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Abstract 3095

RGENIX

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Pharmacodynamic and clinical activity of RGX-104, a first-in-class immunotherapy targeting the liver-X nuclear hormone receptor (LXR), in patients with refractory malignancies

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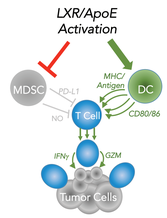
INTRODUCTION

LXR/ApoE Pathway and its Effect on the Innate Immune System in Cancer

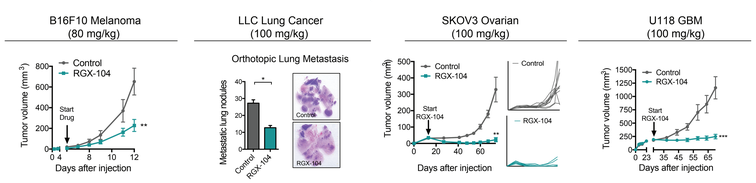
- Low levels of tumoral Apolipoprotein-E (ApoE) expression are associated with reduced survival in patients with cancer, as well as in murine models[1].
- Small-molecule activation of the nuclear hormone Liver-X Receptor (LXR) induces anti-tumor activity in numerous pre-clinical models[2-5] via induction of ApoE[1] expression.
- LXR activation has been found to regulate innate immune cell inflammatory signaling (macrophages) and activation of dendritic cells (DC) in non-cancer settings[6-8].
- Rgenix has discovered a role for the LXR-ApoE pathway in regulating the innate immune system in cancer, via modulation of the activity and abundance of myeloid derived suppressor cells (MDSC) and DC. ApoE binding to Lipoprotein receptor-related protein (LRP) on MDSC induces apoptosis, thus resulting in immune-mediated anti-tumor activity of LXR agonists.
- RGX-104 is an oral first-in-class LXR agonist that robustly induces ApoE expression resulting in innate-immune mediated anti-tumor activity.
- ApoE upregulation also inhibits recruitment of endothelial cells.
- Data presented here demonstrate effects of RGX-104 on ApoE, MDSC and T-cell populations along with concomitant clinical outcomes in patients enrolled in a phase 1a dose escalation trial.



The LXR/ApoE pathway drives the anti-tumor immune response

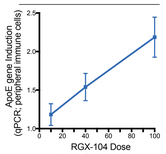
RGX-104 Antitumor Activity is Mediated by ApoE Activation

RGX-104 has anti-tumor activity in various mouse tumor models

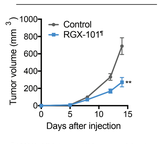


ApoE is required for anti-tumor activity of LXR agonists

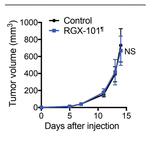
ApoE induction in circulating immune cells in mice *in vivo*



Antitumor acitvity in B16F10 melanoma



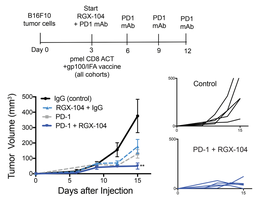
ApoE-depleted B16F10 melanoma in ApoE-/- mice does not respond to an LXR agonist



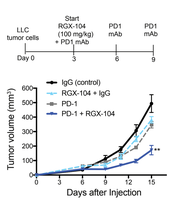
¶ RGX-101 is a LXR agonist tool compound used to dissect the LXR/ApoE mechanism
RGX-101 was dosed at 100 mg/kg/day in chow when tumors reached a volume of 5-10mm³

RGX-104 Enhances the Activity of Checkpoint Inhibitors

PD-1 inhibitor + RGX-104 (B16F10 melanoma)



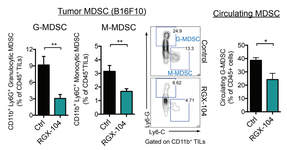
PD-1 inhibitor + RGX-104 (LLC lung cancer)



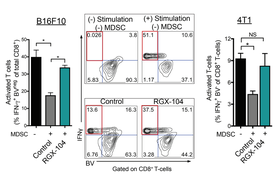
* p< 0.05
** p< 0.01
*** p< 0.001

RGX-104 Drives Anti-tumor Immunity by Regulating the Abundance and Activity of Myeloid Derived Suppressor Cells (MDSC) and Dendritic Cells (DC)

RGX-104 decreases tumor-infiltrating and circulating MDSC

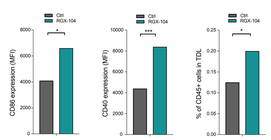


RGX-104 inhibits MDSC immunosuppressive capacity



RGX-104 treatment results in increased numbers of activated DC in the tumor-draining lymph-node (TDL)

