PHASE II STUDY OF DEFACTINIB, VS-6063, A FOCAL ADHESION KINASE (FAK) INHIBITOR, IN PATIENTS WITH *KRAS* MUTANT NON-SMALL CELL LUNG CANCER (NSCLC)

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Disclosures

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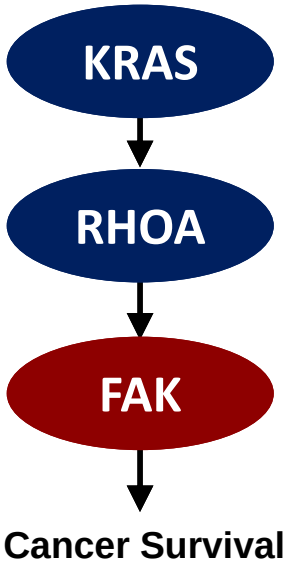
Focal Adhesion Kinase (FAK) represents a therapeutic target in *KRAS* mutant NSCLC

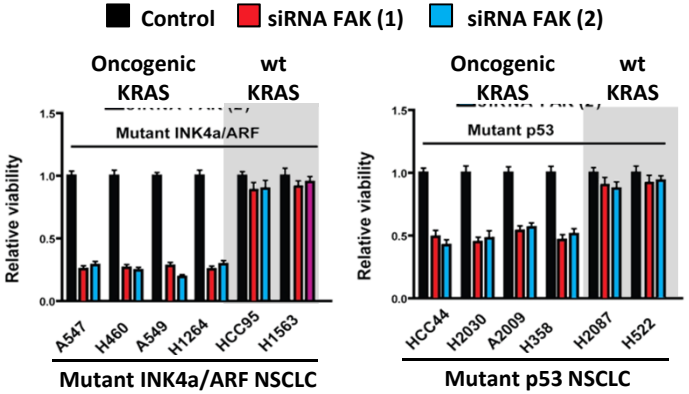
- *KRAS* mutant advanced NSCLC remains a major unmet clinical need
  - **In the Phase 3 INTEREST trial, single agent docetaxel or gefitinib provided 6 weeks median PFS for pretreated KRAS mt NSCLC patients**[1]
- RHOA-FAK axis is a critical downstream mediator of RAS signal transduction
- Preclinical studies suggest that FAK inhibition results in control of tumor growth preferentially in *KRAS* mutant NSCLC



[1] Douillard et al., JCO 2010

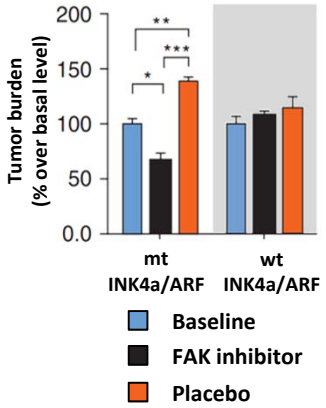
Dysfunction of tumor suppressors (INK4a/ARF/p16, p53) increases preclinical efficacy of FAK inhibition in *KRAS* mt NSCLC

KRAS mt is necessary for sensitivity to FAK inhibition in NSCLC cell lines



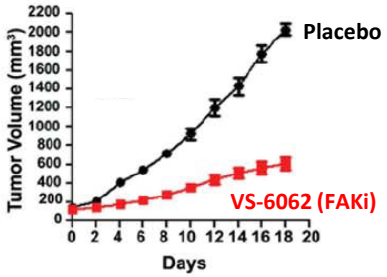
Efficacy of FAK inhibition in KRAS mt NSCLC models is increased by co-mutation of tumor suppressors (INK4a, p53)

Oncogenic K-RAS mice

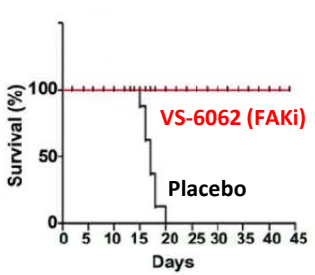


KRAS & INK4α mt A427 NSCLC xenograft

Tumor burden



Overall survival



Konstantinidou G et al. *Cancer Discovery* 2013;3:444-57.

