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Dose-escalation study of sonidegib (LDE225) plus buparlisib (BKM120) in patients with advanced solid tumors

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- I have no disclosures to declare

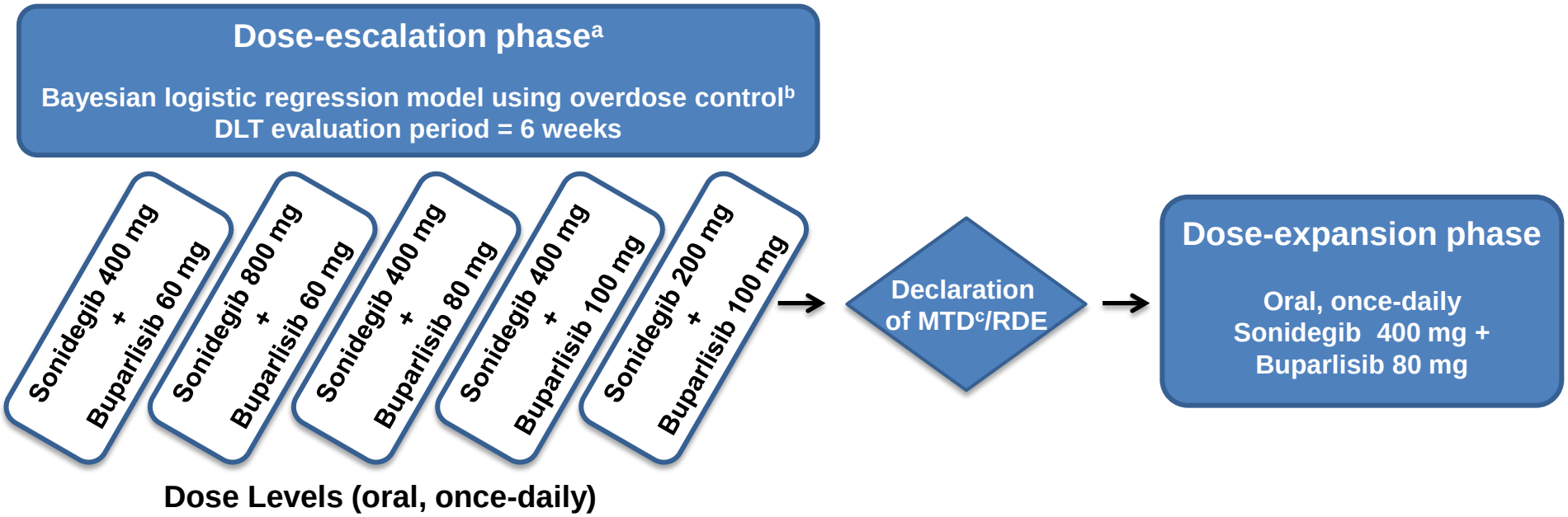
Study Rationale

- Aberrant activation of hedgehog (Hh) signaling has been reported in tumors with dysregulated phosphatidylinositol-3-kinase (PI3K) signaling[1]
- Targeting the Hh pathway (implicated in regulation of cancer stem cells[2]) and the PI3K pathway (frequently activated in cancer[3]) together may provide greater efficacy and overcome resistance to single-agent therapy
- In single-agent phase 1 studies, the Hh pathway inhibitor sonidegib (LDE225; selectively inhibits smoothened) and the pan-class 1 PI3K inhibitor buparlisib (BKM120) have shown antitumor activity[4,5]
  - These agents in combination displayed enhanced activity and delayed resistance in xenograft tumor models[6,7]
- Based on these data, a phase 1b study (NCT01576666) evaluating the safety and efficacy of sonidegib in combination with buparlisib in patients with tumors associated with aberrant Hh and/or PI3K signaling was initiated; data from the dose-escalation phase are presented

1. Riobo NA, et al. *Proc Natl Acad Sci U S A*. 2006;103:4505-4510. 2. Merchant A, Matsui W. *Clin Cancer Res.* 2010;16:3130-3140. 3. Liu P, et al. *Nat Rev Drug Discov*. 2009;8:627-644. 4. Rodon J, et al. *Clin Cancer Res.* 2014;20:1900-1909. 5. Rodon J, et al. *Invest New Drugs.* 2014;32:670-681. 6. Buonamici S, et al. *Sci Transl Med*. 2010;2:51ra70. 7. Gruber Filbin M, et al. *Nat Med.* 2013;19:1518-1523.