CD40 and CD86 expression on CD103+ DCs as well as their total abundance in the TDL
(CT26.LmC model +/- RGX-104)



* p< 0.05
** p< 0.01
*** p< 0.001

Phase 1a First-in-Human Dose Escalation Study

- Eligibility includes adult patients with refractory/resistant solid tumors or lymphomas with any number of prior therapies
- Prior checkpoint inhibitor therapy is allowed

RGX-104 Phase 1 Dose Escalation

3 + 3 Design

Cohort	Number of Patients	Dose	Malignancies (n if >1)	Mean Number of Prior Regimens
1	3	120 mg QD 3 weeks on; 1 week off	Colon, uterine, renal	5
2	4	240 mg QD 3 weeks on; 1 week off	Melanoma (2), cholangiocarcinoma, Ewing's sarcoma	4
3	8	120 mg BID continuous dosing	Soft tissue sarcoma, NSCLC, colon (2), alveolar soft parts sarcoma, breast, bladder, pancreatic	7
4	4	160 mg BID continuous dosing	High-grade neuroendocrine, NSCLC, hepatocellular, bladder	3
5	7	200 mg BID continuous dosing	Colon (3), pancreatic, rectal, NSCLC, ovarian (2)	4

- Dosing schedule for cohorts 1 and 2 consisted of 3 weeks of daily dosing followed by a 1-week drug holiday; the one-week drug holiday was elimated starting with cohort 3 as no adverse events requiring time for recovery were noted in cohorts 1 and 2
- BID administration was introduced starting with cohort 3 so as to potentiate sustained engagement of the LXR receptor
- Efficacy was assessed every 8 weeks or earlier, if clinically warranted

Preliminary Summary of Phase 1a Dose Escalation

Cohort	Dose	Evaluable Patients	Best Response*
1	120 mg QD 3 weeks on; 1 week off	3	• At 8 weeks, 1 of 3 patients had SD
2	240 mg QD 3 weeks on; 1 week off	3	• No response
3	120 mg BID continuous dosing	5	• At 8 weeks, 4 of 5 patients had SD
4	160 mg BID continuous dosing	3	• At 8 weeks, 1 of 3 patients had a partial response: 53% reduction in hepatic metastases, which was confirmed at 16 weeks
5	200 mg BID continuous dosing	6	• At 8 weeks, 2 of 6 patients had SD

160 mg BID is the expansion dose

Combination with nivolumab 240 mg IV Q2W being evaluated with RGX-104 starting at 80 mg BID continuous dosing

CURRENTLY ENROLLING

Single agent dose expansion cohort at 160 mg BID
• Ovarian Cancer

ALSO ENROLLING

Combination with nivolumab dose escalation starting at 80 mg BID of RGX-104
• Melanoma, Non small cell lung cancer, Small cell lung cancer/high grade neuroendocrine, Renal cell carcinoma, Bladder cancer, Triple negative breast cancer

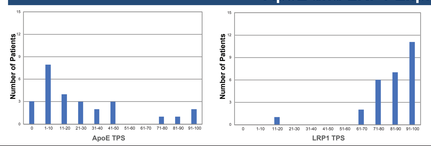
Key Clinical Observations

Adverse Events (n if >1)	
Grade 1	Elevated Cholesterol (12), Elevated triglycerides (7), Leukopenia (5), Nausea (5), Constipation (3), Anorexia (2), Fatigue (2), Vomiting (2), Elevated CPK, Flu, Chills,Mucositis, Neutropenia, Pruritus, Flushing, Skin Discomfort, Diarrhea, Dyspnea, Elevated AST/ALT, Dry Eyes, Hypokalemia, Sinus Tachycardia, Rash, Carpal-Pedal Spasms, Dyspepsia
Grade 2	Elevated Cholesterol (7), Leukopenia (6), Neutropenia (4), Elevated Triglycerides (3), Fatigue (2), Elevated Alkaline Phosphatase (2), Anorexia, Anemia, Dyspnea, Elevated AST/ALT, Vomiting
Grade 3	Neutropenia (3), Anemia (2*), Leukopenia (2), Elevated Triglycerides, Elevated Cholesterol
Grade 4	Neutropenia

* Both patients started on the trial with Grade 2 anemia

- RGX-104 was well-tolerated at all doses
  - On-target neutropenia observed in cohorts 3 and 5 was reversible without use of growth factors; all patients tolerated re-challenge at the same or lower dose of RGX-104
  - On-target hyperlipidemia was observed; two cases of grade 3 were manageable with statin +/- fenofibrate
  - No immune-related adverse events were reported
- Confirmed response in high-grade neuroendocrine malignancy with small cell features demonstrates clinical activity of monotherapy.
- Dose escalation cohorts of combination therapy with nivolumab are currently enrolling in six tumor types. These include checkpoint inhibitor-resistant, immune-sensitive malignancies and checkpoint inhibitor-naive malignancies where these agents are not approved.
- Monotherapy expansion cohort in ovarian cancer, a tumor type that is both immunogenic and responsive to angiogenesis inhibition, is currently enrolling.

