Safety, pharmacokinetics, and antitumor activity findings from a phase 1b, open-label, dose-escalation and expansion study investigating RAF dimer inhibitor lifirafenib in combination with MEK inhibitor mirdametinib in patients with advanced or refractory solid tumors

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Disclosure Information

Benjamin Solomon

I have the following relevant financial relationships to disclose:

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Vertical Inhibition is a Validated Strategy to Target MAPK Aberrant Tumors

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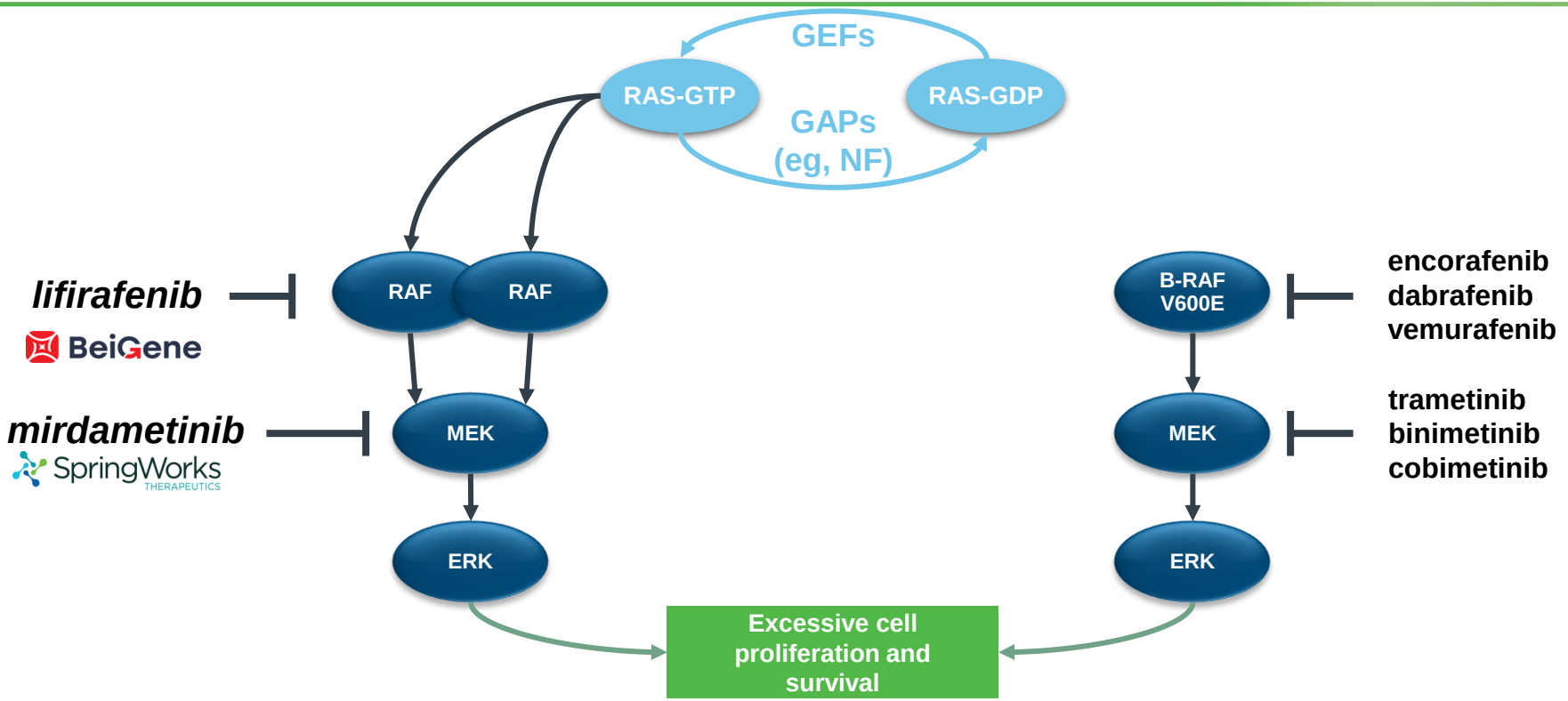

Mol. Oncol. 2020;14(8):1833–1849; Cancer Cell. 2018; 25(5):697–710; Trends in Cancer. 2020;6(9):797-810.

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Lifirafenib + Mirdametinib Lead to Sustained Inhibition of MAPK Pathway Signaling and Significant Tumor Regression