Study Design and Objectives

Phase 1b → Dose-escalation study of sonidegib in combination with buparlisib in patients with metastatic breast cancer, metastatic CRC, advanced pancreatic adenocarcinoma, and recurrent GBM



Primary objectives: MTD[c] and/or RDE of co-administered sonidegib and buparlisib

Secondary objectives: safety, tolerability, PK, and antitumor activity

[a] The starting doses were chosen based on data from single-agent phase 1 studies showing that sonidegib 400 mg and buparlisib 60 mg were well tolerated (without DLTs) and lower than the respective MTDs identified.[1,2]

[b] Decision to dose escalate was based on review of DLTs following completion of 6 weeks of dosing in a minimum of 3 evaluable patients.

[c] The MTD was defined as the highest dose of sonidegib + buparlisib not expected to cause a DLT in > 33% of patients (or DLTs with serious clinical implications in > 16% of patients) within 6 weeks of treatment initiation.

CRC, colorectal cancer; DLT, dose-limiting toxicity; GBM, glioblastoma multiforme; MTD, maximum tolerated dose; PK, pharmacokinetics; RDE, recommended dose for expansion.

1. Rodon J, et al. *Clin Cancer Res.* 2014;20:1900-1909. 2. Rodon J, et al. *Invest New Drugs.* 2014;32:670-681.

Patient Eligibility

Key Inclusion Criteria

- Patients ≥ 18 years of age with histologically/cytologically confirmed metastatic breast cancer, metastatic CRC, advanced pancreatic adenocarcinoma, or recurrent GBM
- Patients progressing after standard therapies or for whom no standard therapy exists
- Measurable disease assessed by RANO[1] (GBM) and RECIST 1.1[2] (all other tumors)
- ECOG[3] performance status ≤ 2
- Adequate bone marrow and organ function
- Provision of fresh or archival tumor sample

Key Exclusion Criteria

- Previous treatment with smoothened or PI3K inhibitors
- Impaired cardiac function or clinically significant cardiac disease, neuromuscular disorders (associated with CK elevation), or gastrointestinal dysfunction
- Patients requiring medications/treatments, including those that are:
  - Recognized to cause rhabdomyolysis[a]
  - Strong inhibitors/inducers of CYP3A4/5 or metabolized by CYP2C9 with low therapeutic index
- Patients embarking on a new strenuous exercise regimen during treatment
- History of depression, mental disorders, or anxiety

[a] HMG CoA inhibitors (statins), cliofibrate, and gemfibrozil. Pravastatin allowed with extra caution to control hyperlipidemia.

CK, creatine kinase; CRC, colorectal cancer; CYP, cytochrome P450; ECOG, Eastern Cooperative Oncology Group; GBM, glioblastoma multiforme; PI3K, phosphatidylinositol-3-kinase; RANO; Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors.

1. Wen PY. *J Clin Oncol*. 2010;10:1963-1972. 2. Eisenhauer EA, et al. *Eur J Cancer.* 2009;45:228-247.
3. Oken M, et al. *Am J Clin Oncol* 1982;5:649-655.

Assessments

- **Safety**: laboratory evaluations, physical and/or neurological examinations, vital signs, ECG, and patient-reported mood scales were assessed from screening until 30 days after final dose; ECHO/MUGA was performed at screening and as clinically indicated
- **Pharmacokinetics**: plasma concentrations for sonidegib and buparlisib were analyzed on day 1 of all cycles, including 2 PK profile days (additional sampling over 24 hours) on day 1 of cycles 1 and 4, and on day 15 of cycles 1 and 2
- **Tumor evaluations**: assessed by RANO[1] criteria (GBM) and RECIST 1.1[2] (all other tumors) at screening and on day 1 of odd cycles until disease progression or start of a new antineoplastic agent

ECG, electrocardiogram; ECHO, echocardiogram; MUGA, multiple gated acquisition scan; RANO; Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors.