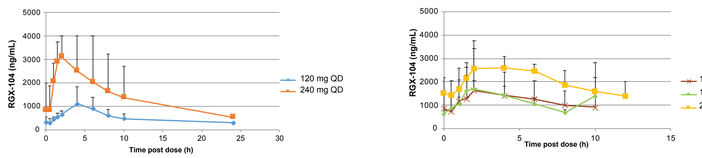
ApoE and LRP1 Expression in Tumor Tissue



- Expression of ApoE and its relevant receptor, LRP1, was measured in tumor tissue using a validated immunohistochemistry method.
- Most patients exhibit low levels of ApoE staining and/or high levels of LRP1 staining.
- The patient with radiographically confirmed partial response had low ApoE and high LRP1 expression.
- Utility of ApoE and/or LRP1 expression as a stratification marker for clinical outcomes is being addressed in currently enrolling cohorts.

Pharmacokinetics and Pharmacodynamics

Steady State (Cycle 1 Day 15) Plasma Concentration of RGX-104 vs. Time in Dose Escalation Cohorts



Preliminary Non-compartmental PK analysis for Cohorts 1, 2, 3, 4 and 5

Cohort	$AUC_{0\text{-}24}$ (ng*h/mL)		Cmax (ng/mL)		Tmax (h)		$T_{1/2}$ (h)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
120 mg QD	12200	3780	1110	722	10	12.2	7.5	0.36
240 mg QD	35800	31700	3320	1120	3.33	2.31	14.5	13.2

Cohort	$AUC_{0\text{-}t}$ (ng*h/mL)§		Cmax (ng/mL)		Tmax (h)		$T_{1/2}$ (h)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
120 mg BID	10000	7800	1780	1430	3.6	1.67	NC	NC
160 mg BID	9640	2060	1810	493	2.5	1.32	4.35	NC
200 mg BID	26656	5016	3028	863	4.7	2.4	7.4	1.0

§: Sampling interval for the 120 mg and 160 mg BID cohort was 8 hours after the first dose; sampling interval for the 200 mg BID cohort was 12 hours after the first dose

- At steady state, Cycle 1 Day 15, exposure to RGX-104 as measured by AUC increased in a greater than dose-proportional manner from 120 mg to 240 mg in cohorts that were dosed QD.
- In cohorts receiving 120 mg and 160 mg BID, PK samples were drawn only up to 8 hours after the first dose thus suggesting that the calculated AUC is an underestimate of actual daily exposure.
- T1/2, as calculated in the BID cohorts is estimated to be approximately 4-7 hours.

RGX-104 Target gene (ApoE) expression measured in whole blood samples from Cohorts 1, 2, 3, 4 and 5

Target	120 mg QD	240 mg QD	120 mg BID	160 mg BID	200 mg BID
ApoE fold increase Median (IQR)	4.1 (3.0)	11.7 (23.6)	2.8 (2.2)	5.4 (11.9)	5.3 (3.4)

- ApoE gene expression, as a pharmacodynamic marker of target engagement by RGX-104, was monitored by qPCR in whole blood speciments drawn at various times during steady state. Data presented above are from samples drawn pre-dose on Day 15 of Cycle 1.
- General increase in ApoE induction was observed with increasing daily dose; sustainability of induction through the treatment cycle was better with BID dosing compared to that resulting from QD dosing
- Extent of gene induction in cohorts 4 and 5 is comparable

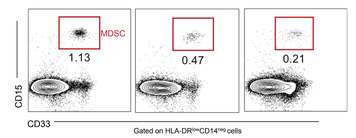
RGX-104 Demonstrates Broad Immune-Stimulatory Activity in Patients

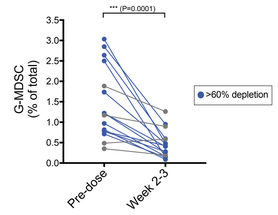
- Immune monitoring of patients treated with RGX-104 was conducted by flow cytometry analysis of circulating innate immune cell populations (MDSC and DC) as well as T cells (Serametrix Corporation).
- RGX-104 demonstrated broad immune-stimulatory activity with rapid on-target depletion of granulocytic MDSC (G-MDSC; also known as PMN-MDSC) and stimulation of DC, resulting in subsequent activation of PD-1$^+$CD8$^+$ T cells in the majority of treated patients.
- MDSC depletion correlated with T cell activation in patients treated with RGX-104; this was associated with radiographic stable disease and/or partial response in evaluable patients.

