Determination of Biomarker Response in a Phase II Window of Opportunity Study of Defactinib (VS-6063), a Focal Adhesion Kinase (FAK) Inhibitor, in Patients with Resectable Malignant Pleural Mesothelioma

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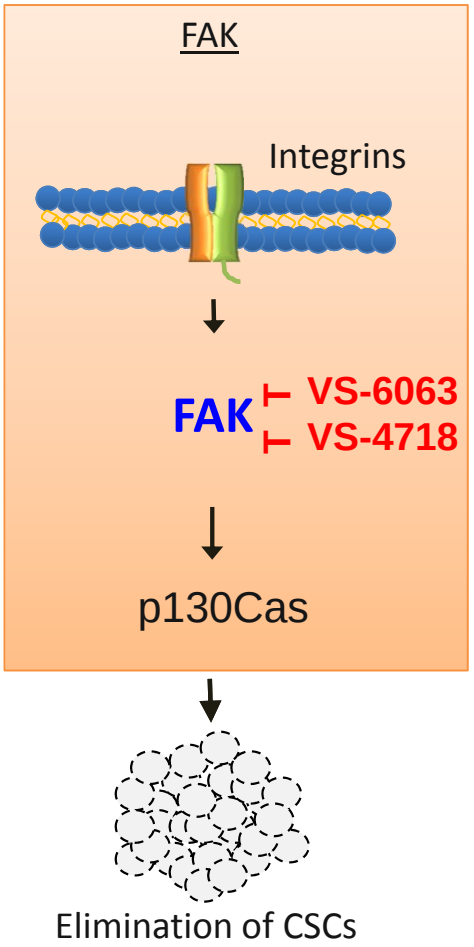
Window of Opportunity Study in Surgically Resectable Mesothelioma

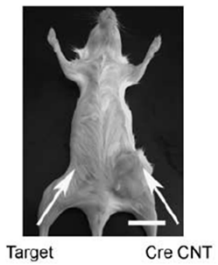
- Mesothelioma is highly lethal and without effective therapies for most patients
- Time to relapse after most standard therapies is measured in months
- We need to change strategies to be effective
- The neo-adjuvant or “window” setting prior to surgery offers a unique opportunity to rapidly examine the biological activity of novel drugs.
  - Similar approaches used successfully in Neoadjuvant breast studies (I-SPY)

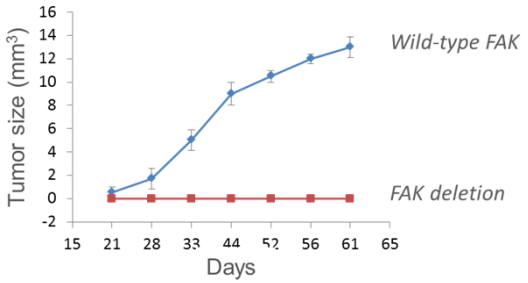
Focal Adhesion Kinase (FAK) is Critical for Cancer Stem Cells



- Targeted deletion of FAK reduces tumor initiating capability

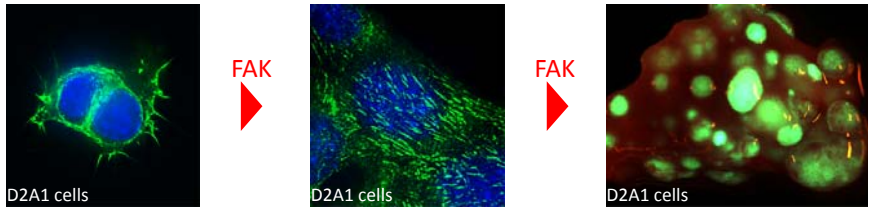
Luo et al, Cancer Res (2009) 69:466





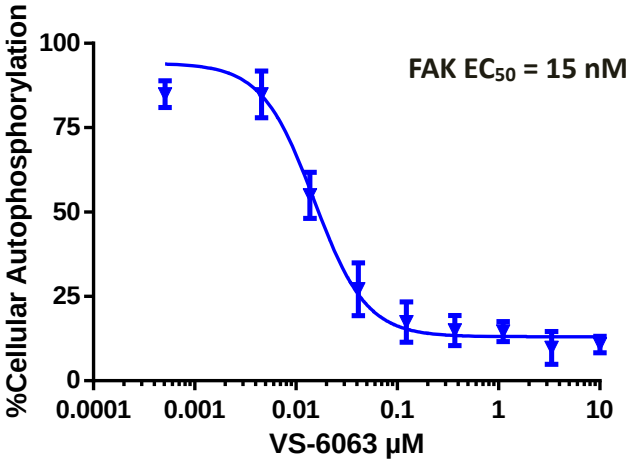
- FAK is a critical pathway for cancer stem cells and disease progression