1. Wen PY. *J Clin Oncol*. 2010;10:1963-1972. 2. Eisenhauer EA, et al. *Eur J Cancer.* 2009;45:228-247.

Patient Demographics

Baseline Characteristics	N = 46
Median age, years	59.0
Age ≥ 65 years, %	26.1
Sex, male, %	43.5
Race, %	
White	89.1
Black	2.2
Asian	2.2
Other	4.3
Unknown	2.2
Tumor type, n (%)	
Colorectal	19 (41.3)
Glioblastoma multiforme	11 (23.9)
Pancreatic	9 (19.6)
Breast	7 (15.2)

Patient Disposition

Patient Disposition[a]	N = 46
Treatment ongoing, n (%)	2 (4.3)
Treatment discontinued, n (%)	44 (95.7)
Primary reasons for discontinuation, n (%)	
Progressive disease	29 (63.0)
Adverse event	7 (15.2)
Patient/guardian decision	4 (8.7)
Death	3 (6.5)
Lost to follow-up	1 (2.2)

[a] Data cutoff date of December 12, 2013.

Adverse Events (any grade)

Adverse Events (any grade, ≥ 20% all patients, regardless of study drug), n (%)[a]	Dose Level (once daily), mg					
	Cohort 1: Sonidegib 400; Buparlisib 60 n = 6	Cohort 2: Sonidegib 800; Buparlisib 60 n = 7	Cohort 3: Sonidegib 400; Buparlisib 80 n = 15	Cohort 4: Sonidegib 400; Buparlisib 100 n = 9	Cohort 5: Sonidegib 200; Buparlisib 100 n = 9	All N = 46
All	6 (100)	7 (100)	15 (100)	9 (100)	8 (88.9)	45 (97.8)
Appetite decreased	2 (33.3)	5 (71.4)	6 (40.0)	5 (55.6)	2 (22.2)	20 (43.5)
Fatigue	2 (33.3)	4 (57.1)	6 (40.0)	4 (44.4)	4 (44.4)	20 (43.5)
AST increased	1 (16.7)	4 (57.1)	1 (6.7)	7 (77.8)	3 (33.3)	16 (34.8)
ALT increased	1 (16.7)	3 (42.9)	1 (6.7)	6 (66.7)	4 (44.4)	15 (32.6)
Nausea	0	4 (57.1)	3 (20.0)	2 (22.2)	4 (44.4)	13 (28.3)
Vomiting	0	3 (42.9)	6 (40.0)	3 (33.3)	1 (11.1)	13 (28.3)
Diarrhea	1 (16.7)	3 (42.9)	3 (20.0)	3 (33.3)	2 (22.2)	12 (26.1)
Hyperglycemia	1 (16.7)	4 (57.1)	2 (13.3)	4 (44.4)	1 (11.1)	12 (26.1)
CK increased	0	4 (57.1)	2 (13.3)	4 (44.4)	0	10 (21.7)

[a] Adverse events were assessed according to Common Terminology Criteria for Adverse Events v4.03.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase.

Adverse Events (grade 3/4)

Adverse Events (grade 3/4, ≥ 5% all patients, regardless of study drug), n (%)[a]	Dose Level (once daily), mg					
	Cohort 1: Sonidegib 400; Buparlisib 60 n = 6	Cohort 2: Sonidegib 800; Buparlisib 60 n = 7	Cohort 3: Sonidegib 400; Buparlisib 80 n = 15	Cohort 4: Sonidegib 400; Buparlisib 100 n = 9	Cohort 5: Sonidegib 200; Buparlisib 100 n = 9	All N = 46
All	3 (50.0)	7 (100)	13 (86.7)	8 (88.9)	3 (33.3)	34 (73.9)
AST increased	1 (16.7)	3 (42.9)	1 (6.7)	4 (44.4)	1 (11.1)	10 (21.7)
ALT increased	1 (16.7)	3 (42.9)	1 (6.7)	4 (44.4)	1 (11.1)	10 (21.7)
CK increased	0	4 (57.1)	2 (13.3)	2 (22.2)	0	8 (17.4)
Hyperglycemia	1 (16.7)	2 (28.6)	1 (6.7)	0	0	4 (8.7)
Fatigue	0	1 (14.3)	1 (6.7)	0	1 (11.1)	3 (6.5)
Nausea	0	2 (28.6)	1 (6.7)	0	0	3 (6.5)
ALP increased	0	1 (14.3)	1 (6.7)	0	1 (11.1)	3 (6.5)
Aphasia	0	0	3 (20.0)	0	0	3 (6.5)

[a] Adverse events were assessed according to Common Terminology Criteria for Adverse Events v4.03.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase.

