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Phase I/II study of nivolumab and vorolanib in patients with refractory thoracic tumors

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BACKGROUND

- Nivolumab results in limited responses (19-25%) in thoracic tumors[1], combination therapies are necessary to increase response rates
- Evidence exists to suggest that antiangiogenic agents have the potential to stimulate the immune system[2,3]
- Pilot studies of nivolumab + sunitinib or pazopanib in renal cell carcinoma (RCC) demonstrated that the combinations outperformed either single agent[4,5]; however, the combinations were not well tolerated at full doses of the agents
- Avelumab + axitinib was recently approved by the United States FDA for standard first-line treatment in RCC based on improved response with the combination compared to single-agent sunitinib[6,7]; pembrolizumab + axitinib was recently approved based on improved profression-free and overall survival[8]

VOROLANIB

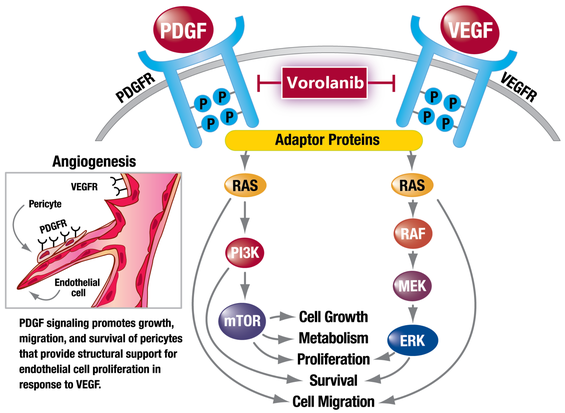


Figure 1. Vorolanib Mechanism of Action. Definitions: mTOR; mechanistic target of rapamycin; PI3K: phosphoinositide 3-kinase; PDGFR: platelet-derived growth factor receptor; RAS, RAF, MEK. ERK: mitogen-activated protein kinase pathway; VEGFR: vascular endothelial growth factor receptor

- Vorolanib (X-82) is an oral, tyrosine kinase inhibitor (TKI) with multiple targets (Figure 1)
- Vorolanib is structurally similar to sunitinib but designed with a shorter half-life to have intermittent inhibition and limited tissue accumulation to improve safety profile
- Phase I study in advanced solid tumors explored vorolanib doses ranging from 20-800 mg once-daily and 140-200 mg twice-daily, but did not identify a maximum tolerated dose (MTD)[9]
  - 75% of patients experienced treatment-related toxicities, mostly Grade 1/2
  - Most frequent being dysphagia (46%), fatigue (31%), nausea (25%), and diarrhea (23%)

STUDY DESIGN

Study Objectives

Multi-institution, open-label study in refractory thoracic tumors:

- **Phase I Endpoint:** MTD of the combination
- **Phase II Endpoint:** Objective response rate
- **Exploratory Endpoints:**
  - Mass cytometry will be used to monitor serial changes in multiple immune markers on individual circulating cells
  - Single cell gene expression analysis from peripheral blood will be correlated with response

Dose Escalation

- Standard 3+3 dose escalation design (Table 1)
- **Dose-limiting Toxicity (DLT):** during first 28 days, any ≥ G3/4 non-hematological toxicity lasting >3 days (except fatigue, rash, tumor flare, infusion-related, elevated serum amylase/lipase not associated with pancreatitis); ≥G3 febrile neutropenia, bilirubin or hepatic transaminases, pneumonitis, adrenal insufficiency, immune-mediated hepatitis, colitis, encephalitis; ≥G4 hematologic toxicity

Table 1. Dose Escalation Table

	Vorolanib (mg PO, QD)	Nivolumab (mg IV q2W)
Level -1	100	240
Level 1	200	240
Level 2	300	240
Level 3*	400	240

PO: oral; QD: once daily; IV: intravenous; q2W: every two weeks in 8-week cycles. *Level not evaluated due to tolerability of the combination