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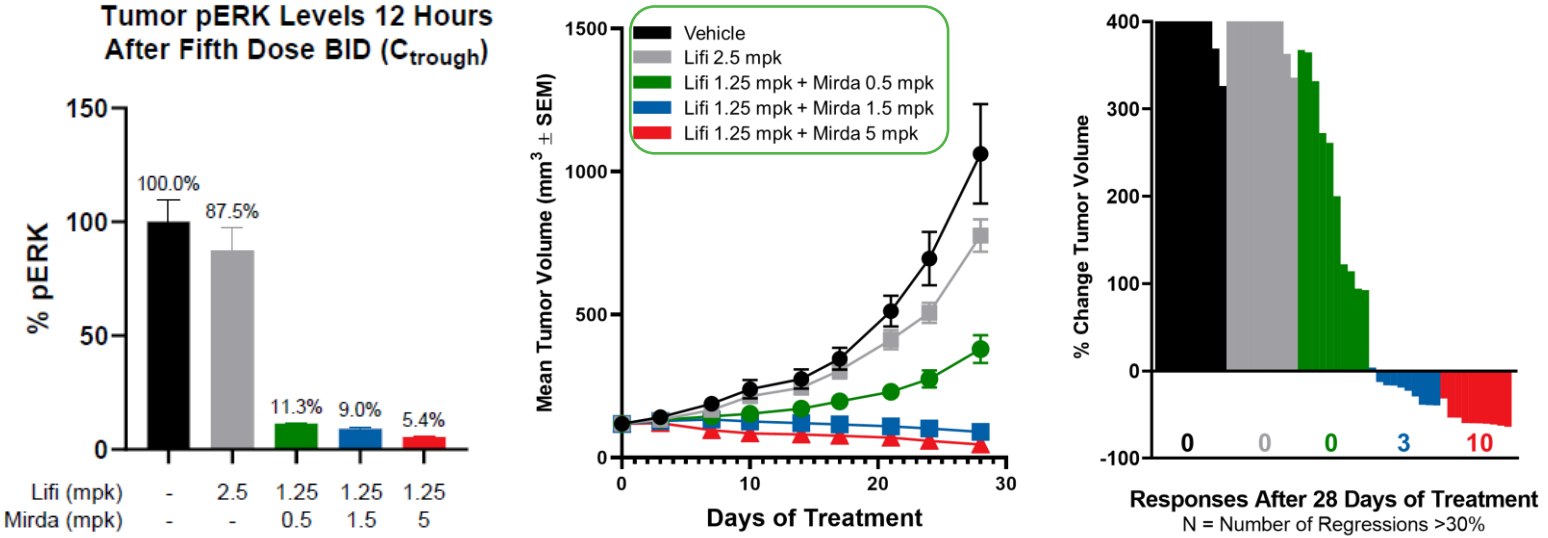
Calu-6 KRAS^{Q61K} NSCLC Xenograft Model



Combination led to rapid MAPK inhibition with durable and sustained pERK inhibition after multiple doses and achieved synergistic antitumor response, resulting in a 100% ORR at 1.25 mpk lifi + 5 mpk mirda in the Calu-6 model.

Lifi, lifirafenib; Mirda, mirdametinib; mpk, mg/kg.

Xi Yuan, et al. *Cancer Res.* 2020;80 (suppl 16):6415.

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Dose-Escalation/Dose-Finding Study Design/Schema

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9 dose levels, with a DLT window in Cycle 1 of 28 days, with and without lifirafenib lead-in dosing, as follows:

- Continuous dosing
  - Level 1: **M 2 mg QD + L 15 mg QD**
  - Level 2: **M 2 mg QD + L 20 mg QD**
- 5 days on, 2-day off (5/2-day intermittent)
  - Level 3a: **M 3 mg QD + L 20 mg QD**
  - Level 4a: **M 4 mg QD + L 20 mg QD**
- Lead-in dosing (5/2-day intermittent) for 14 days, then 5/2-day intermittent dosing for each 28-day cycle
  - Level 3b: (lead-in dose of M 3 mg QD + L 10 mg QD) **M 3 mg QD + L 20 mg QD**
  - Level 3c: (lead-in dose of M 2 mg BID + L 10 mg QD) **M 2 mg BID + L 15 mg QD**
  - Level 4b: (lead-in dose of M 2 mg BID + L 10 mg QD) **M 2 mg BID + L 20 mg QD**
  - Level 4c: (lead-in dose of M 3 mg BID + L 10 mg QD) **M 3 mg BID + L 15 mg QD**
  - Level 5c: (lead-in dose of M 4 mg BID + L 10 mg QD) **M 4 mg BID + L 15 mg QD**

Objectives for Dose Escalation/ Dose Finding

- Establish MTD and/or RP2D
- Evaluate PK of mirdametinib (and its active metabolite PD 0315209) in combination with lifirafenib

Study Population

- Patients with a known mutation in the MAPK pathway and a histologically or cytologically confirmed advanced tumor

BID, twice a day; DLT, dose-limiting toxicity; **L, lifirafenib; M, mirdametinib;** MTD, maximum tolerated dose; PK, pharmacokinetic(s); QD, once a day; RP2D, recommended phase 2 dose.