- Serious AEs (SAEs) occurred in 14 of 46 patients (30.4%) and in all dose cohorts except for cohort 4 (sonidegib 400 mg + buparlisib 100 mg)
  - The only SAE reported in more than 5% of all patients was increased CK (6.5%)

Dose-Limiting Toxicities

	Dose Level (once daily), mg					
	Cohort 1: Sonidegib 400; Buparlisib 60 n = 6	Cohort 2: Sonidegib 800; Buparlisib 60 n = 7	Cohort 3: Sonidegib 400; Buparlisib 80 n = 15	Cohort 4: Sonidegib 400; Buparlisib 100 n = 9	Cohort 5: Sonidegib 200; Buparlisib 100 n = 9	All N = 46
No. of patients with DLTs[a]/No. of evaluable patients[b]	0/4	2/5	1/7	3/9	1/4	7/29
DLTs, n						
CK increased (G3 or G4)	0	2	1	0	0	3
AST (G3)	0	1	0	1	0	2
ALT (G3)	0	0	0	1	1	2
Appetite decreased (G3)	0	1	0	0	0	1
Rash (G3)	0	0	0	1	0	1
Photosensitivity (G2)	0	0	0	1	0	1

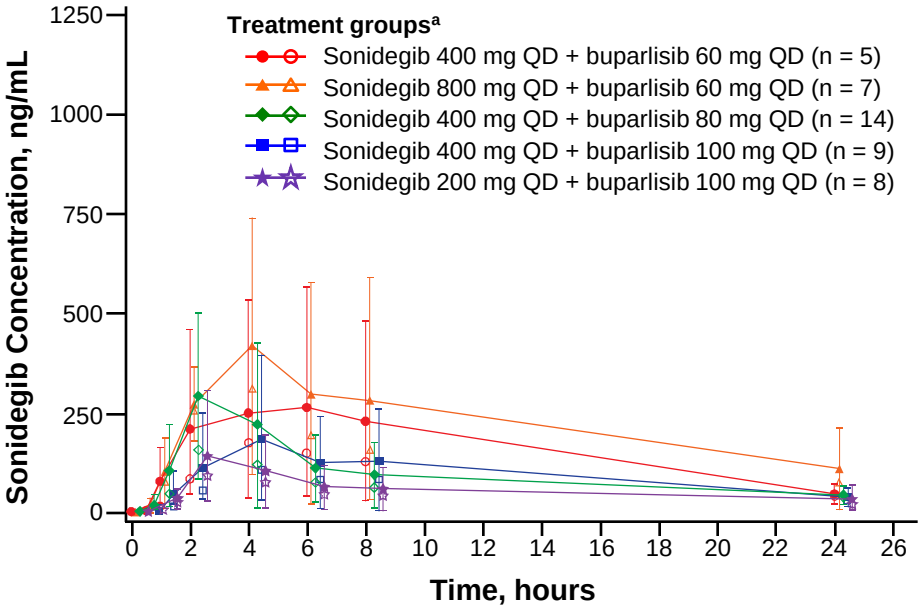
[a] Patients with multiple occurrences of a DLT at 1 dose level were each counted once.
[b] Patients who met the minimum exposure criteria to be included in the dose-determining set.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; DLT, dose-limiting toxicity; G, grade.