Dose Expansion

- Five dose expansion cohorts (Figure 2)
- Two-stage MinMax design (Table 2) will be used to evaluate efficacy as measured by the objective response

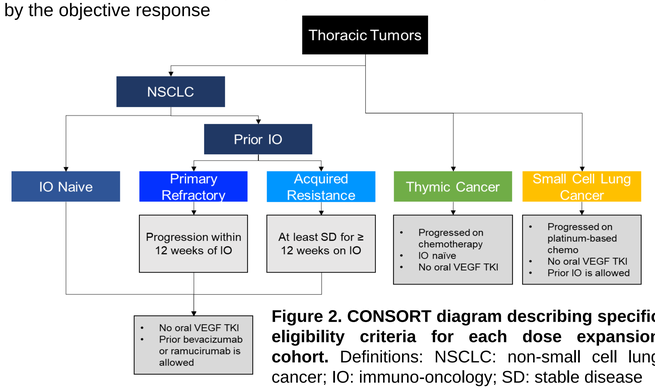


Figure 2. CONSORT diagram describing specific eligibility criteria for each dose expansion cohort. Definitions: NSCLC: non-small cell lung cancer; IO: immuno-oncology; SD: stable disease

Table 2. Two-stage MinMax Design

Tumor Cohort	Stage 1: Stop if	Stage 2: Success if	Power Analysis
IO Naïve	< 6/23 responses	≥ 14/39 responses	b = 90%; a = 10%; H_0 = 25%; H_1 = 45%
IO Primary Refractory	< 3/15 responses	≥ 6/21 responses	b = 90%; a = 10%; H_0 = 15%; H_1 = 40%
IO Acquired Resistance	< 3/15 responses	≥ 6/21 responses	b = 90%; a = 10%; H_0 = 15%; H_1 = 40%
Thymic Cancer	< 5/22 responses	≥ 12/41 responses	b = 80%; a = 10%; H_0 = 20%; H_1 = 35%
Small Cell Lung Cancer	< 3/18 responses	≥ 9/37 responses	b = 80%; a = 10%; H_0 = 15%; H_1 = 30%

PRELIMINARY RESULTS

Dose Escalation – Completed

- 10 patients (eight NSCLC and 2 thymic) were enrolled (Table 3); 1 patient was not evaluable for DLT and was replaced
- **Dose Level 1 (n=3):** No DLT
- **Dose Level 2 (n=6):** Grade 3 elevated alanine transaminase (ALT) occurred in 2 of 6 patients just beyond the DLT period but deemed clinically significant
- Recommended phase II dose is 200 mg vorolanib and 240 mg nivolumab

Dose Expansion – Ongoing

- As of August 1, 2019, 14 patients enrolled in the dose expansion (12 NCSLC,1 thymic cancer, and 1 small cell lung cancer; Table 3)

Patient Demographics

Table 3. Patient Baseline Characteristics (n=24)

Gender - No. (%)	
Male	15 (63)
Female	9 (37)
Median age - No. (range)	68 (33 - 78)
Race/Ethnicity - No. (%)	
White	22 (92)
Black	1 (4)
Race, Unknown or Not Reported	1 (4)
Not Hispanic or Latino	23 (96)
Ethnicity, Unknown or Not Reported	1 (4)
Smoking status - No. (%)	
Never smoker	3 (12)
Former smoker	17 (71)
Current smoker	4 (17)
PS (ECOG) - No. (%)	
0	6 (25)
1	18 (75)
NSCLC (n=20): Immunotherapy status – No. (%)	
Naïve	5 (25)
Primary Refractory	9 (45)
Acquired Resistance	6 (30)

