

A Phase I Trial of LXS196, a PKC Inhibitor for Uveal Melanoma

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Disclosures

- Sophie Piperno-Neumann
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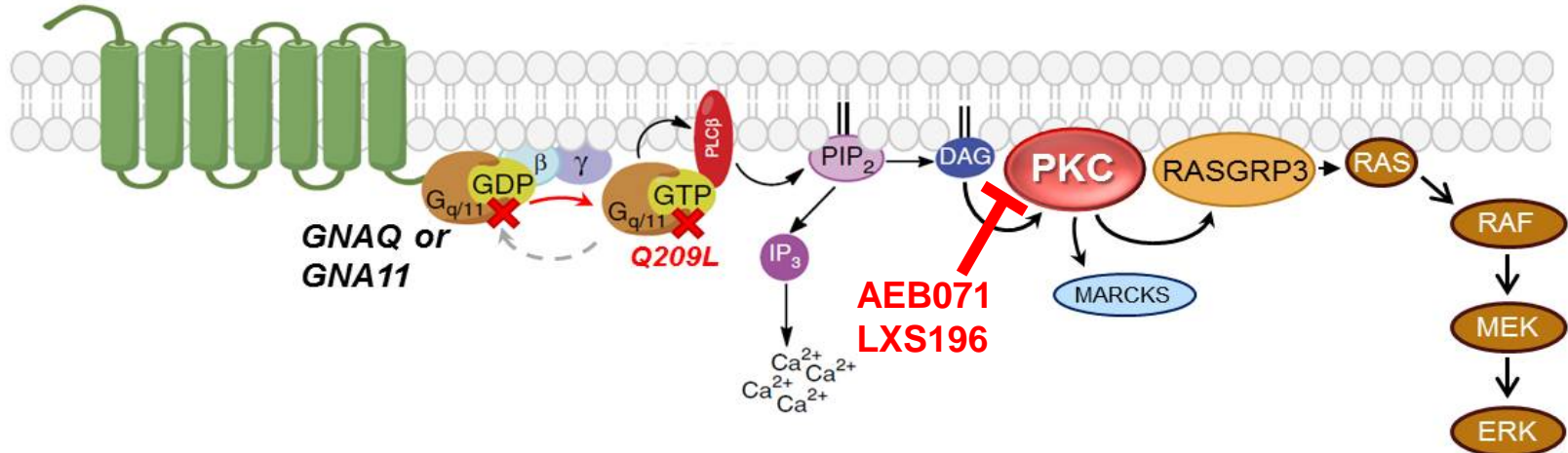
Background

- Uveal melanoma (UM) is the most common primary intraocular malignancy in adults representing 3% to 5% of all melanomas.^{1,2}
- About 50% of patients develop metastases to the liver within 15 years of their initial diagnosis.³
- One-year survival for metastatic patients is 15% with the median survival ranging from 4 to 15 months.^{4,5}
- Currently, there are no approved therapies for patients with metastatic UM.

1. Bakalian S, et. al. *Clin Cancer Res* 2008;14:951-956; 2. Buder K, et. al. *Cancer Med* 2013;2:674-686;
3. Wu X, et. al. *Mol Cancer Ther* 2012;11:1905-1914; 4. Collaborative Ocular Melanoma Study Group. *Arch Ophthalmol* 2006;124:1684-1693;
5. Postow M, et. al. *J Clin Oncol* 2014;32:(suppl):Abstract 9074.

Mutations in *GNAQ/11* May Be the Genetic Drivers in Uveal Melanoma

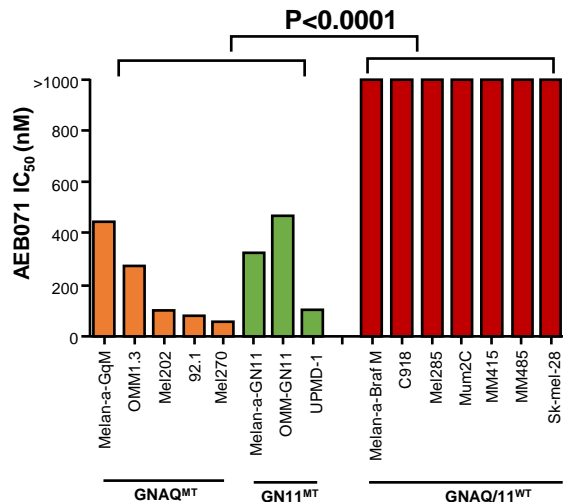
- Activating mutations in G α subunits of G protein coupled receptors (GPCRs) have been identified in 90% of patients with metastatic UM.¹⁻³
- A key downstream pathway of the constitutively active Gq alpha subunits is the phospholipase C (PLC)/protein kinase C (PKC) signaling pathway.