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Patient Demographics and Baseline Characteristics

Demographics and Baseline Characteristics (N=71)	
Age (years), median (range)	55.9 (23-78)
Sex, male/female, n (%)	18 (25)/53 (75)
Race, white/other, n (%)	56 (79)/15 (21)
ECOG PS 0/PS 1, n (%)	42 (59)/29 (41)
Prior lines of therapy, median (range)	1 (1-8)
Primary cancer type, n (%)	
Ovarian cancer	31 (44)
NSCLC	13 (18)
Colorectal cancer	9 (13)
Endometrial cancer	4 (6)
Melanoma	2 (3)
Pancreatic cancer	1 (1)
Other	11 (16)

Mutation Type (N=71)	
Mutation type, n (%)	
KRAS	41 (57.7)
BRAF	13 (18.3)
BRAF-V600E	10 (14.1)
Non-V600	3 (4.2)
NRAS	8 (11.3)
NF1	3 (4.2)
CRAF/RAF1	2 (2.8)
RASA1	1 (1.4)
CIC	1 (1.4)
PAK2	1 (1.4)
H-RAS	1 (1.4)

Data cutoff date: 20 January 2023. ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung carcinoma; PS, performance status.

Treatment-Emergent Adverse Events (≥ 10% of All Events) Related to Lifirafenib and/or Mirdametinib

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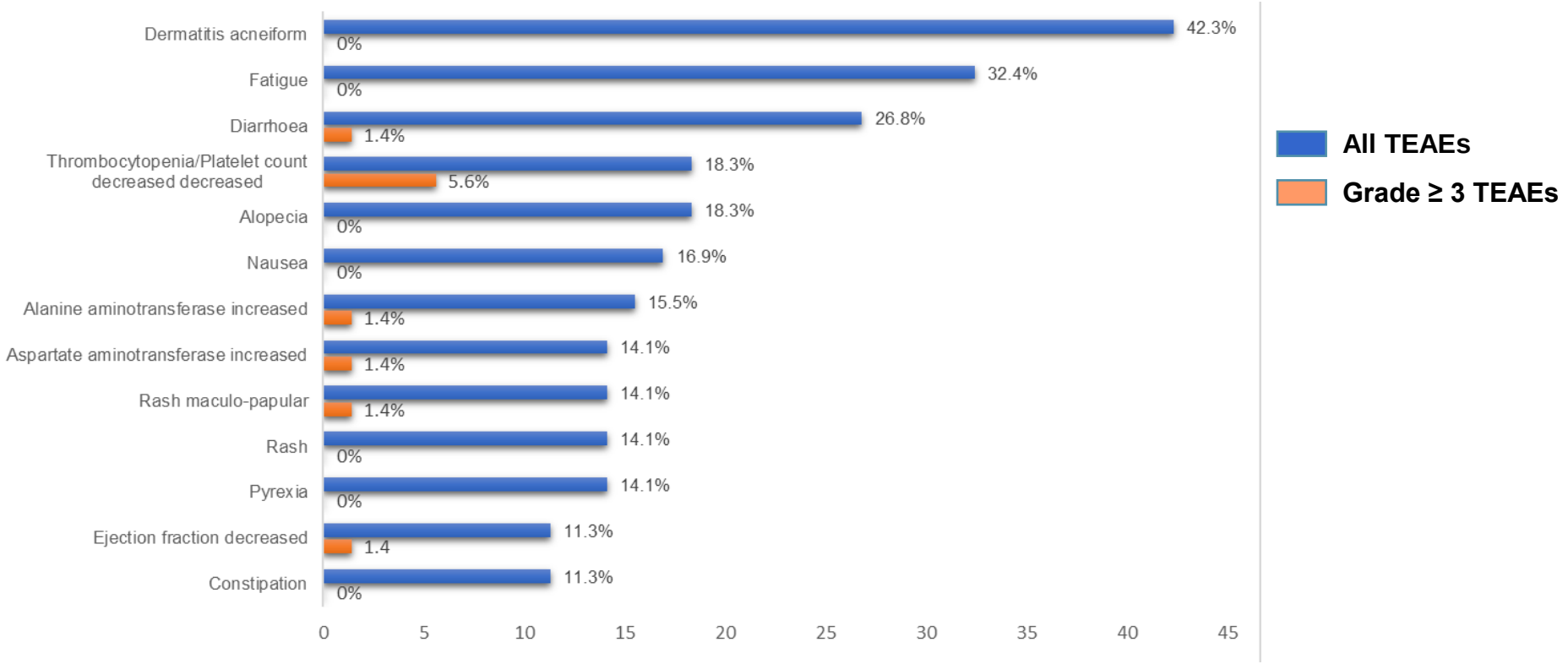

Data cutoff date: 20 January 2023.

Overall Summary of Safety

	Number (%) of Patients		
	Without Lead-In Dosing (n=31)	With Lead-In Dosing [a] (n=40)	Overall (N=71)
TEAE	31 (100)	40 (100)	71 (100)
TEAE related to lifirafenib	28 (90.3)	34 (85.0)	62 (87.3)
TEAE related to mirdametinib	28 (90.3)	35 (87.5)	63 (88.7)
SAE	17 (54.8)	13 (32.5)	30 (42.3)
SAE related to lifirafenib	7 (22.6)	3 (7.5)	10 (14.1)
SAE related to mirdametinib	4 (12.9)	4 (10.0)	8 (11.3)
TEAE of Grade ≥ 3	17 (54.8)	15 (37.5)	32 (45.1)
DLT TEAE	6 (19.4)	1 (2.5)	7 (9.9)
TEAE leading to dose modification	22 (71.0)	19 (47.5)	41 (57.7)
TEAE leading to treatment discontinuation	2 (6.5)	2 (5.0)	4 (5.6)
TEAE leading to death [b]	1 (3.2)	3 (7.5)	4 (5.6)

Data cutoff date: 20 January 2023. DLT, dose limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a] Lead-in dosing occurred for 14 days as follows: DL 3b (M 3 mg QD + L 10 mg QD), DL 3c (M 2 mg BID + L 10 mg QD), DL 4b (M 2 mg BID + L 10 mg QD), and DL 4c (M 3 mg BID + L 10 mg QD).