RGX-104 Depletes Circulating MDSC and Activates Circulating DC

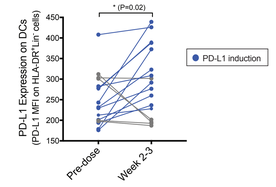
- 12/17 evaluable patients achieved >60% MDSC depletion on therapy.
  - Up to 95% G-MDSC (HLA-DR^{low}CD33$^+$CD15$^+$CD14^{neg}) depletion (median = 78% decrease) was observed.
  - Effect was generally observed starting 1-2 weeks after treatment initiation.

Depletion of G-MDSC
High-grade small cell neuroendocrine carcinoma
(confirmed Partial Response)





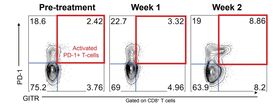
- Activated dendritic cells induce expression of PD-L1[9].
- 12/17 evaluable patients had induced PD-L1 expression on circulating HLA-DR$^+$Lin^{neg} dendritic cells (median = 34% increase).
- Effect generally observed starting 1-2 weeks after treatment initiation.

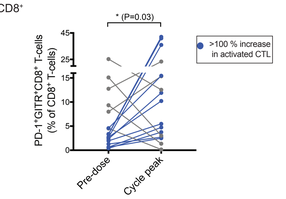


RGX-104 Induces Expansion and Activation of Exhausted PD1$^+$CD8$^+$ T Cells

- Expansion/activation of circulating PD-1$^+$CD8$^+$ T-cells is associated with anti-tumor immunity and response to check-point inhibitors[10-12].
- 11/17 evaluable patients achieved >100% increase in activated (GITR$^+$) PD-1$^+$CD8$^+$ T-cells (CTLs).
- Up to 12 fold increase was observed (median = 287% increase).
- Effect was generally observed starting 2-4 weeks after treatment initiation.

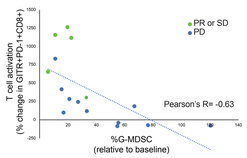
Activation of PD-1$^+$CD8$^+$ T cells
High-grade small cell neuroendocrine carcinoma
(confirmed Partial Response)





- Correlation is observed between MDSC depletion and activated T cells (CTLs) in evaluable patients.
- In the absence of significant MDSC depletion or DC stimulation, subsequent T cell activation was not observed.
- MDSC depletion and concomittant T-cell activation is associated with radiographic stable disease and/or partial response.

Correlation of MDSC abundance and T-cell activation



Conclusions

- Antitumor activity has been demonstrated with RGX-104 monotherapy in several syngeneic and xenograft tumor models, including melanoma, lung cancer, ovarian cancer, GBM and others. The anti-tumor activity of LXR-agonism is related to constitutive upregulation of ApoE expression.
- RGX-104, a first-in-class LXR agonist, has completed dose escalation. 26 patients with a variety of refractory solid tumors were treated at doses ranging from 120 mg QD to 200 mg BID.
- On-target AEs included reversible hyperlipidemia and neutropenia.
- A generally dose dependent increase in systemic exposure to RGX-104 was observed; target engagement as measured by induction of effector gene, ApoE, was found to be optimal at a dose of 160 mg BID.
- Flow-cytometry analysis of peripheral blood samples demonstrates that RGX-104 has broad immune-stimulatory activity. Rapid depletion of granulocytic MDSC (G-MDSC; also known as PMN-MDSC) and stimulation of DC resulted in subsequent activation of PD-1$^+$CD8$^+$ T cells in the majority of treated patients[13].
- RP2D of 160 mg BID was selected based on safety, efficacy, PK and PD. A confirmed radiographic partial response by irRC (>50% reduction in index lesions) was observed in a patient with high grade neuroendocrine malignancy with small cell features.
- Recruitment to combination dose escalation with nivolumab is ongoing for patients with refractory melanoma, NSCLC, SCLC, RCC, bladder cancer and TNBC; expansion cohorts for each of these diseases are planned. Recruitment to RGX-104 monotherapy expansion cohort is ongoing for patients with refractory ovarian cancer. Approximately 20 US sites are participating.

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