1085P: Phase I/II Study of PI3Kβ inhibitor GSK2636771 (G771) in combination with pembrolizumab (P) in patients (pts) with PTEN loss and melanoma or other advanced solid tumors.

Elizabeth M. Burton[1], Ecaterina E. Dumbrava[1], Weiyi Peng[2], Denái R. Milton[1],Rodabe N. Amaria[1], Jennifer L. McQuade[1], Isabella C. Glitza[1], David S. Hong[1], Sapna Pradyuman Patel[1], Jordi Rodon[1], Timothy A. Yap[1], Aung Naing[1], Sarina Piha-Paul[1], Gener Balmes[1], Alexander Lazar[1], Funda Meric Bernstam[1], Patrick Hwu[3], Michael A. Davies[1], Hussein A. Tawbi[1]

[1]The University of Texas MD Anderson Cancer Center [2]University of Houston [3]Moffit Cancer Center

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Background & Rationale

- Immune checkpoint blockade (ICB) improves survival in metastatic melanoma, but many pts progress and ultimately die from their disease.
- PTEN loss occurs in up to 30% of metastatic melanoma pts, activates the PI3K-AKT pathway, and correlates with decreased tumor infiltrating lymphocytes(TIL) and lower response rates (RR) to ICB[1]
- In preclinical models with PTEN-null melanoma, selective inhibition of PI3Kβ with GSK266771 (G771) + ICB was superior to pan-PI3K inhibition and increased CD4+/CD8+ TIL and survival **(Figure 1)** [1]

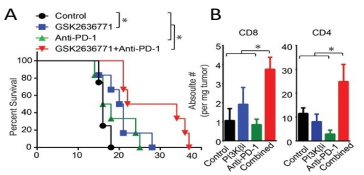


Figure 1: PI3Kβ inhibitor enhances the anti-tumor activity of T-cell mediated ICB in mice bearing PTEN-loss tumor. BRAF V600E/+ mice with measurable tumors were randomly treated with either vehicle + control antibody. (A) Survival curves of mice treated with G771 and/or anti-PD-1 demonstrates statistical significance (P<0.05). (B) Statistically significant (p <0.05) increase in post treatment tumor infiltrating T cells in mice treated with G771 and/or anti-PD-1 vs either agent alone.

Hypothesis

We hypothesized that pembrolizumab in combination with the PI3Kβ inhibitor GSK2636771 will be safely tolerated and demonstrate clinical activity in patients with PTEN loss

Study Schema

NCT01458067

Pts with advanced solid tumors and PTEN Loss

Ph I Dose Escalation
n = up to 18 pts

Dose Level	GSK23667 71 PO QD	Pembro IV q3wks
2	400 mg	200 mg
1	300 mg	200 mg
-1	200 mg	200 mg

RP2D

Ph II Dose Expansion
n = 35 pts at RP2D

Objectives

Primary Objective

- Phase I: To determine recommended phase 2 dose (RP2D) for GSK2636771 + pembrolizumab
- Phase II: To determine the safety, tolerability, and response rate (by RECIST 1.1)

Secondary Objectives

- PK evaluation of GSK2366771
- PD effects of combination in the blood & tumor

Patient Eligibility

- Unresectable stage III/IV malignancies with PTEN loss defined by loss of function genomic alterations or loss of protein expression by IHC
- Pts, including melanoma, must have progressed or failed to respond to anti-PD1 based therapy
- Pts with prostate, endometrial, or triple negative breast malignancies must have either progressed or refused standard therapies.
- Baseline tissue was required
- No history of autoimmune disorders

Statistical Design

- Single institution, open label, single arm phase I/II study evaluating GSK2636771 in combination with pembrolizumab in patients with PTEN loss and advanced malignancies.
- Phase I dose escalation with patients treated in the 3+3 format
- Phase II expansion: Continuous monitoring for safety and futility performed using a Bayesian model

Patient Demographics

Characteristic	Patients (N=27)
Age n (%)	
< 65 years	13 (48)
≥ 65 years	14 (52)
Gender n (%)	
Male	18 (67)
Female	9 (33)
Primary Cancer n (%)	
Prostate	12 (44)
Melanoma	10 (37)
Triple Negative Breast	2 (7)
Colon	1 (4)
Endometrial	1 (4)
Lung	1 (4)

Accrual by Dose

Starting Dose GSK2636771	Patients (N=27)
Phase I	
300mg	5
400mg	5
Phase II	
200mg	17

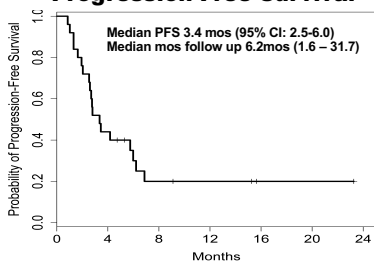
- Trial accrual started at dose level 1 of GSK2636771 at 300mg QD
- Following the study plan, the dose was escalated to 400mg QD
- Due to a DLT of acute kidney injury and data from other ongoing studies by the industry sponsor, GSK, the RP2D was set at 200mg
- GSK ceased further development of GSK2636771 and accrual was stopped after 27 patients met eligibility and received treatment