[b] These TEAEs leading to death were considered by the investigator to be not related to study treatment.

Clinical Activity During Dose Escalation in All Evaluable Patients

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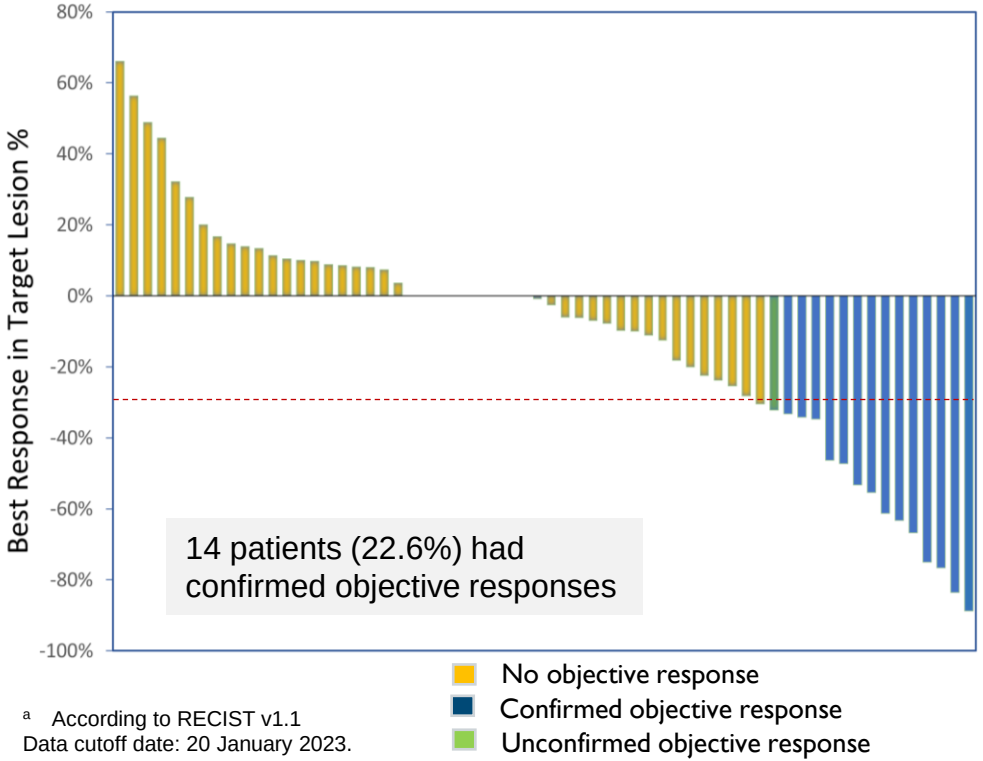
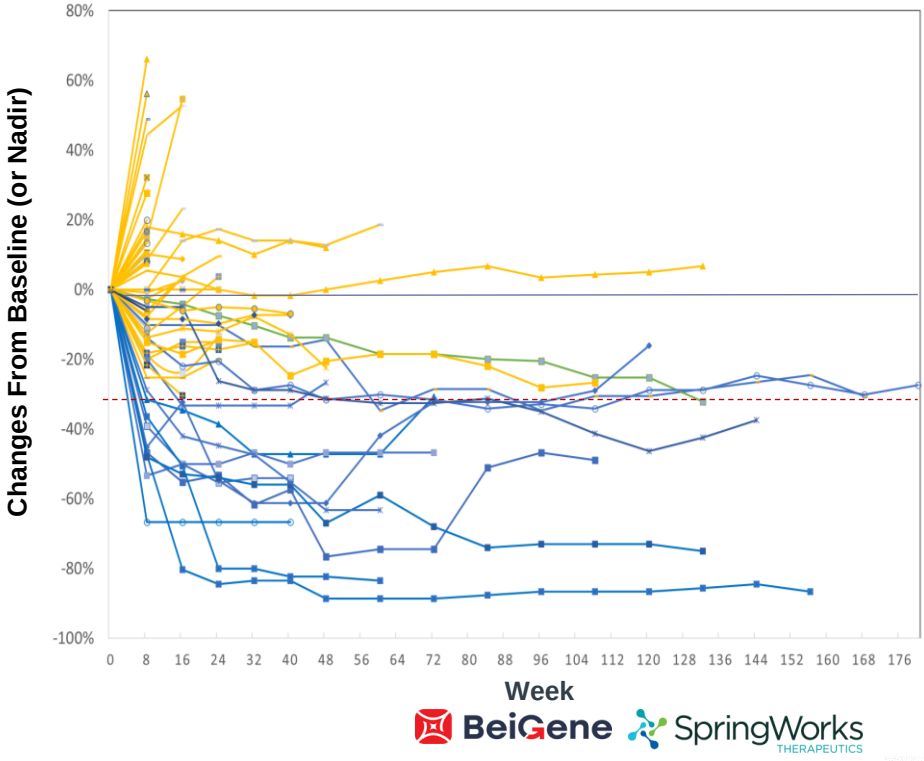
Best Overall Response [a]
(n=62)