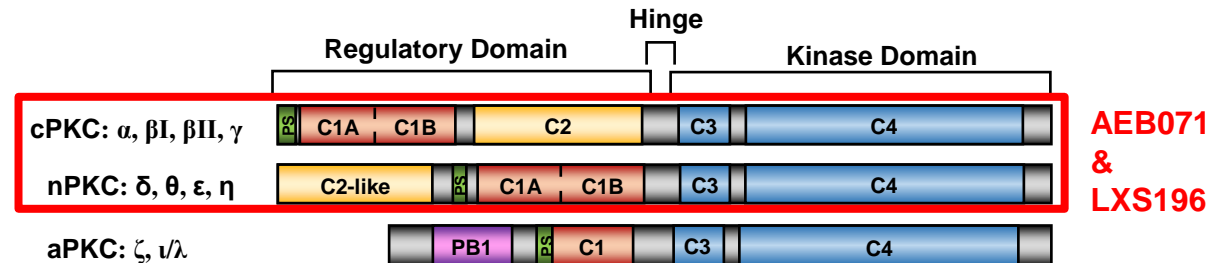
1. Van Raamsdonk CD, et. al. *Nature* 2009;457:599-602; 2. Van Raamsdonk CD, et. al. *N Engl J Med* 2010;363:2191-2199;
3. Piperno-Neumann S, et. al. *J Clin Oncol* 2014;32:(suppl):Abstract 9043.

PKC Inhibitors May Be a Viable Treatment Option for Metastatic Uveal Melanoma

- Preclinical data showed selective sensitivity of UM cell lines carrying Gα subunit mutations in PKC inhibitors.¹
- AEB071 (Sotrastaurin) - a first generation, small molecule, oral, inhibitor of PKC is an inhibitor of the both the classical (α, β), and novel (δ, ε, η, θ) isoforms of PKC.



PKC, protein kinase C; UM, uveal melanoma.