- MTD was not reached; the RDE is sonidegib 400 mg + buparlisib 80 mg once daily

Sonidegib Exposure

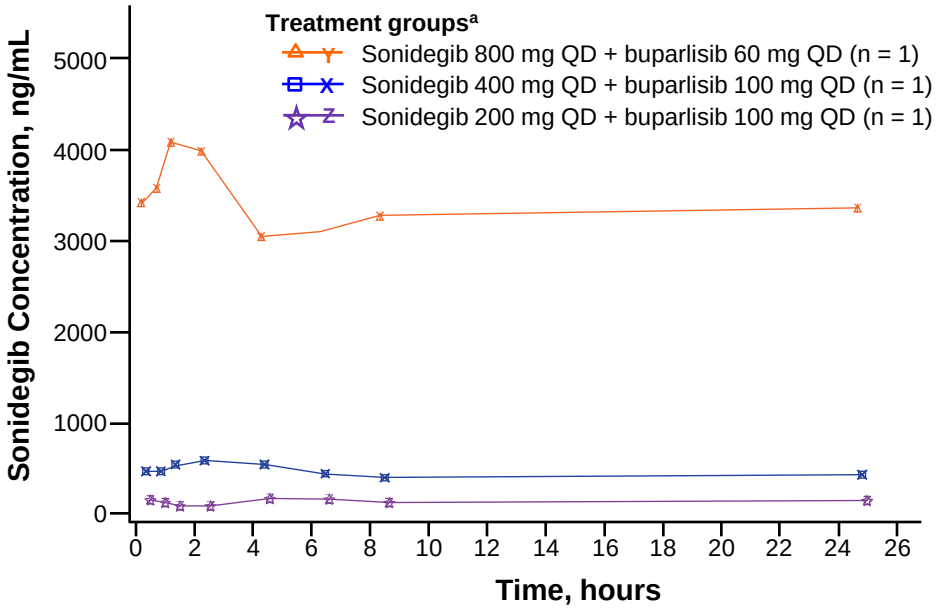
Concentration-Time Profiles of Sonidegib

Day 1 of Cycle 1



QD, once daily.
[a] Filled shapes represent arithmetic means; open shapes represent geometric means. Error bars represent standard deviation of the mean.

Day 1 of Cycle 4



QD, once daily.
[a] Shapes represent arithmetic means; letters represent geometric means.

- Most patients discontinued treatment before reaching cycle 4
- Interindividual variability of sonidegib on day 1 of cycle 1 was ≈ 67%