Changes in Tumor Response Over Time [a]
(n=62)



[a] According to RECIST v1.1
Data cutoff date: 20 January 2023.

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Clinical Activity During Dose Escalation in All Evaluable Patients By Tumor Types

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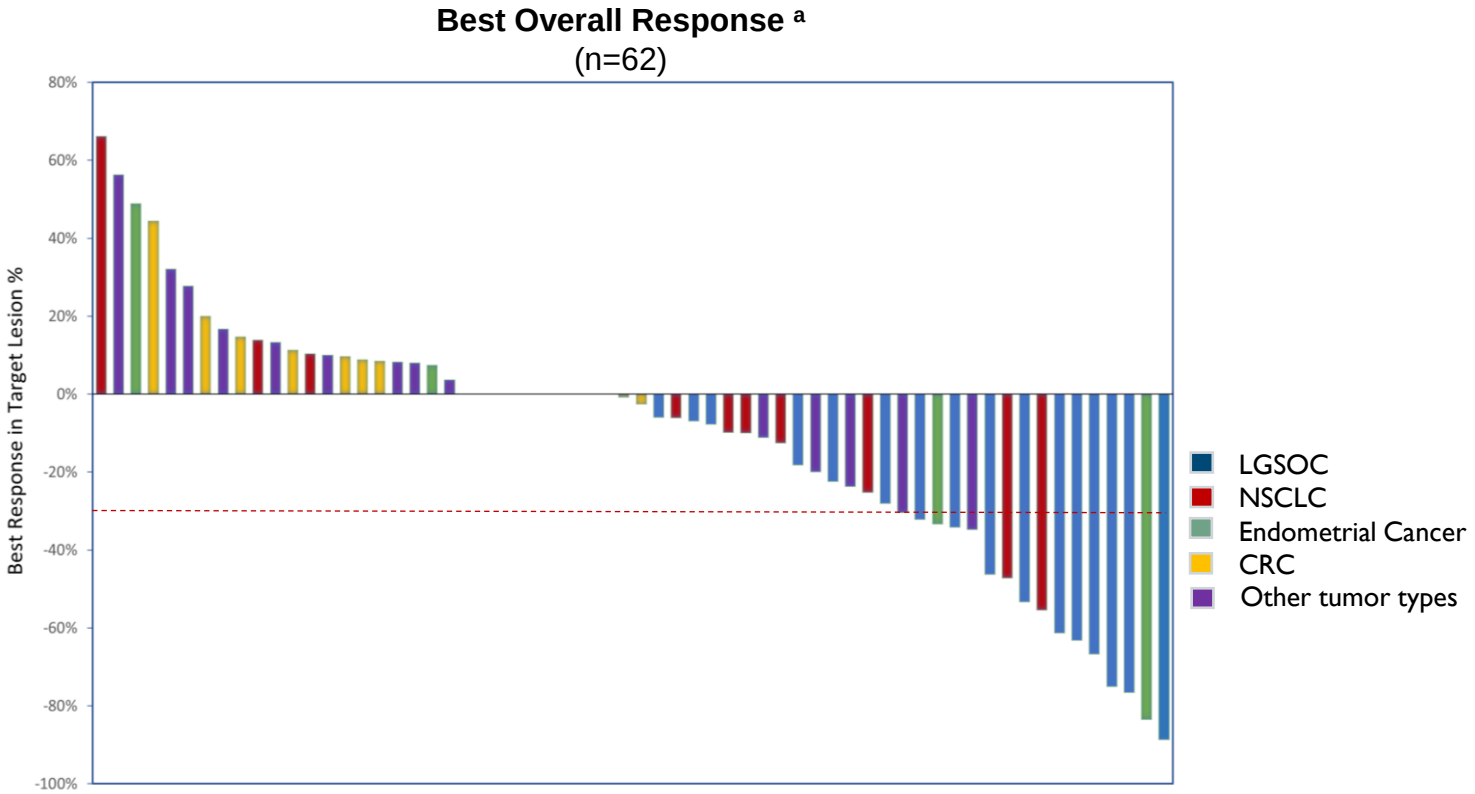

[a] According to RECIST v1.1
Data cutoff date: 20 January 2023.