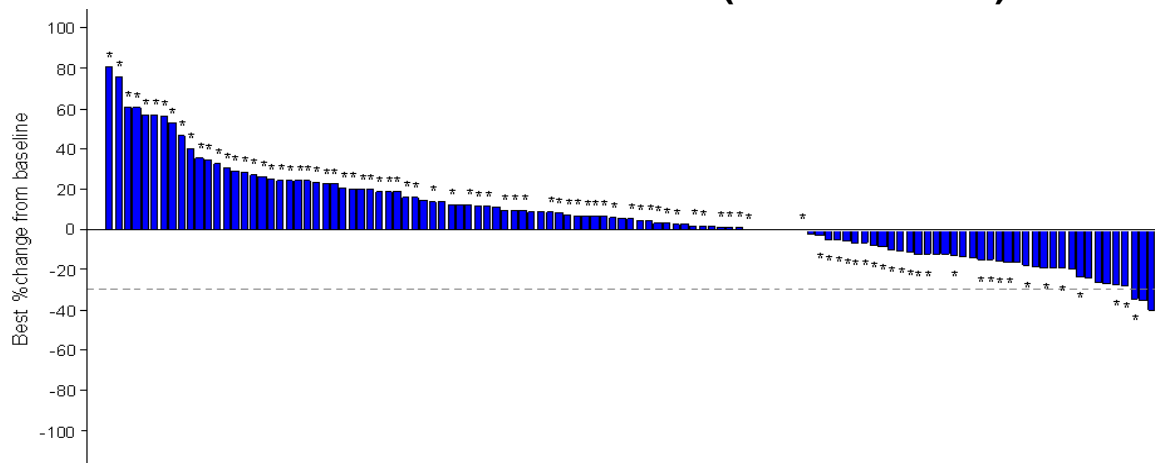


1. Chen X, et al. *Oncogene* 2014;33(39):4724-4634.

AEB071 Achieved Only Minimal Activity in a Ph I Study

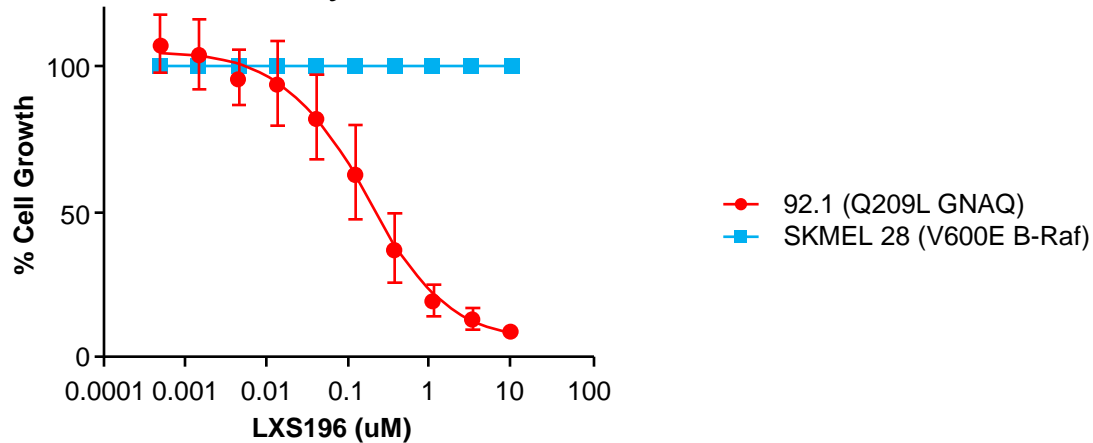
- Of 141 patients, 2 pts achieved PR, 70 pts (50%) had SD, and the median PFS was 15 weeks.¹
- Dose escalation led to a less than proportional increase in exposure and higher doses were associated with increased incidence of dose limiting GI toxicities.¹

Best Percentage Change From Baseline in Sum of Longest Diameters of Target Lesions for All Patients at all Doses (NCT01430416)



LXS196 is a Potent, Second-generation, Oral PKC Inhibitor

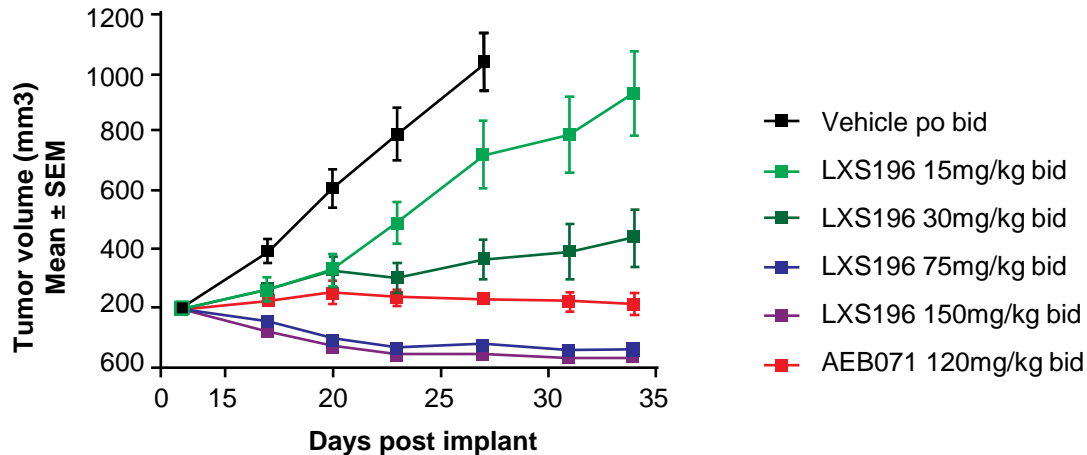
- LXS196 is rapidly absorbed and well tolerated in preclinical studies.
- LXS196 has a highly selective kinase profile with cellular activity restricted to UM cell lines containing mutant GNAQ or GNA11 and no activity observed in melanoma cell lines driven by mutant B-Raf or N-Ras.