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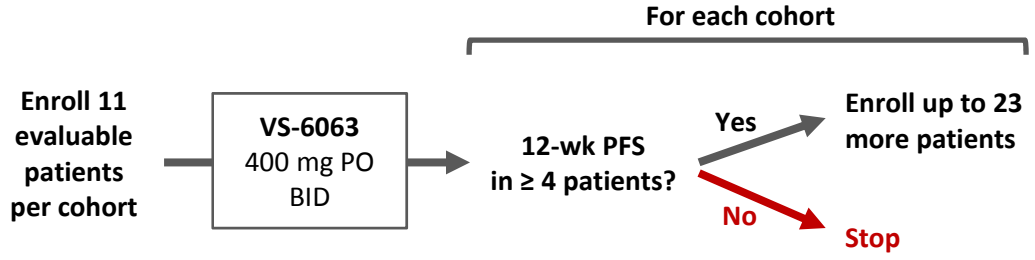
Phase II trial of oral 400mg BID VS-6063 for advanced *KRAS* mutant NSCLC

mt status	KRAS	p16*	p53
Cohort A	✓		
Cohort B	✓	✓	
Cohort C	✓		✓
Cohort D	✓	✓	✓



Patients, n (%)	55 (100)
A: KRAS	12 (22)
B: KRAS / p16*	13 (24)
C: KRAS / p53	13 (24)
D: KRAS / p16* + p53	11 (20)
E: KRAS / Undetermined	6 (11)
Efficacy evaluable	**44 (80)**

Sex, n (%)	
Male	27 (49.1)
Female	28 (50.9)
ECOG PS, n (%)	
0	8 (14.5)
1	46 (83.6)
2	1 (1.8)

Prior systemic therapy regimens, n (%)	
0	0 (0)
1	9 (16.4)
2	18 (32.7)
3	12 (21.8)
≥ 4	16 (29.1)
≥ 2	**46 (83.6)**

KRAS mt frequency, n (%)	
G12	15 (28)
G13	14 (25)
Q61	8 (14)
Other	18 (33)

* p16 mt: *INK4a/ARF* mutation or inactivation

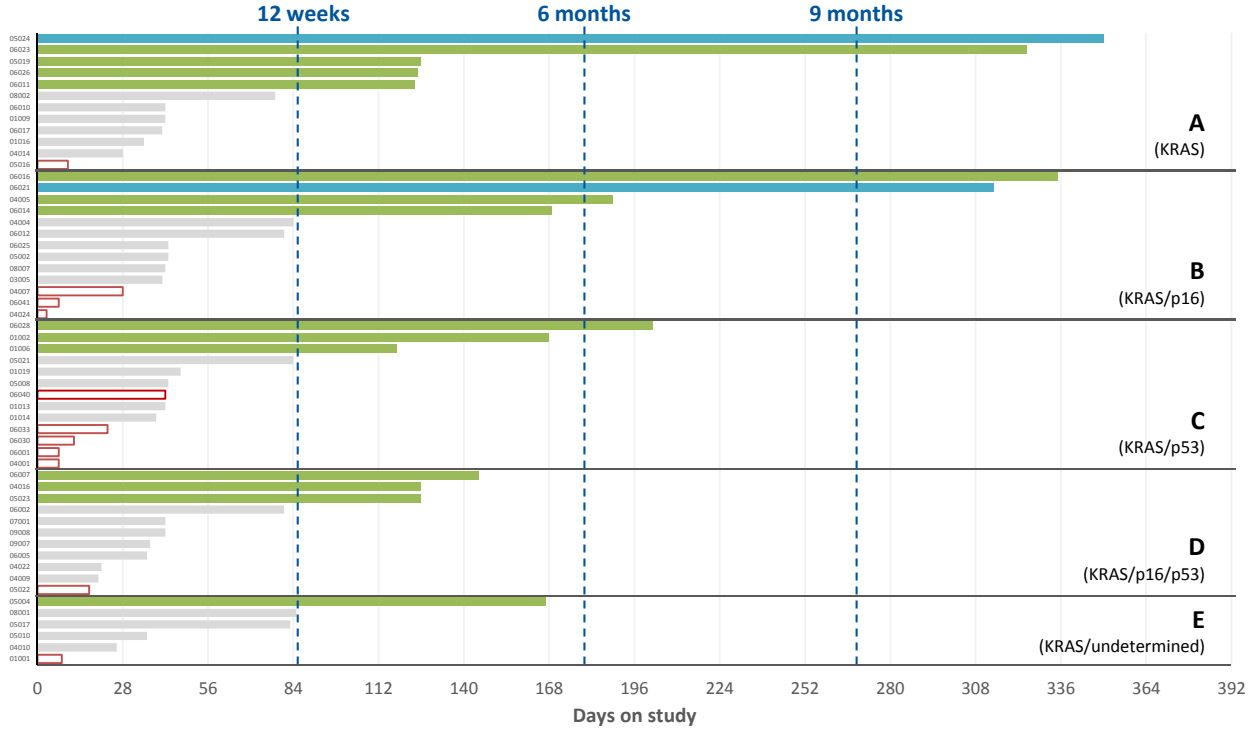
Treatment emergent adverse events (≥10% of patients)