Clinical Activity During Dose Escalation in All Evaluable Patients By Mutation Types

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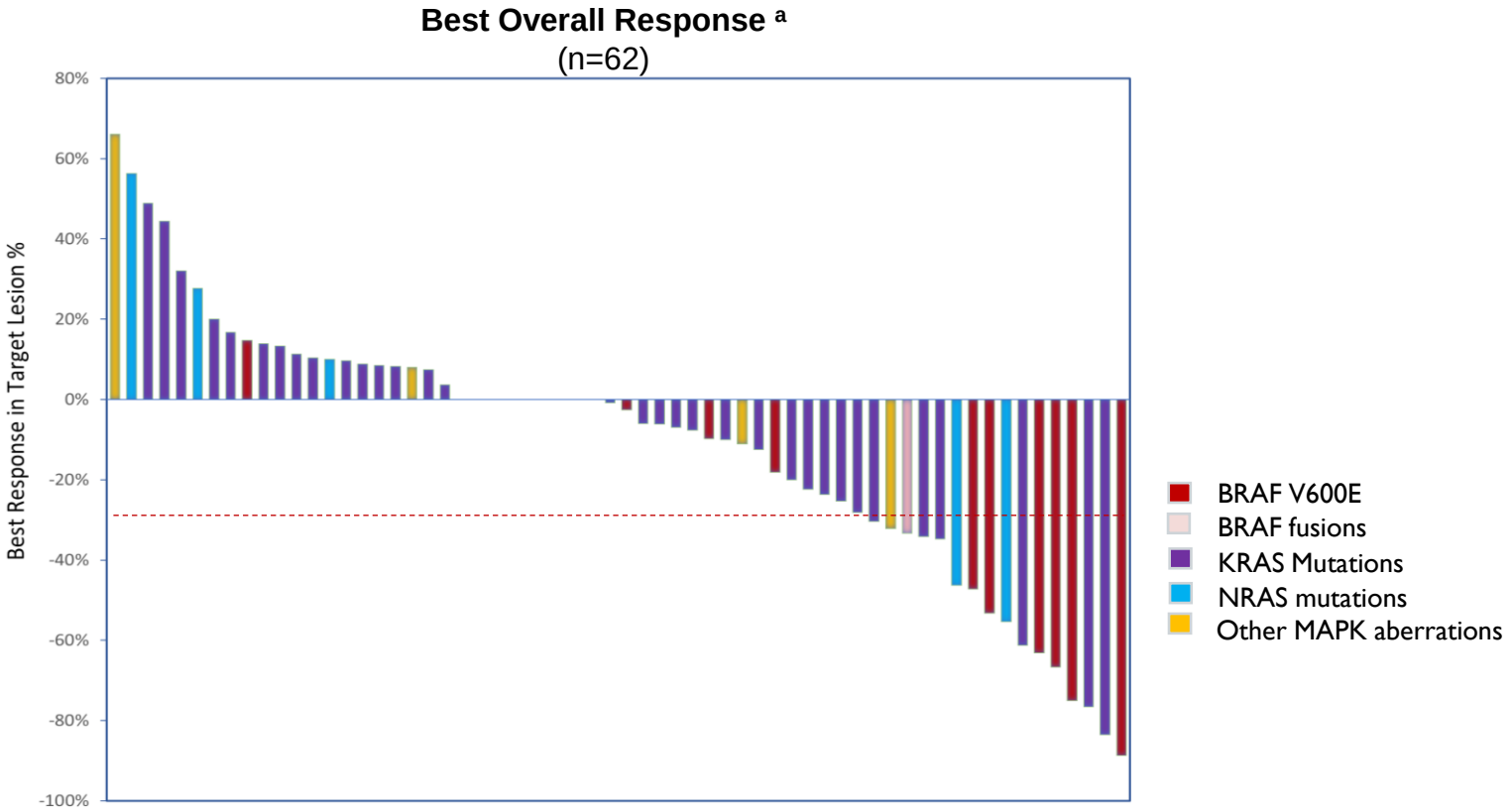

[a] According to RECIST v1.1
Data cutoff date: 20 January 2023.