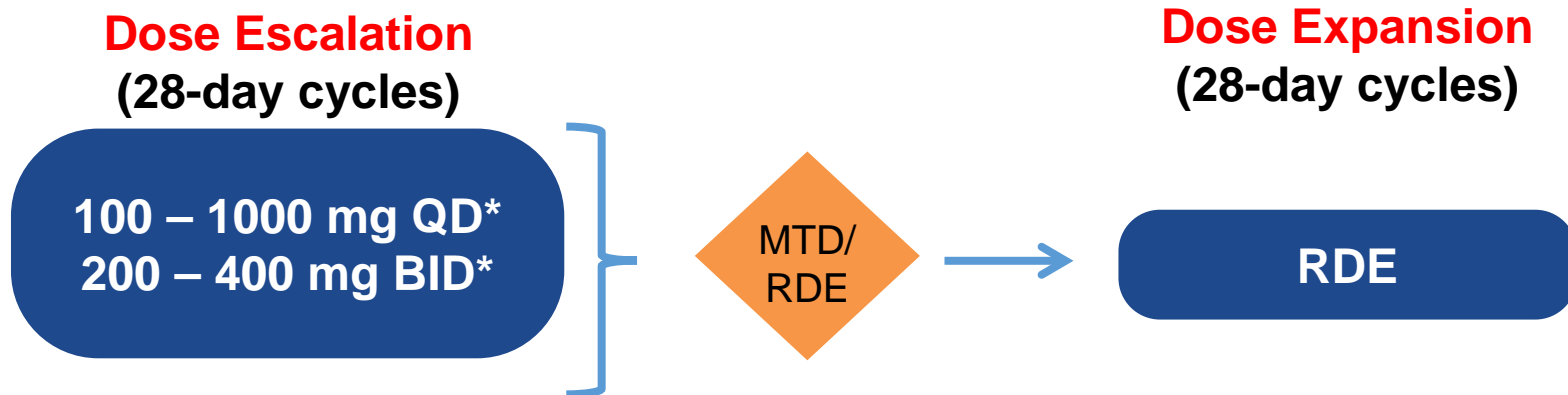
- LXS196 is more active against the novel than the classical PKC isoforms compared to AEB071 which has similar activity against both.

Preclinically, Tumor Regression Is Achieved With LXS196 at Multiple Doses

- In the 92.1 human UM mouse xenograft model, LXS196 dosed as a single-agent, induced tumor regression at doses below its MTD, in contrast to AEB071 where maximum efficacy at its MTD is only stasis.



Phase I, Open-label Study of LXS196 in Patients With Metastatic Uveal Melanoma



- LXS196 dosed orally, either QD or BID except for C1D2 when dosing is omitted
- Dose escalation guided by an adaptive BLRM along with the EWOC principle in addition to available information on AEs, safety and PK

Study Objectives

Primary:

- Characterize safety and tolerability of LXS196 in patients with metastatic uveal melanoma. AEs to be assessed continuously according to CTCAE version 4.0.
- Determine MTD and/or RDE of LXS196 for future studies.

Secondary:

- Evaluate the preliminary antitumor activity of LXS196, ie, ORR and PFS by RECIST v1.1.
- Characterize the PK of LXS196.
- Assess the PD effects of LXS196.

Exploratory:

- Assess the markers that may correlate with prediction of response and/or resistance (eg, by whole genome and exome sequencing of tumor tissue from patients at baseline and at disease progression).

Eligibility Criteria

Key Inclusion Criteria

- Adult patients with biopsy-proven uveal melanoma with progressive metastatic and measurable disease.
- Willingness to provide newly obtained tumor tissue at baseline and on treatment (C1D15).
- Patients may be naive to treatment or have received any number of prior therapies.
- ECOG performance status (PS) ≤ 1 .
- Adequate organ function.

Key Exclusion Criteria

- Symptomatic or untreated CNS metastases or spinal cord compression.
- Impaired cardiac function or clinically significant cardiac disease.
- Patients receiving medications known for QT prolongation, strong inducers, or inhibitors of CYP3A4/5.

Assessments

- Response was assessed by CT or MRI according to RECIST v1.1 on C3D1 and every 2 cycles thereafter until the end of treatment.
- PK evaluations were performed on C1D1 and C1D15 in addition to trough samples on D2, 3 and 16 of each cycle up to C6D1.
- Fresh tumor biopsies were taken at baseline (prior to first dose) and at C1D15 to evaluate modulation of PKC substrate proteins in tumor following exposure to LXS196.
- Whole blood (PBMCs) were taken on pre-dose on C1D1 and C1D15 and post-dose on C1D1, D2, D3, D15, and D16 to evaluate the modulation of PKC substrate proteins in surrogate tissue.

Patient Characteristics

Characteristic		All QD (N=38)	All BID (N=25)	All (N=63)
Median Age, years (range)		55 (26-76)	57 (33-78)	56 (26-78)
Gender, n (%)	Male	22 (58)	12 (48)	34 (54)
	Female	16 (42)	13 (52)	29 (46)
ECOG PS, n (%)	0	37 (97)	21 (84)	58 (92)
	1	1 (3)	4 (16)	5 (8)
Baseline LDH, n (%)	> ULN	23 (61)	12 (48)	35 (56)
	≤ ULN	15 (39)	13 (52)	28 (44)
Prior Therapies, n (%)	0	3 (8)	6 (24)	9 (14)
	1	19 (50)	13 (52)	32 (51)
	2	12 (32)	2 (8)	14 (22)
	>2	4 (10)	4 (16)	8 (13)
Sites of metastases, n(%)	Liver Only	11 (29)	12 (48.0)	23 (36)
	Liver + Other	22 (58)	10 (40.0)	32 (51)
	Other	5 (13)	3 (12.0)	8 (13)

Data cutoff date: August 15, 2017

BID, twice daily, ECOG, Eastern Co-operative Oncology Group; LDH, lactate dehydrogenase; QD, once daily; ULN, upper limit of normal.