Adverse Event*, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total (n = 55)
Fatigue	11 (20.0)	9 (16.4)	1 (1.8)	0	0	21 (38.2)
Nausea	11 (20.0)	5 (9.1)	4 (7.3)	0	0	20 (36.4)
Diarrhea	13 (23.6)	3 (5.5)	1 (1.8)	0	0	17 (30.9)
Vomiting	7 (12.7)	3 (5.5)	3 (5.5)	0	0	13 (23.6)
Hyperbilirubinemia	4 (7.3)	6 (10.9)	3 (5.5)	0	0	13 (23.6)
Dyspnea	4 (7.3)	5 (9.1)	4 (7.3)	0	0	13 (23.6)
Constipation	9 (16.4)	3 (5.5)	0	0	0	12 (21.8)
Edema Peripheral	10 (18.2)	1 (1.8)	0	0	0	11 (20.0)
Decreased Appetite	5 (9.1)	5 (9.1)	0	0	0	10 (18.2)
Cough	4 (7.3)	3 (5.5)	0	0	0	7 (12.7)
Arthralgia	3 (5.5)	2 (3.6)	1 (1.8)	0	0	6 (10.9)
Anxiety	5 (9.1)	1 (1.8)	0	0	0	6 (10.9)

*Related and unrelated AE's occurring in ≥ 10% of population

Unlocked, in-progress data as of 10 August 2015

Cohorts A (KRAS) and B (KRAS/p16) met interim threshold of ≥4 patients with ≥12 weeks PFS



For all cohorts A-E:

- **16/44 (36%)** evaluable patients alive and progression free at 12 weeks
- Median PFS: 11.7 weeks
- Best overall response (RECIST)**:**
  PR = 1; SD = 26; PD = 15; NE = 2
- Cohorts A & B both met interim threshold of ≥4 patients with ≥12 weeks PFS
- 6 patients on study for > 6 months and 4 for > 9 months