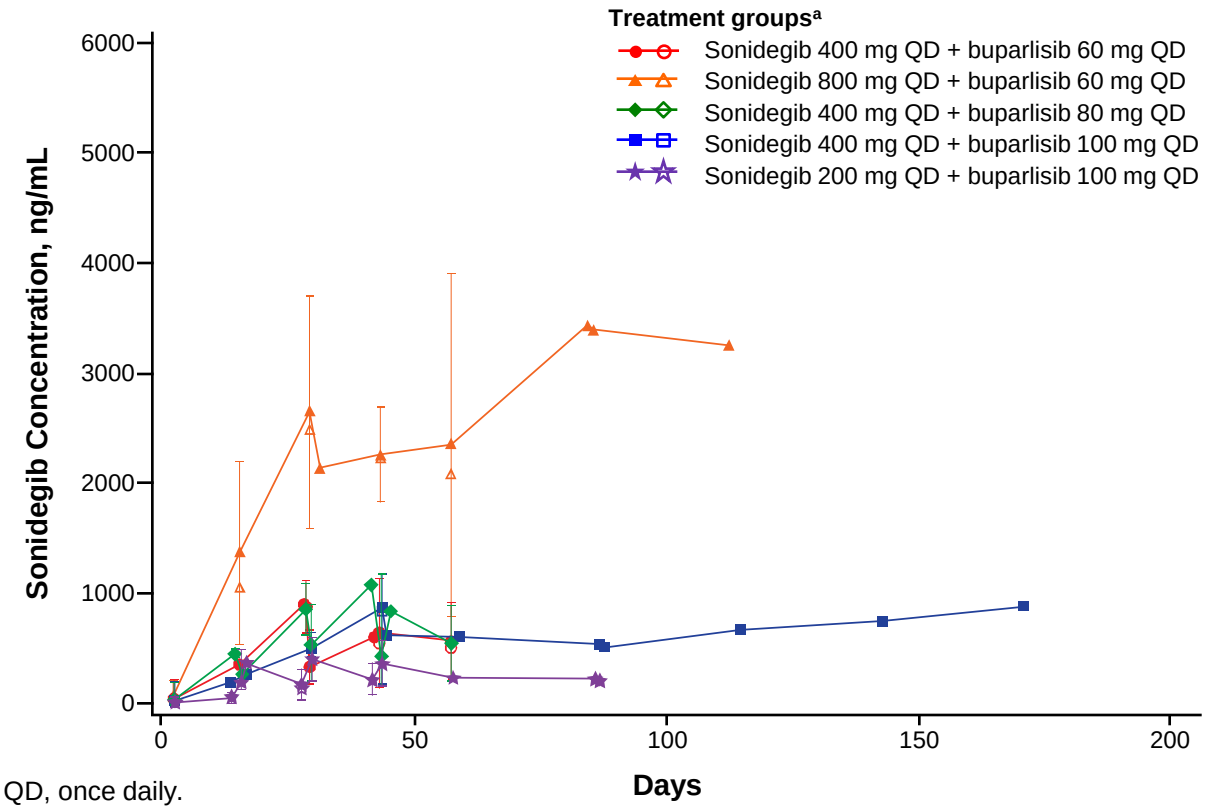
Sonidegib PK Summary

PK Parameter		Dose Level (once daily), mg				
		Cohort 1: Sonidegib 400; Buparlisib 60 n = 6	Cohort 2: Sonidegib 800; Buparlisib 60 n = 7	Cohort 3: Sonidegib 400; Buparlisib 80 n = 15	Cohort 4: Sonidegib 400; Buparlisib 100 n = 9	Cohort 5: Sonidegib 200; Buparlisib 100 n = 9
$AUC_{0\text{-}24h}$, ng•h/mL n Mean (SD)	Cycle 1	5 3750 (3340)	7 5200 (4650)	14 2380 (1560)	9 2220 (1910)	8 1240 (1330)
	Cycle 4	NA	1 81900	NA	1 12300	1 5380
C_{max}, ng/mL n Mean (SD)	Cycle 1	5 437 (270)	7 477 (297)	15 331 (226)	9 244 (213)	9 146 (163)
	Cycle 4	NA	1 4110	NA	1 663	1 261
T_{max}, h n Median (min-max)	Cycle 1	5 2.02 (2.00-6.17)	7 2.00 (1.98-7.00)	15 2.03 (1.03-24.0)	9 4.00 (1.00-6.98)	9 2.00 (2.00-6.02)
	Cycle 4	NA	1 1.00	NA	1 1.97	1 4.47
R_{acc} n Value	Cycle 4	NA	1 29.9	NA	1 15.6	1 8.51

$AUC_{0\text{-}24h}$, area under the plasma concentration-time curve from time zero to 24 hours; C_{max}, peak plasma concentration; NA, not applicable; R_{acc}, accumulation ratio; SD, standard deviation; T_{max}, time to reach C_{max}.

Sonidegib Trough Exposure

Trough Concentration-Time Profiles of Sonidegib



QD, once daily.

[a] Filled shapes represent arithmetic means; open shapes represent geometric means. Error bars represent standard deviation of the mean.

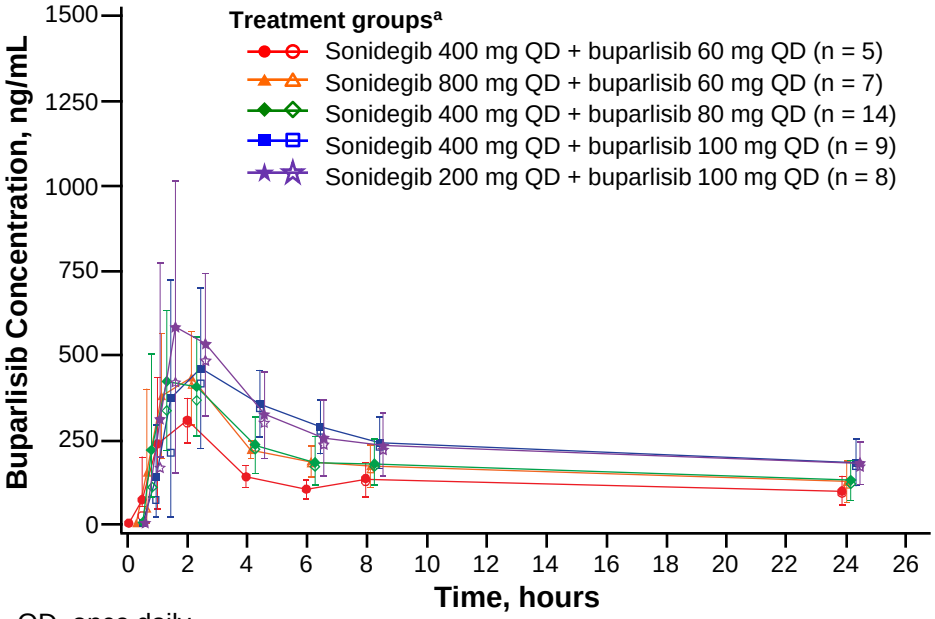
- Trough levels of sonidegib in combination with buparlisib aligned with single-agent exposures[1,2]