Dose Escalation and MTD Declaration

- During dose escalation, 56 patients received LXS196 orally in 1 of 2 dosing schedules, either QD (38 patients) or BID (18 patients).
- Patients were initially treated on a QD schedule (100-1000 mg QD), however, due to toxicities reported at doses ≥ 500 mg QD, a BID schedule was then tested (200-400 mg BID).
- The MTDs were declared at 500 mg QD and 400 mg BID, based on the BLRM and EWOC principles (<25% of posterior probability of the true DLT rate being >33% at this dose level).
- Following the BLRM recommendation guided by EWOC and review of all available safety and PK data, the RDE was declared at 300 mg BID.

Dose-Limiting Toxicities

DLT Events	LXS196 QD Schedule (mg)							LXS196 BID Schedule (mg)				All
	100 N=3	200 N=4	300 N=15	500 N=11	800 N=1	1000 N=4	All QD N=38	200 N=5	300 N=6	400 N=6	All BID N=17	N=55
	n	n	n	n	n	n	N (%)	n	n	n	N (%)	N (%)
Hypotension	0	0	0	2 (grade 3)	1 (grade 4)	2 (grade 4 and grade 2)	5 (13)	0	0	1 (grade 3)	1 (6)	6 (11)
Nausea and vomiting	0	1 (grade 3)	0	0	0	0	1 (3)	0	0	0	0	1 (2)
Neutropenia	0	0	0	1 (grade 4)	0	0	1 (3)	0	0	0	0	1 (2)
Generalized Edema	0	0	0	0	0	0	0	0	0	1 (grade 3)	1 (6)	1 (2)
Total	0	1	0	3	1	2	7 (18)	0	0	2	2 (12)	9 (16)

Data cutoff date: August 15, 2017

BID, twice daily; DLT, dose-limiting toxicity; QD, once daily.

Safety Summary - Dose Escalation

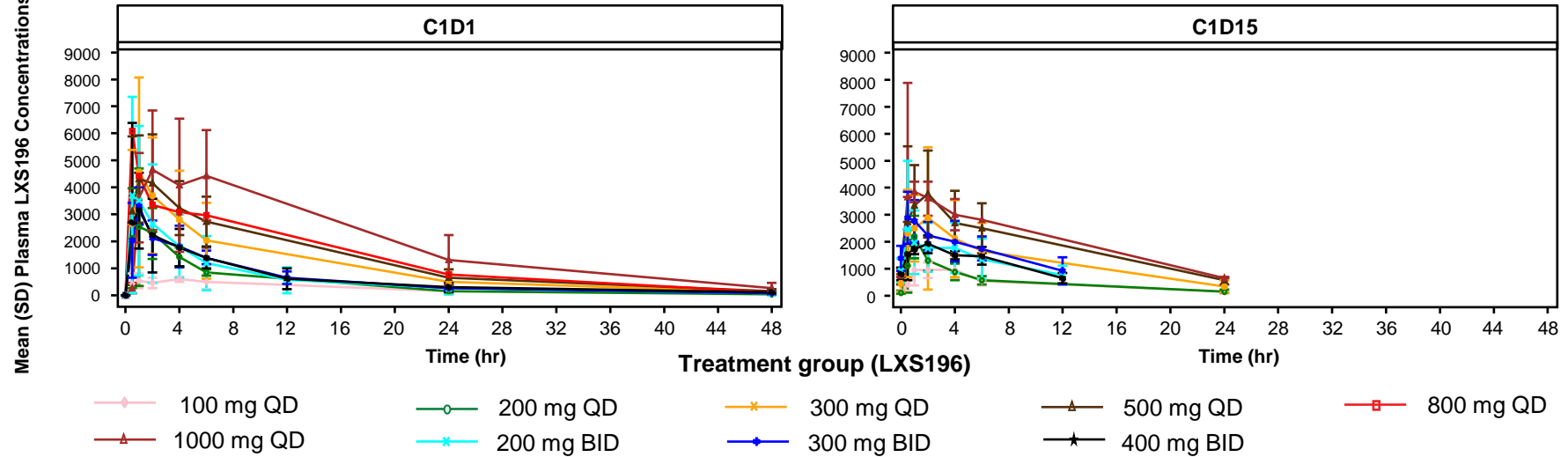
- The most common LXS196-related AEs (all grades, all doses) were nausea (57%), diarrhea (35%), vomiting (25%), and hypotension (22%).
 - All other AEs occurred in <20% of patients.
- AEs of grade ≥ 3 occurred in 21% of patients, the most common being hypotension.
 - Grade 3 or 4 hypotension was more common in the QD vs BID schedule (13% vs 4%).
 - Symptomatic hypotension occurs within 1 to 4 hours of first or second LXS196 dose.
 - No corresponding increase in HR, no ECG changes, no others signs of drug allergy, and routine laboratory tests within normal range.
 - All events were manageable and resolved quickly with intravenous fluids, LXS196 interruption, and dose reduction.
- GI toxicities are generally of low grade (grade 1 or grade 2) and manageable.
 - GI toxicities are more common in the QD schedule.
- Peripheral edema is low grade (grade 1 or 2) and more common in the BID schedule (24% vs 13%).