PS: performance status; ECOG: Eastern Cooperative Oncology Group

Adverse Events

Table 4. Most Frequent (≥ 10%) Treatment-related Toxicities

Adverse Event^	All grades (%)	Grade ≥3* (%)
Fatigue	8 (33)	1 (4)
Elevated alanine aminotransferase	6 (25)	2 (8)
Elevated aspartate aminotransferase	6 (25)	1 (4)
Diarrhea	6 (25)	0
Anorexia	5 (21)	0
Decreased platelet count	5 (21)	0
Nausea	4 (17)	0
Decreased neutrophil count	3 (13)	1 (4)
Decreased white blood count	3 (13)	0

^Highest grade toxicity observed per patient reported
*Other related grade 3 events: hypertension, elevated serum amylase. Other related grade 4 events: hyperglycemia and elevated lipase

Preliminary Anti-tumor Activity

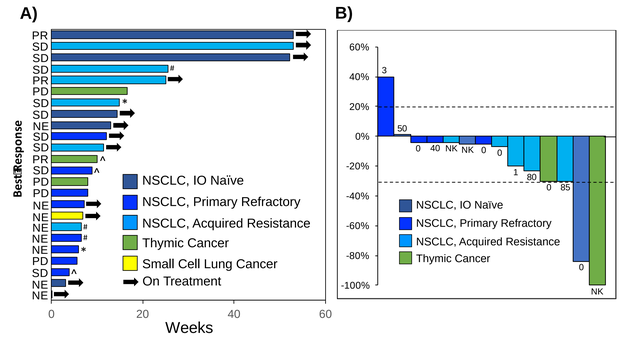
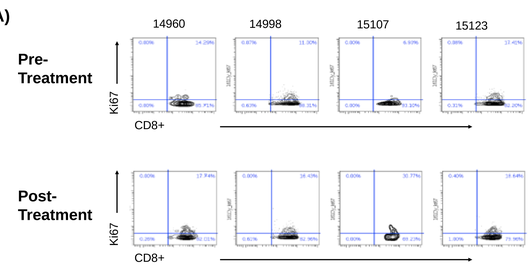


Figure 3. A) Swimmer's plot presenting time on treatment for each patient. Best response is listed along the y-axis. *Off study due to disease progression; ^Off study due to toxicity; #Expired due to disease progression. B) Waterfall plot demonstrating best response in all efficacy-evaluable patients (n=14); number listed below each bar is PD-L1%.

Proposed Study Correlatives



B) Ki67% change in CD8+ T cells

	14960	14998	15107	15123
Pre	14.29	11.0	6.9	17.41
Post	17.74	16.43	30.77	18.64
Best Response	PR >12 months	PR >12 months	PR > 6 months	PD

PR: partial response; SD: stable disease; PD: progressive disease

C)

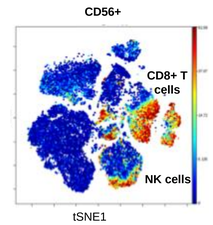


Figure 4. Understanding the biology behind response to combination immunotherapy using mass cytometry. A.) Mass cytometry was performed from peripheral blood on pre- and post-PD1 treated patients with NSCLC. Flow plots show Ki67% in individual patient samples on the Y axis in CD8 cells (x-axis). B). Quantification showing variation in Ki67% CD8+ T cells across patients. C) tSNE plot organized using T cell markers showing expression of CD56 from a patient treated with PD-1 blocking antibody with high CD56+ in subset of CD8+ T cells and NK cells.

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For questions, email Dr. Leora Horn at **Leora.Horn@vumc.org**.

REFERENCES

1. J Immunother Cancer. 2016 Aug 16;4:48
2. J Thorac Oncol. 2017 Feb;12(2):194-207
3. J Natl Cancer Inst 2014;106(11)
4. N Engl J Med. 2015 Nov 5;373(19):1803-13
5. J Immunother Cancer. 2018 Oct 22;6(1):109
6. N Engl J Med. 2019 Feb 16. *e-pub*
7. Ann Oncol 2018 Oct; 29(Suppl 8), mdy424.036
8. N Engl J Med. 2019 Mar 21;380(12):1116-27
9. Vorolanib Investigator's Brochure V1.6

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