A Phase 1/2 Study of IDE196 in Patients With Metastatic Uveal Melanoma or Solid Tumors Harboring *GNAQ/11* Mutations or *PRKC* Fusions

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Abstract

Activating mutations in *GNAQ* & *GNA11* (*GNAQ/11*) Gα subunits of G-protein coupled receptors have been seen in >90% of patients with uveal melanoma (UM) and are considered genetic disease drivers. *GNAQ/11* mutations in other solid tumors, including cutaneous and mucosal melanoma, have also been seen in The Cancer Genome Atlas (TCGA) database. IDE196 (previously known as LXS196) is a selective protein kinase C inhibitor which has demonstrated preliminary anti-tumor activity in patients (pts) with metastatic UM (MUM). Patients with other solid tumors harboring *GNAQ/11* activating mutations may also benefit from IDE196.

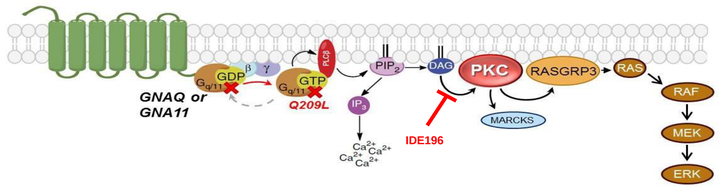
In a phase 1 study (NCT02601378) in which 30 MUM patients were treated with IDE196 at doses of 200, 300 or 400 mg BID, 4 partial responses (PR) and 2 unconfirmed PRs were reported, for an overall response rate (ORR) of 13% (95% CI, 4%–31%), and a disease control rate of 73%. The most frequent DLT was transient hypotension, which was manageable. As of May 2019, 5 of 30 pts on BID dosing remained on IDE196 > 18 months, and 3 have been on > 2 years.

Study IDE196-001 (NCT03947385), a phase 1/2, multicenter, open-label study, will evaluate the safety & efficacy of IDE196 in patients with MUM and other solid tumors harboring *GNAQ/11* mutations or *PRKC* fusions. Approximately 40 MUM & non-MUM pts will be enrolled in dose escalation starting at 300 mg BID on a 28-day cycle. For phase 2 there will be a dedicated cohort for MUM and exploratory expansion cohorts for non-MUM patients with *GNAQ/11* mutations or *PRKC* fusions. The 1° endpoints are safety, pharmacokinetics, and ORR by RECIST v1.1; 2° endpoints are duration of response, pharmacodynamic biomarkers, and central confirmation of genetic alterations. This will be a global study.

Background

- Metastatic uveal melanoma (MUM) is a disease of high unmet need, with poor prognosis and no approved therapies
- Despite therapeutic efforts, the one-year survival of patients with MUM remains about 50%[1-3]
- Somatic mutations in the heterotrimeric G-proteins, *GNAQ* or *GNA11 (GNAQ/11),* have been identified in 90% of patients with UM, leading to activation of the Protein Kinase C (PKC) pathway and tumor dependence on downstream PKC signaling[4-6]
- For the remaining 5-10% of UM tumors that lack *GNAQ/11* mutations, gain-of-function mutations have been identified in either *PLCB4* or *CYSLTR2*, which are also upstream of the PKC signaling cascade[7,8]
- PKC inhibition may be effective against tumor cells that are dependent on these pathways

PKC Signaling Pathway Through Upstream Mediators



IDE196 Background

- IDE196 (also known as LXS196) is an oral, potent and selective inhibitor of the classical (α, β) and novel (δ, ε, η, θ) isoforms of PKC
- In a previous global Phase 1 study*, IDE196 was generally well tolerated and demonstrated anti-tumor activity in MUM[9]
  - The most common IDE196-related AEs (all grades, all doses) were nausea (66%), diarrhea (46%), vomiting (31%), hypotension (22%), increased ALT (22%), and fatigue (21%)
  - In 30 patients treated at 200, 300, or 400 mg BID,
    - ORR was 13% (95% CI 4%, 31%)
    - Disease control rate (DCR) was 73% (95% CI 54%, 88%)
  - As of September 13, 2019**, five of 30 patients in the monotherapy BID cohort continue on therapy for more than two years
    - One of these patients has a confirmed complete response at 31 months
    - Two of these patients have ongoing stable disease
    - Two patients experienced disease progression, one from a partial response and one from stable disease (per RECIST v1.1) after approximately 25 months and 22 months of treatment, respectively, but experience clinical benefit and remain on study as allowed per protocol