AEs Regardless of Relationship ($\geq 5\%$ of All Patients)

Adverse Event	All QD patients (N=38)		All BID patients (N=25)		All Patients (N=63)	
	All	Gr 3/4	All	Gr 3/4	All	Gr 3/4
Nausea	27 (71)	1 (3)	12 (48)	0	39 (62)	1 (2)
Diarrhea	20 (53)	0	8 (32)	0	28 (44)	0
Vomiting	15 (40)	1 (3)	5 (20)	0	20 (32)	1 (2)
Hypotension	8 (21)	5 (13)	6 (24)	1 (4)	14 (22)	6 (9)
Asthenia	8 (21)	0	7 (28)	0	15 (24)	0
Fatigue	12 (32)	0	1 (4)	0	13 (21)	0
Increased ALT	8 (21)	2 (5)	5 (20)	1 (4)	13 (21)	3 (5)
Increased AST	5 (13)	2 (5)	5 (20)	1 (4)	10 (16)	3 (5)
Increased creatinine	3 (8)	0	4 (16)	0	7 (11)	0
Constipation	10 (26)	0	5 (20)	0	15 (24)	0
Dyspepsia	2 (5)	0	4 (16)	0	6 (9)	0
Rash	4 (10)	0	3 (12)	0	7 (11)	0
Decreased appetite	5 (13)	0	1 (4)	0	6 (9)	0
Dizziness	5 (13)	0	2 (8)	0	7 (11)	0
Peripheral edema	5 (13)	0	6 (24)	0	11 (17)	0
Dry skin	3 (8)	0	2 (8)	0	5 (8)	0
Neutropenia	5 (13)	2 (5)	1 (4)	0	6 (9)	2 (3)

Pharmacokinetics

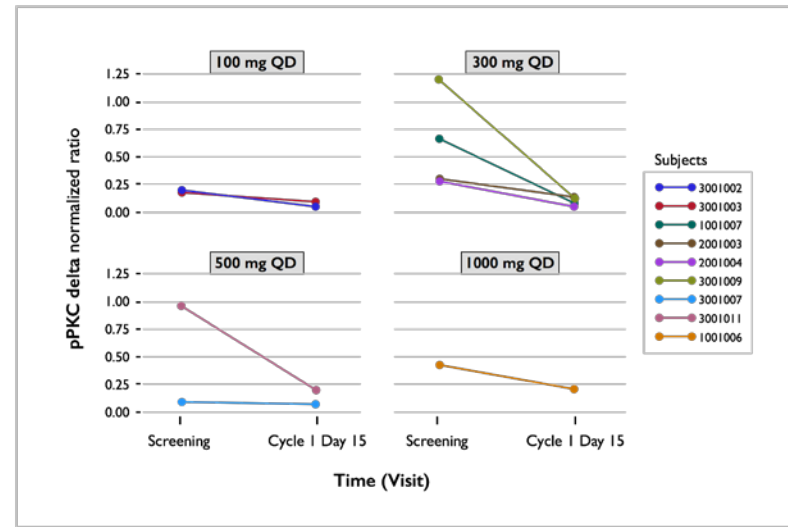
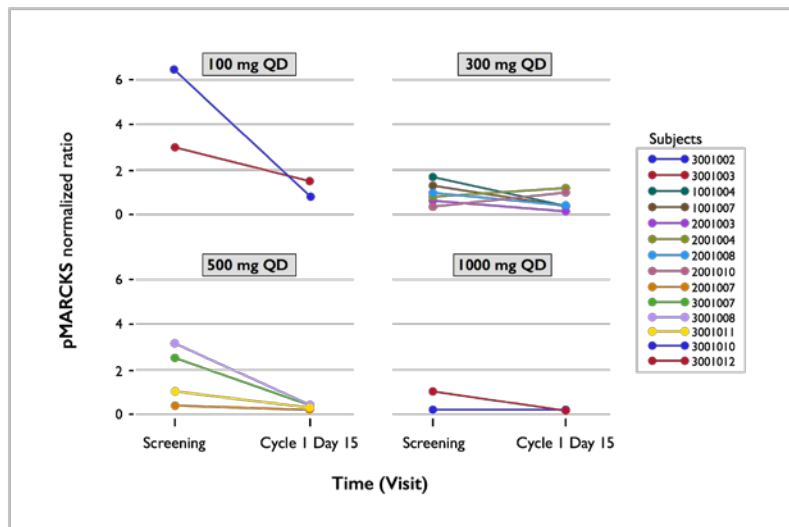
Mean LXS196 Total Plasma Concentration Profiles (Linear View) on Cycle 1 Day 1 and Day 15 Following Multiple Oral Doses of 100 to 1000 mg QD and 200 to 400 mg BID