1. Rodon J, et al. *Clin Cancer Res.* 2014;20:1900-1909. 2. Rodon J, et al. *Invest New Drugs.* 2014;32:670-681.

Buparlisib Exposure

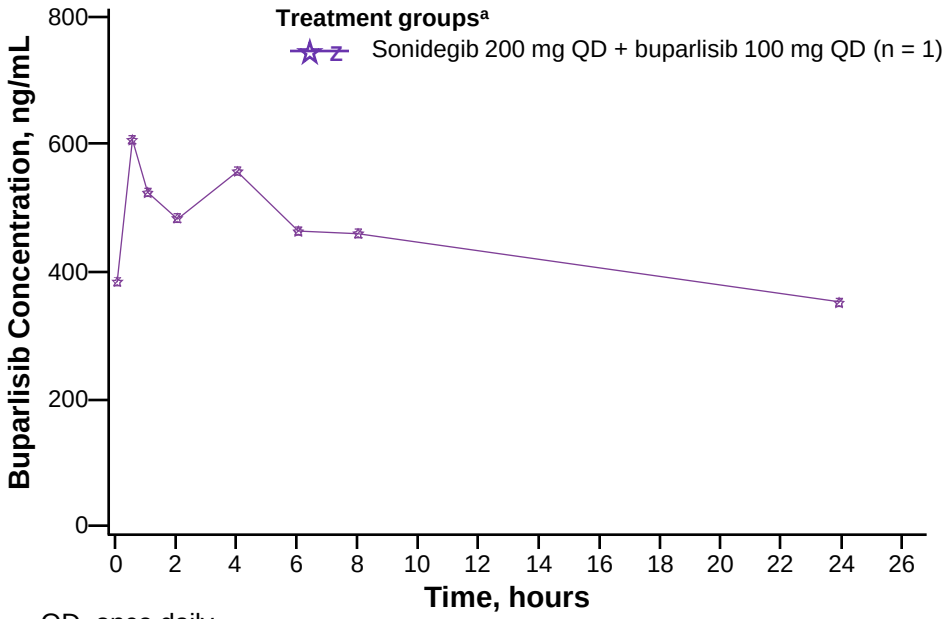
Concentration-Time Profiles of Buparlisib

Day 1 of Cycle 1



QD, once daily.
[a] Filled shapes represent arithmetic means; open shapes represent geometric means. Error bars represent standard deviation of the mean.

Day 1 of Cycle 4



QD, once daily.
[a] Shapes represent arithmetic means; letters represent geometric means.

- Most patients discontinued treatment before reaching cycle 4
- Interindividual variability of buparlisib on day 1 of cycle 1 was ≈ 30%

