatment;
Data cut-off as of April 2, 2020

Efficacy

Summary	
Patients evaluable for response* (irRC)	9
Partial Response (PR) n	2
melanoma (CPI resistant); HNSCC (CPI/chemo resistant)	
Stable Disease (SD) n	3
ovarian (chemo resistant); melanoma (CPI resistant); neuroendocrine (chemo resistant)	
ORR	22%
DCR (PR+SD)	56%

Best response in evaluable patients

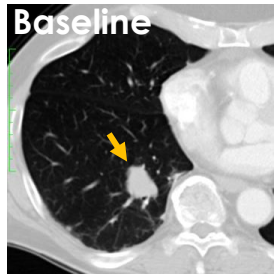
Clinical activity observed in cohorts 2 and 3

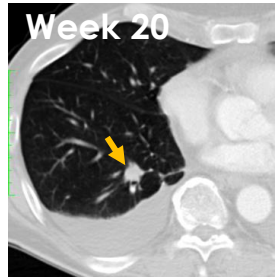


*Patients were evaluable for response if they had measurable disease and at least one follow up scan with at least one cycle of treatment. Data cut-off 04/02/20 (open database). One patient was deemed by investigator to have pseudoprogression which was defined as stable disease by investigator.

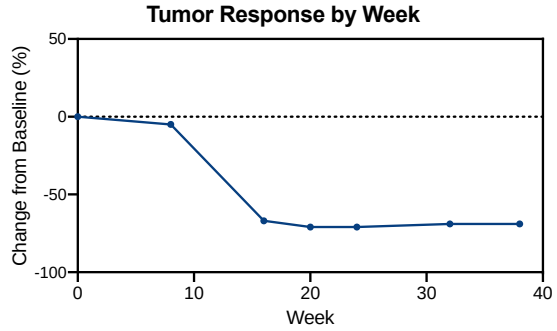
Partial Response in CPI resistant melanoma patient

- 80 y/o male; best response to prior nivo/ipi was PD
- 71% reduction in target lesions on RGX-104 + docetaxel at week 20
- 5-fold increase in total CD8 T cells; 7-fold increase in LAG-3^{+} CD8 T cells
- Patient remains on study at cycle 10 (week 40)



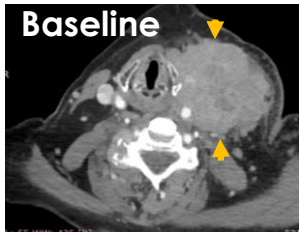


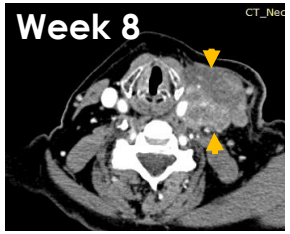
Target lesions included metastatic lung nodule (~3cm)



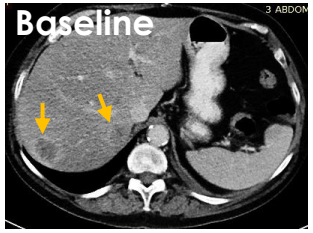
Partial Response in CPI/chemo resistant HNSCC

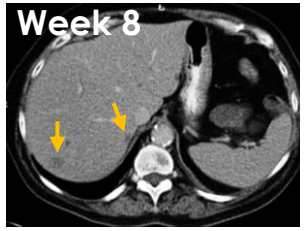
- 62 y/o female; best response to prior nivolumab was PD
- 62% reduction in target lesions on RGX-104 + docetaxel at week 8
- 5-fold increase in LAG-3^{+} CD8 T cells; 76-fold serum IFNγ increase
- Patient remained on treatment to cycle 4 (week 16)





Target lesions included ~7cm supraclavicular mass





Metastatic liver nodules (largest >3cm)

Summary & future clinical development

Enrollment

- 3 Dose Escalation Cohorts completed enrollment (n=11)

Safety

- Observed AEs consistent with individual toxicity profiles of RGX-104 and docetaxel
- 4 patients with Grade 3-4 AEs related to RGX-104 (neutropenia in 2 patients most common) and only dose-limiting in cohort 1
- AEs of neutropenia/low WBC markedly reduced on 5/2 regimen of RGX-104 (cohorts 2, 3) while robust pharmacodynamic activity achieved
- MTD not reached at 100 mg RGX-104 BID (5/2) and 28mg/m^2 docetaxel weekly x 3 (cohort 3)

Efficacy

- Clinical activity and target pharmacodynamic activity observed in cohorts 2 and 3, without dose-limiting toxicity
- 22% ORR; 56% DCR; activity observed in chemo/CPI resistant patients including durable ongoing PR in CPI resistant melanoma patient
- Clinical activity associated with RGX-104-related MDSC depletion and T cell response

Review of safety, efficacy, and PK/PD led to recommendation that RGX-104 100mg BID (5/2) schedule with Docetaxel at 28mg/m^2 weekly x 3 should be tested as expansion dose

Current Status

Enrolling in Expansion → **2L SCLC/HG-NET**
RGX-104 + Docetaxel
n~20

Enrolling in 1st Dose Escalation Cohort → **1L non-squamous NSCLC (PD-L1 < 1%)**
RGX-104 + Pembrolizumab + Carboplatin/Pemetrexed
n~30

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