- Moderate pharmacokinetic variability: 10 - 80% for C_{max} and AUC_{tau}
- Rapid absorption (T_{max} ~ 1 hr post dose)
- Consistent terminal half-life across different doses (8 - 13 hr, median ~ 11 hr)
- No or minimal accumulation (accumulation ratio: 0.718 ~ 1.27 fold) with repeated administration

AUC, area under curve; BID, twice daily; QD, once daily.

Reduction of pMARCKS and pPKCdelta Observed at All Doses in On-treatment Tumor Biopsies



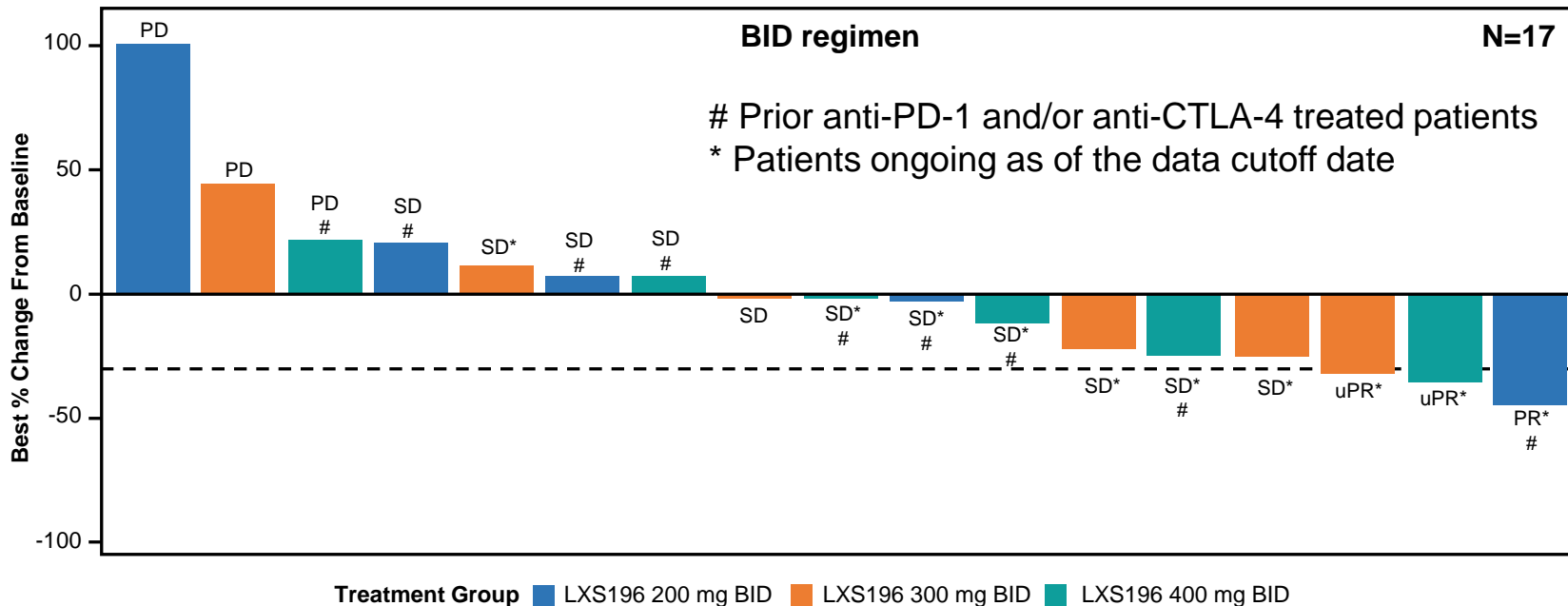
- LXS196 resulted in reduction of pMARCKS and pPKC delta, evident of target engagement in on-treatment tumor biopsies.