Clinical Activity During Dose Escalation in Evaluable Patients With LGSOC

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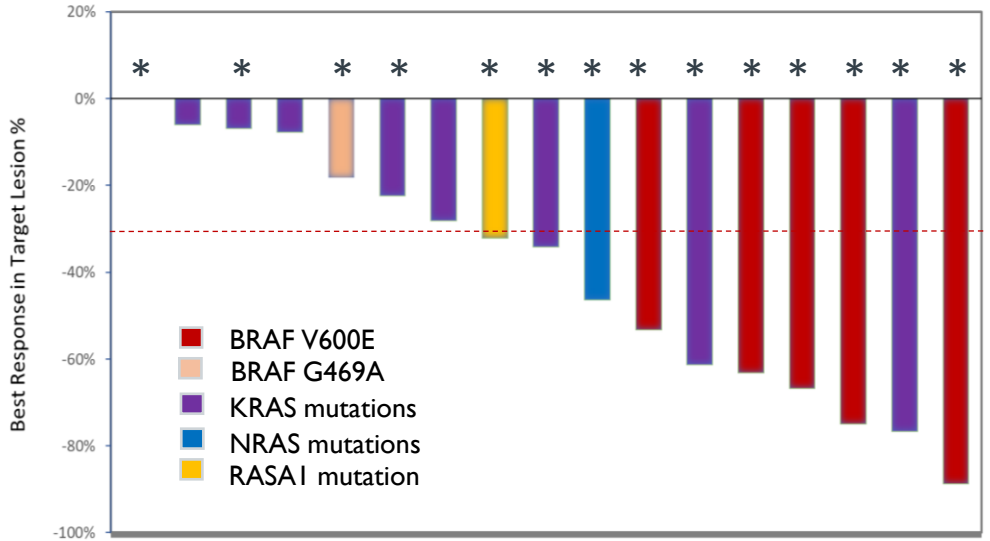
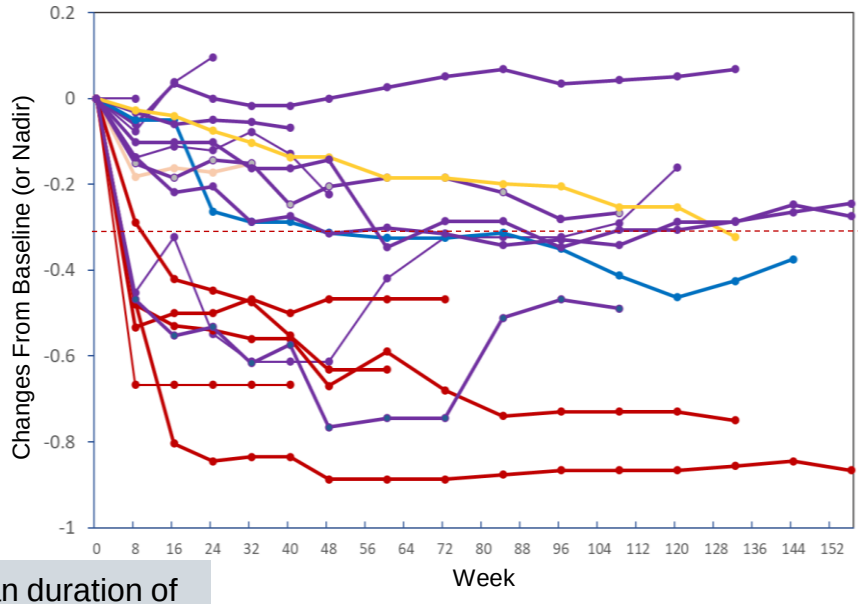
Best Overall Response by Mutation Type in Patients With LGSOC (n=17)



Changes From Baseline in Tumor Response Over Time [a] in Patients With LGSOC (n=17)



10 patients with LGSOC (58.8%) had objective responses; median duration of treatment ~26 months; 14/17 pts still on treatment as of 20 Jan 2023

Data cutoff date: 20 January 2023. LGSOC, low-grade serous ovarian carcinoma.
[a] According to RECIST v1.1 * Pts still on treatment at DCO

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Clinical Activity During Dose Escalation in Evaluable Patients with NSCLC and Endometrial Cancer

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NSCLC (n=11)

- BRAF V600E
- HRAS G12D
- KRAS Mutations
- NRAS Q61K

2/11 patients with NSCLC (18%) had objective responses

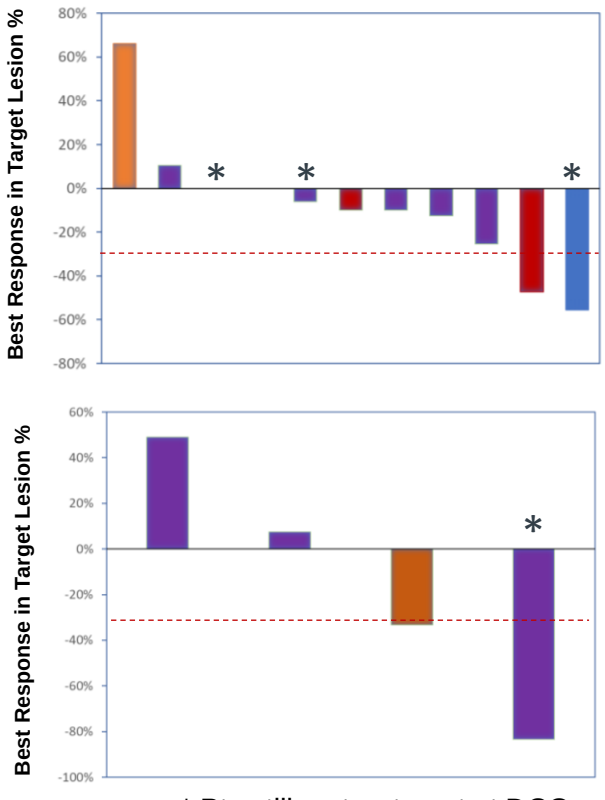
Endometrial Cancer (n=4)