**Clinicaltrials.gov identifier NCT02601378*
***Data on file*

GNAQ/GNA11 Mutations Found in Multiple Tumors

- Outside uveal melanoma, mutations in *GNAQ/11* are also found in other solid tumors
- The first case demonstrating *GNA11* mutation was reported in a cutaneous melanoma patient[10]
- Analysis of *GNAQ/11* mutation prevalence (both hotspot and non-hotspot) from TCGA reveals multiple tumors affected
- Additionally, mutations in *GNAQ/11* are generally mutually exclusive with other *RAS* pathway genes

Cancer Type	N	GNAQ (%)	GNA11 (%)	Total (%)
Uveal Melanoma (UM)	80	50	45	95
Cut. Melanoma (CM)	290	2.1	2.8	4.9
Colorectal	367	2.7	1.9	4.6
Pancreatic	126	0.8	1.6	2.4
Stomach	393	0.8	1.5	2.3
Cervical	194	1.0	1.0	2.0
Lung Adeno	533	0.9	0.8	1.7
Bladder	394	0.8	0.8	1.6

Data estimates for GNAQ/GNA11 mutations (hotspot and non-hotspot) from The Cancer Genome Atlas in cBioPortal; data on file

IDE196-001 Basket Study Overview & Schema

- IDE196-001 is a Phase 1/2 multi-center, open-label dose escalation and expansion study in patients with both MUM and *GNAQ/11*-mutated tumors
  - Because of the high prevalence of *GNAQ/11* in UM, mutation testing for patients with MUM is not required for enrollment, but will be conducted retrospectively
  - Non-MUM patients with *GNAQ/11* mutated tumors must have tumors tested on a CLIA/CAP-approved sequencing platform. Tumor samples are required for retrospective central testing
- Dosing cohorts
  - Cohort 1: 300 mg BID
  - Cohort 2: 200 mg BID for the first 7 days (C1D1-C1D7); then 400 mg BID for all subsequent doses
    - This dosing schema was not tested in the monotherapy cohorts in the previous Phase 1 trial
  - Because of dose limiting toxicity (DLT) seen at higher doses in the previous Phase 1 trial, no further dose escalation was pursued
- Once a DLT cohort cleared, additional patients with MUM or *GNAQ/11*-mutated non-MUM tumors were eligible to enroll

IDE196-001 Study Schema

[a] Recommended Phase 2 Dose
[b] Simon Two-Stage design

Key Objectives & Endpoints

Objectives	Outcome Measures
• To evaluate the safety profile of IDE196 in enrolled subjects	• Dose-limiting Toxicity • Maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) • Adverse events
• To characterize the pharmacokinetic (PK) profile of IDE196 (Phase 1 dose escalation)	• Plasma Concentrations of IDE196 over time
• To evaluate the anti-tumor activity of IDE196 in subjects with MUM (Phase 2 expansion)	• Overall response rate (ORR) per RECIST v1.1 • Duration of response (DOR) per RECIST v1.1

Exploratory analyses with tumor and blood biomarkers will also be assessed

Summary of Main Inclusion/Exclusion Criteria

Inclusion Criteria

- Patient must be ≥18 years of age
- Diagnosis of one of the following:
  - MUM: Uveal melanoma with histological or cytological confirmed metastatic disease
  - Non-MUM: Advanced cutaneous melanoma, colorectal cancer, or other solid tumor that has progressed following prior standard therapies or that has no satisfactory alternative therapies and has evidence of *GNAQ/11* hotspot mutation
- Measurable disease
- Eastern Cooperative Oncology Group ≤1
- Adequate organ function at screening
- Adequate contraceptive measures for non-sterilized male and female patients of childbearing potential

Exclusion Criteria

- Another malignancy
- Known microsatellite instability-high (MSI-H) tumors
- Adverse events from prior anti-cancer therapy that have not resolved
- Untreated or symptomatic central nervous system metastases
- Human immunodeficiency virus, acquired immunodeficiency syndrome related illness, hepatitis B virus, or hepatitis C virus
- Recent surgery or radiotherapy
- Females who are pregnant or breastfeeding
- Impaired cardiac function
- Allergy to mammalian meat or gelatin