Preliminary Clinical Activity

- As of the data cutoff date (August 15, 2017), 55 patients had completed at least 1 postbaseline assessment.
- Of these, 3 patients achieved PRs and 2 patients achieved uPRs.
- A further 38 patients achieved SD as their BOR.
- More than half of all patients (33 of 55; 60%) had received prior I-O therapy (anti-PD-1± anti-CTLA-4). No patient was reported to have responded to prior I-O.
- Responses to LXS196 was observed in both prior I-O treated and naive patients.

Preliminary Clinical Activity – BID Schedule

Best % Change From Baseline in Sum of Longest Diameters With Best Overall Response



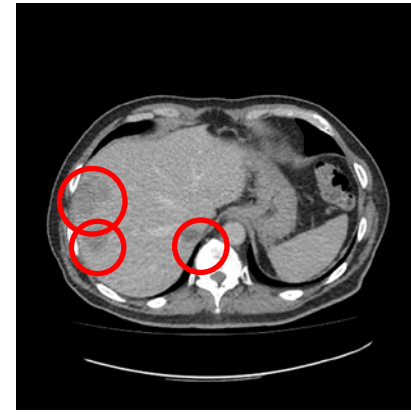
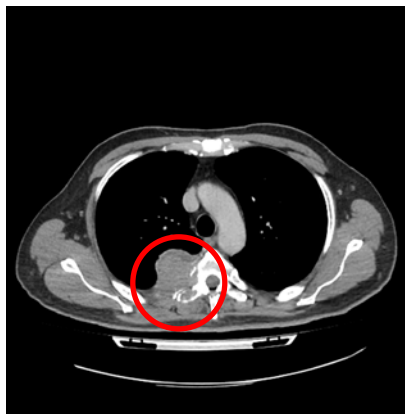
Data cutoff date: August 15, 2017

BID, twice daily; CTLA4, cytotoxic T-lymphocyte-associated antigen 4; PD, progressive disease; PD-1, programmed cell death protein-1; PR, confirmed partial response; SD, stable disease; uPR, unconfirmed partial response.

Confirmed PR in a 72 y/o Male Patient With Metastatic Uveal Melanoma on LXS196

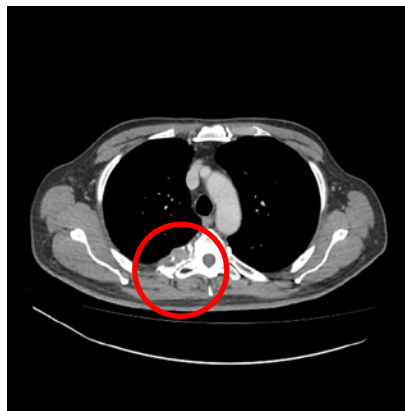
- History of primary uveal melanoma resected 2009
- Developed metastatic disease involving liver, lung, adrenal and bone Apr-2016
- Progressive disease after treatment with Pembrolizumab (May to Jun-2016)

Baseline



- Commenced 300 mg QD LXS196 (Jul-2016)
- PR (-41% reduction) after 2 cycles, subsequently confirmed after 4 cycles
- Progressive disease with new liver lesion after 8 cycles

C5D1



Summary and Conclusions

- Single-agent LXS196 demonstrated encouraging clinical activity with manageable toxicities in patients with metastatic UM.
- The majority of AEs are mild to moderate, manageable, and reversible without dose reduction.
- Symptomatic hypotension occurs infrequently soon after the first or second dose and is manageable with IV fluids, discontinuation, and then dose reduction of LXS196.
- Evidence of PKC inhibition observed through suppression of pMARCKS and pPKC delta in on-treatment tumor biopsies.
- Preliminary data showed 5 PRs (3 confirmed, 2 unconfirmed) among 55 response evaluable patients treated at all dose levels in dose escalation.
- The RDE is currently being further evaluated for safety, tolerability, PK, PD, and preliminary efficacy in an expansion cohort of 12 patients.
- LXS196 may be a suitable combination partner for future studies in metastatic UM.

Acknowledgments

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