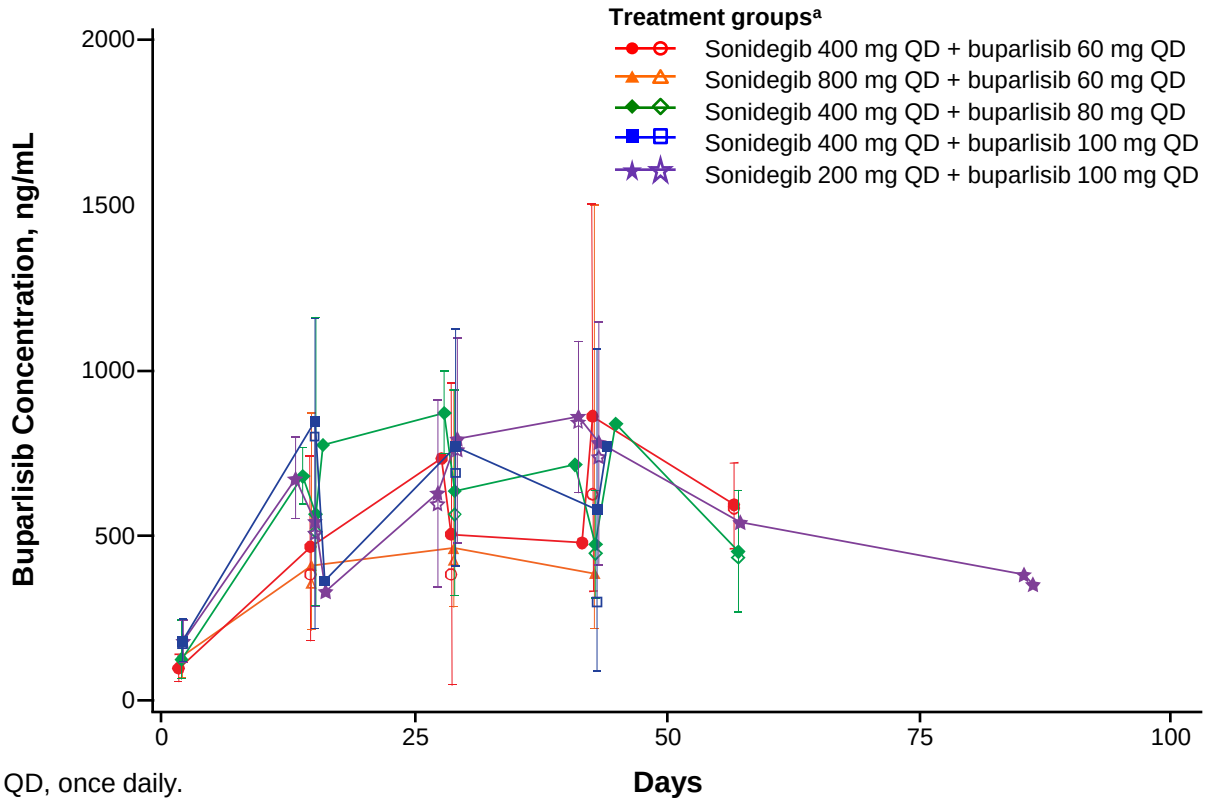
Buparlisib PK Summary

PK Parameter		Dose Level (once daily), mg				
		Cohort 1: Sonidegib 400; Buparlisib 60 n = 6	Cohort 2: Sonidegib 800; Buparlisib 60 n = 7	Cohort 3: Sonidegib 400; Buparlisib 80 n = 15	Cohort 4: Sonidegib 400; Buparlisib 100 n = 9	Cohort 5: Sonidegib 200; Buparlisib 100 n = 9
$AUC_{0\text{-}24h}$, ng•h/mL n Mean (SD)	Cycle 1	5 3200 (698)	7 4280 (851)	14 4110 (1050)	9 5830 (1370)	8 5600 (1940)
	Cycle 4	NA	NA	NA	NA	1 10400
C_{max}, ng/mL n Mean (SD)	Cycle 1	5 333 (121)	7 494 (139)	15 509 (175)	9 578 (225)	9 745 (420)
	Cycle 4	NA	NA	NA	NA	1 604
T_{max}, h n Median (min-max)	Cycle 1	5 1.93 (1.00-2.02)	7 1.93 (0.58-2.00)	15 1.13 (0.57-7.92)	9 2.00 (0.98-5.95)	9 2.00 (0.58-2.00)
	Cycle 4	NA	NA	NA	NA	1 0.67
R_{acc} n Value	Cycle 4	NA	NA	NA	NA	1 2.64

$AUC_{0\text{-}24h}$, area under the plasma concentration-time curve from time zero to 24 hours; C_{max}, peak plasma concentration; NA, not applicable; R_{acc}, accumulation ratio; SD, standard deviation; T_{max}, time to reach C_{max}.

Buparlisib Trough Exposure

Trough Concentration-Time Profiles of Buparlisib



QD, once daily.

[a] Filled shapes represent arithmetic means; open shapes represent geometric means. Error bars represent standard deviation of the mean.

- Trough levels of buparlisib in combination with sonidegib aligned with single-agent exposures[1,2]

1. Rodon J, et al. *Clin Cancer Res.* 2014;20:1900-1909. 2. Rodon J, et al. *Invest New Drugs.* 2014;32:670-681.

Conclusions

- Sonidegib and buparlisib administered in combination are tolerable, with AEs and DLTs consistent with those observed in the respective single-agent phase 1 studies
  - The RDE is sonidegib 400 mg + buparlisib 80 mg once daily
- No obvious drug-drug interactions between sonidegib and buparlisib were observed
  - The pharmacokinetics of each agent in combination appear similar to those observed in single-agent studies

RDE, recommended dose for expansion.

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  - Oncologisch Centrum Sint-Augustinus, Antwerp, Belgium
  - Dana-Farber Cancer Institute, Boston, MA
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