- BRAF fusion
- KRAS Mutations

2/4 patients with endometrial cancer (50.0%) had objective responses

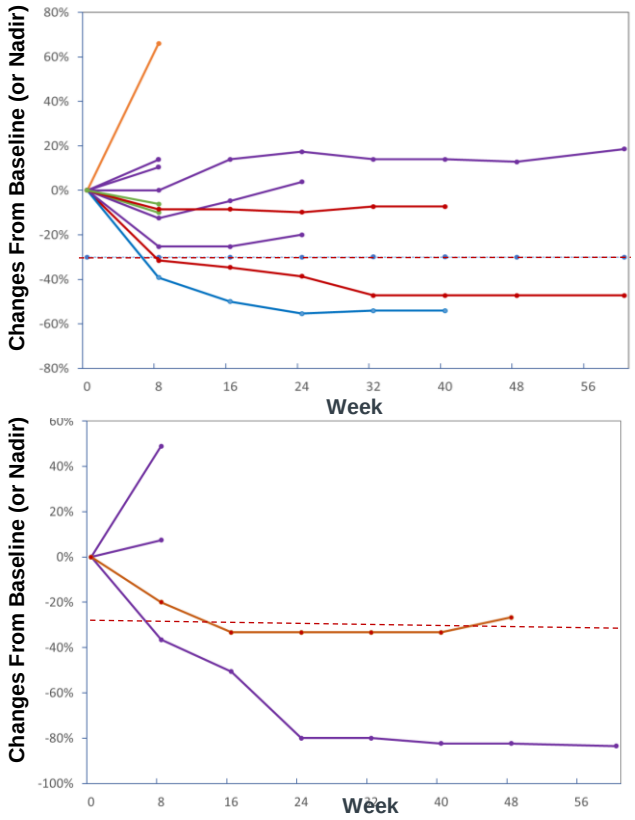
Data cutoff date: 20 January 2023.
NSCLC, non-small cell lung cancer.
[a] According to RECIST v1.1.

Best Overall Response [a]



* Pts still on treatment at DCO

Changes in Tumor Response Over Time [a]



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75-year-old Endometrial Cancer Patient With *KRAS G12A* Mutation

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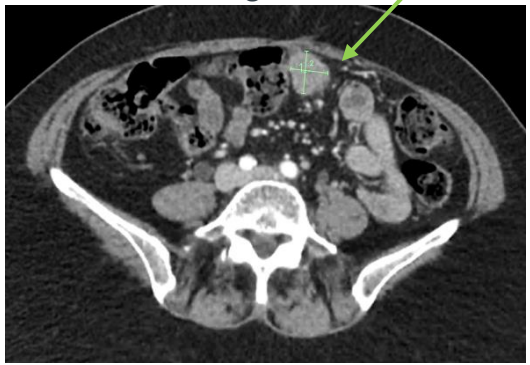
Diagnosis:
Metastatic endometrial cancer (*KRAS G12A* mutation)

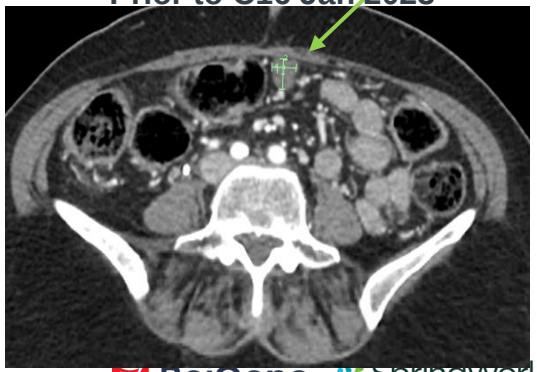
Prior Treatment:
11/2017 – 01/2018: neoadjuvant carboplatin + paclitaxel x 3 - PR
02/2018 – 03/2018: adjuvant carboplatin + paclitaxel x 3 - CR
04/2020 – 08/2020: carboplatin + liposomal doxorubicin - PR
01/2021 – 03/2021: OX40 inhibitor - PD
04/2021 – 05/2021: OX40 inhibitor + PD-1 - PD
05/2021 – 06/2021 : PARPi + TMZ, discontinued due to Grade 4 thrombocytopenia

11/2021 - now: lifirafenib + mirdametinib – PR
continue on treatment as of Jan 20, 2023

Screening Oct 2021



Prior to C16 Jan 2023



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Conclusions

- Lifirafenib in combination with mirdametinib demonstrated a favorable safety profile, with limited DLTs and discontinuations.
- Lifirafenib plus mirdametinib showed antitumor activity in patients with various *KRAS*, *NRAS*, and *BRAF* mutations across several solid tumor types:
  - LGSOC appears to be very sensitive to this combination treatment, with *BRAF* mutations seeming to have deeper and faster responses compared with other MAPK pathway aberrations;
  - Other sensitive tumor types included NSCLC (especially with *NRAS* and *BRAF* mutations) and endometrial cancer with *KRAS* and *BRAF* mutations
- The combination of lifirafenib and mirdametinib demonstrated a desirable risk-benefit profile and warrants further clinical investigation; the dose-expansion portion of the study is planned to start in the second half of 2023 with a focus on biomarker selected patient population with a tumor agnostic approach.

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