Baseline Characteristics

		300mg BID (n = 6)	400 mg BID[1] (n = 6)	Total (n= 12)
Age (years) [median (range)]		64 (48-79)	57 (26-70)	60 (26-79)
Gender [n (%)]	F	4 (67%)	1 (17%)	5 (42%)
	M	2 (33%)	5 (83%)	7 (58%)
ECOG [n (%)]	0	4 (67%)	4 (67%)	8 (67%)
	1	2 (33%)	2 (33%)	4 (33%)
Presence of liver metastases [n (%)]		6 (100%)	6 (100%)	12 (100%)
Time since initial UM diagnosis (months) [median (range)]		34.1 (18.5-58.7)	77.8 (19.8-163.9)	46.9 (18.5-163.9)
Number of prior systemic lines of therapy [2] [n (%)]	1	2 (33%)	1 (17%)	3 (25%)
	2	3 (50%)	1 (17%)	4 (33%)
	≥ 3	0	2 (33%)	2 (17%)

[1] Patients received 200 mg BID for the first week of treatment
[2] Systemic therapy in the metastatic setting; Does not include local therapy (e.g., liver-directed therapy)

Adverse Events

Adverse Events occurring in ≥ 2 patients regardless of attribution (n=12 patients)

Adverse Event	All Grades	≥ Grade 3
Nausea	6 (50%)	0
Diarrhea	4 (33%)	0
Fatigue	4 (33%)	0
Vomiting	3 (25%)	0
Abdominal Pain	2 (17%)	0
Back Pain	2 (17%)	0

- No Dose Limiting Toxicities (DLT) were reported in Cohort 1 or Cohort 2

Patient Disposition

As of 28Oct2019, all 12 patients in the DLT cohorts remained on therapy
- 6 patients receiving 300 mg BID
- 6 patients receiving 400 mg BID

Dose Cohort	Median Duration of Treatment Months (range)
300 mg BID (n = 6)	3.3 (2.7-4.0)
400 mg BID (n = 6)	1.7 (1.3-2.1)

Additional Phase 1 patients enrolled:
- MUM (n= 14), non-MUM (n=1)
  - 300 mg BID: 6 additional MUM patients and 1 non-MUM patient
  - 400 mg BID: 8 additional MUM patients

Example of Non-MUM *GNA11*-mutated Tumor

- 69 year old male with Stage IV cutaneous melanoma (scalp) with metastases to the liver, soft tissues and lymph nodes
  - Mutations: *GNA11* Q209L, monosomy 3
- Prior therapies included:
  - Pembrolizumab adjuvant therapy, followed by pembrolizumab + TVEC[a]
  - Ipilimumab/nivolumab
  - Trametinib
  - Carboplatin/vinblastine/dacarbazine[b]
  - Ipilimumab/nivolumab + TVEC[a]
  - IPI 549[c] + nivolumab
  - Stereotactic Body Radiation Therapy (SBRT) to liver metastases
- Patient initiated treatment with IDE196 300mg BID

[a] talimogene laherparepvec [b]patient received 1 cycle [c]PI3Kγ inhibitor

Conclusions

- IDE196-001 is the first "basket" study to test a PKC inhibitor in patients with *GNAQ/11*-mutated tumors
  - Potential registration-enabling (accelerated approval) Phase 2 study for IDE196 in patients with MUM
  - Partnership with Foundation Medicine SmartTrials™ for non-MUM patient identification
- IDE196, administered at either 300 mg BID or 400 mg BID with a 7-day 200 mg run-in, was well tolerated with no dose-limiting toxicities
- Phase 2 dose selection and expansion into MUM and non-MUM cohorts is anticipated to initiate in Q4 2019
  - MUM Phase 2 expansion will target enrollment of 60 evaluable MUM patients with the primary endpoint of overall response rate (ORR) as determined by blinded independent central review (BICR), supported by BICR-determined duration of response (DOR) as a secondary endpoint
  - The non-MUM cohorts will focus on *GNAQ/11*-mutated cutaneous melanoma, colorectal cancer and others
- Interim data with efficacy for GNAQ/11 Phase 1/2 basket trial expected in Q2/Q3 2020

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