Reached 12 wk PFS, Ongoing

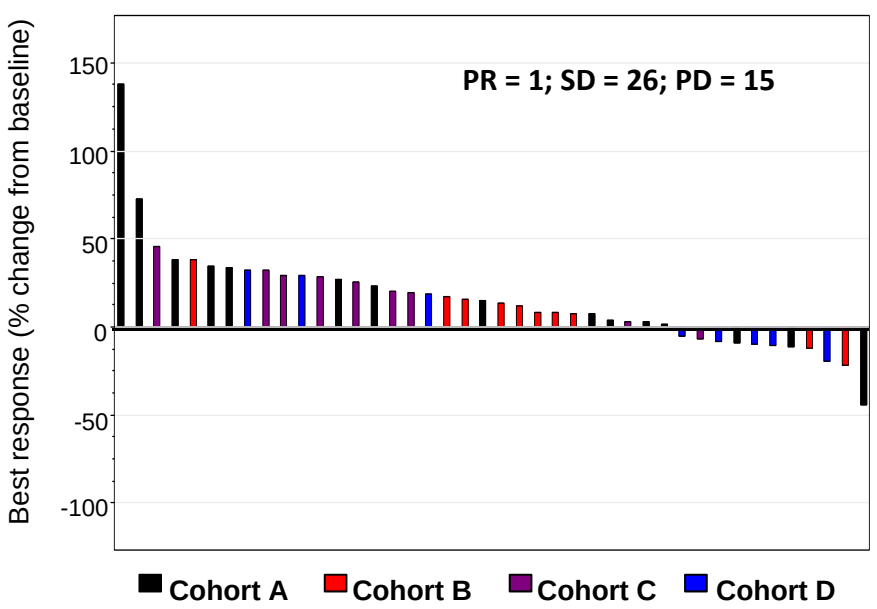
Reached 12 wk PFS, Off study

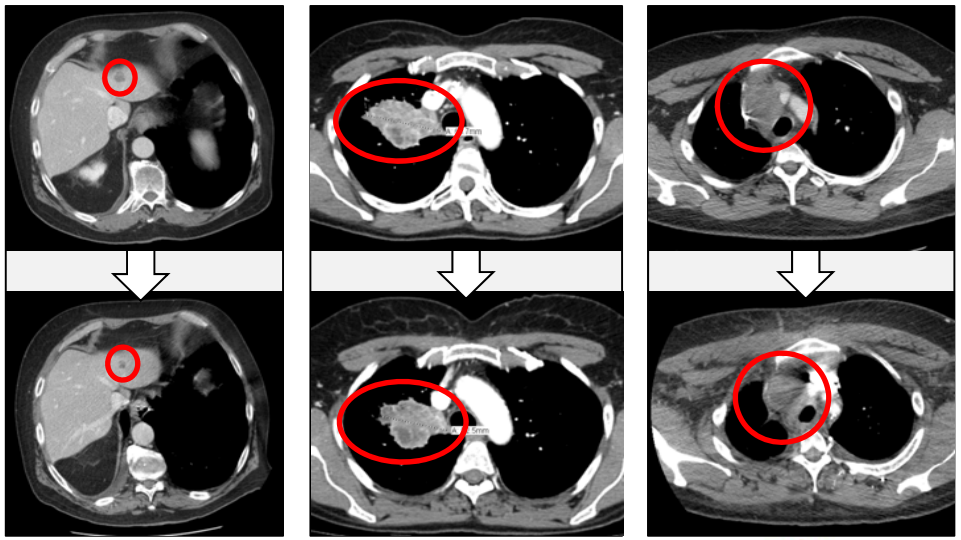
Off study

Not evaluable

Unlocked, in-progress data as of 3 August 2015

~25% of patients experienced tumor shrinkage with single-agent VS-6063





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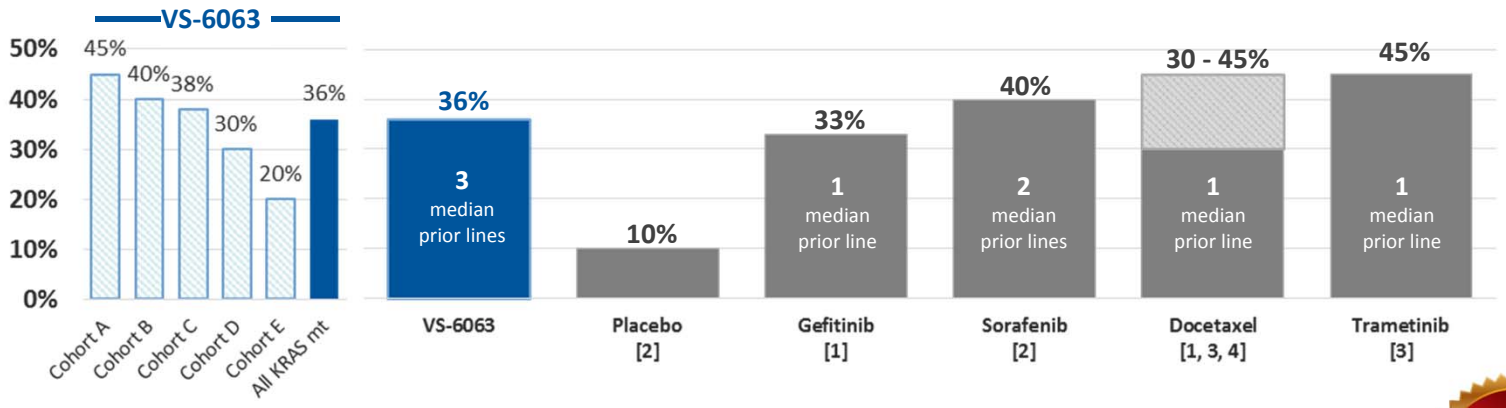
Efficacy: 12-wk PFS rate of VS-6063 appears comparable to docetaxel and other investigational monotherapies

- Overall, VS-6063 achieved a 12 week PFS rate of 36% in heavily pretreated KRAS mt NSCLC patients
- Single agent VS-6063 achieves comparable activity to docetaxel and other investigational monotherapies, despite greater median prior lines of therapy (3 vs. 1-2)

Est. 12 week PFS rate of experimental agents for KRAS mt NSCLC



[1] Phase 3 INTEREST, Douillard et al., JCO 2010 [2] Phase 3 MISSION, Mok et al., ESMO 2012 [3] Phase 2, Blumenschein et al., Ann Oncol 2015 [4] Phase 2, Janne et al., Lancet 2013

Conclusions

- Enrollment biomarkers including KRAS, INK4a/ARF/p16, and p53 are feasible in a multi-center trial
- Defactinib (VS-6063) was generally well tolerated and suitable for long-term dosing
  - Principal treatment-emergent toxicities included fatigue, N/V, diarrhea, dyspnea, hyperbilirubinemia
- Overall, defactinib achieved a 12-week PFS rate of 36%
- Efficacy did not appear to correlate with INK4a/ARF/p16 status
- In this cohort of heavily pretreated patients, there were signs of single-agent activity comparable to other targeted agents and docetaxel
  - 12 week PFS rate estimated at 30 – 45% for gefitinib[1], sorafenib[2], trametinib[3], and docetaxel[1,3,4] in KRAS mt NSCLC with 1-2 median prior lines
- Future directions include possible combination studies with existing standard and emerging therapies
  - e.g., PD-1/PD-L1, MEK inhibitors, chemotherapy

[1] Phase 3 INTEREST, Douillard et al., JCO 2010 [2] Phase 3 MISSION, Mok et al., ESMO 2012 [3] Phase 2, Blumenschein et al., Ann Oncol 2015 [4] Phase 2, Janne et al., Lancet 2013