Clinical Responses

Best Objective Response (RECIST 1.1)	Ptients (N=25)
Partial Response n (%)	3 (12)
Prostate	2 (8)
Melanoma	1 (4)
Stable Disease n (%)	10 (40)
Prostate	5 (5)
Melanoma	3 (12)
Lung	1 (4)
Partial Response + Stable Disease by cancer type/ # enrolled per cancer (%)	
Prostate	7/12 (58)
Melanoma	4/10 (40)

- 25 of the 27 pts were evaluable for response
- Of the patients with stable disease, 2 pts remained stable for more than one year

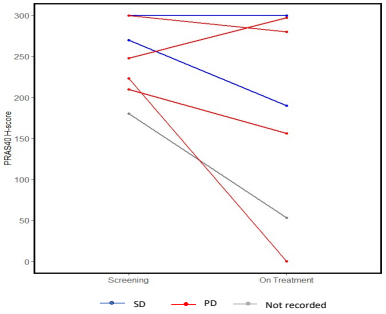
Progression Free Survival



Correlative Immunohistochemistry Analysis

- Several paired core biopsies (baseline and on treatment) were obtained for correlative evaluation

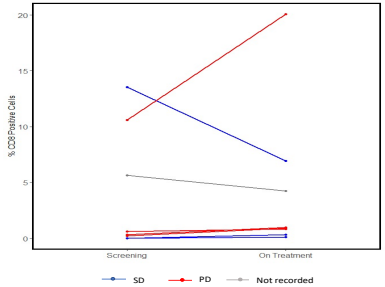
PRAS40 H-Score Change by Patient



- **The majority of pts experienced a decrease in phospho-PRAS40, regardless of response, from baseline to post treatment**
- **One pt with progressive disease did demonstrate an increase**
- **One pt was inevaluable for response**

Methods phosphor PRAS40:
The percentage of phospho-PRAS40-positive tumor cells was evaluated by a pathologist. The intensity of cytoplasmic staining was recorded as: Negative (0+), Weak (1+), Moderate (2+) or Intense (3+). H-Score = [(%tumor cells 0+) x 0] + [(%tumor cells 1+) x 1] + [(%tumor cells 2+) x 2] + [(%tumor cells 3+) x 3).

%CD8 Change by Patient



- **Overall, there were no marked changes seen in CD8% from baseline to post treatment. One patient was inevaluable for response**

Methods CD8:
Image analysis software (Aperio ImageScope) measured the number of positive CD8 cells within designated areas. The tumor area of interest was circled by a pathologist and given a measurement in mm². For each tumor region, the numbers of positive cells were summed, and the total number of positive cells was divided by the total area (mm²) in which cells were counted.

TX Related AEs >20% pts or any grade 3/4 event

Adverse Event Name	Gr 1/2	Gr 3/4	Total
Diarrhea	9	0	9
Hypophosphatemia	5	3	8
Fatigue	8	0	8
Rash maculo-papular	4	2	6
Aspartate aminotransferase increased	6	0	6
Hypocalcemia	4	1	5
Alanine aminotransferase increased	5	0	5
Hyperglycemia	5	0	5
Nausea	3	1	4
Administration site reaction	2	1	3
Skin and subcutaneous tissue disorders	2	1	3
Lymphocyte count decreased	0	2	2
Anemia	1	1	2
Rash acneiform	1	1	2
Creatinine increased	1	1	2
Hyperthyroidism	1	1	2
Rash pustular	0	1	1
Hypotension	0	1	1
Hyperuricemia	0	1	1

- 44% of pts experienced grade 3 or 4 toxicities
- There were no grade 5 events
- 3 pts discontinued due to toxicities

Conclusions

- The primary objective of the Phase I portion of the study was met in determining the RP2D of GSK2636771 at 200mg PO QD in combination with pembrolizumab 200mg q3wks
- We demonstrated feasibility of a biomarker-selected clinical trial designed to reverse a specific mechanism of PD1 resistance
- There were durable partial responses and some pts achieved long term clinical benefit indicating a potential role for reversal of PD1 resistance by targeting the PI3K/AKT pathway
- Patients with prostate cancer demonstrated a high rate of disease control (58%)
- There were no marked CD8 changes observed in tissue samples collected.
- The majority of pts experienced a decrease in phospho-PRAS40
- More correlative analyses are underway to provide further insights into how targeting this pathway may be a mechanism to overcome resistance to PD1 in pts with PTEN loss

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Corresponding Author
Hussein Tawbi, MD, PhD | (htawbi@mdanderson.org)
Presenting author (EM Burton) has no conflicts of interest to disclose

References
[1]Peng, Weiyi et al. Loss of PTEN Promotes Resistance to T Cell- Mediated Immunotherapy, Cancer Discovery February 2016.