Shibue et al, Cancer Discovery (2012) 2:706



Cell mobility **Proliferation** **Tumor initiation**

Defactinib (VS-6063): Potent, Selective FAK Inhibitor



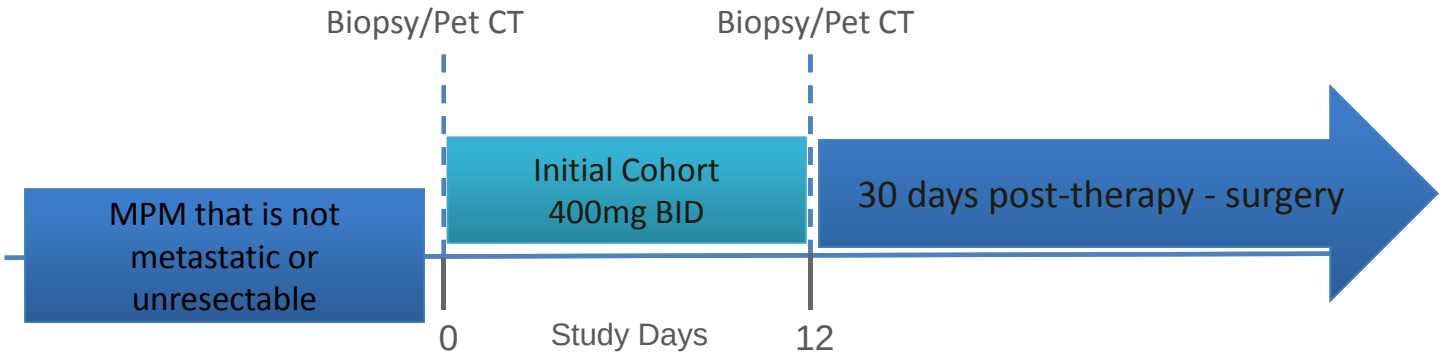
- Oral compound with good safety profile & initial signs of activity in Phase 1
- Reduces pFAK & CSCs in tumors from treated patients
- Currently under clinical investigation. Indications of interest:
  - Mesothelioma
    - Maintenance (COMMAND – ongoing)
    - Adjuvant (planned)
    - Window (ongoing)
  - NSCLC – Kras mutant (ongoing)
  - SCLC (proposed)
  - Ovarian (ongoing)
  - TNBC (proposed)

VS-6063-203 Study Objectives

- **Primary Objectives**
  - To assess biomarker responses in patient derived tumor and other surrogate tissues including but not limited to:
    - inhibition of phospho-FAK
    - changes in cancer stem cells and markers
    - alterations in markers of cell cycle and apoptosis
- **Secondary Objectives**
  - To evaluate the safety of defactinib in patients with malignant mesothelioma.
  - To evaluate the pharmacokinetics of defactinib in plasma of subjects with malignant mesothelioma.
  - To evaluate tumor response by PET/CT by RECIST modified for mesothelioma

VS-6063-203: "WINDOW" Study Design

- Preoperative patients receive defactinib (400 mg BID orally) for 12 days
- Pre- and post-treatment biopsies and PET/CT
- Surgical resection of tumor 30 days post last dose of defactinib
- Biopsies analyzed by immunohistochemistry, Next Gen Sequencing, and RNA seq.



- Study Initiated in December, 2013
- 10 subjects enrolled to date. Plan to enroll up to 20-25 subjects

Eligibility Criteria

- Histologically confirmed malignant pleural mesothelioma that is not metastatic or unresectable.
- Participants are eligible to undergo excisional surgery such as extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/DC) or any other mesothelioma surgery.
- Localized disease. The malignancy is confined to one affected hemithorax. Mediastinal N2 lymph nodes via cervical mediastinoscopy or EBUS must be negative in order to be eligible.
- Normal pulmonary, cardiac function, renal, hepatic hematologic and performance functions.
- ECOG 0-1 or Karnofsky >80%
- Age ≥ 18 years of age

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Exclusion Criteria

- Prior chemotherapy or radiotherapy for mesothelioma.
- History of upper gastrointestinal bleeding, ulceration, or perforation within 12 months prior to the first dose of study drug.
- Known history of stroke or cerebrovascular accident within 6 months prior to first dose of study drug.
- Known infection with HIV or AIDS
- Confirmed Hepatitis A, B or C.
- Active treatment for a secondary malignancy or any malignancy within the last 5 years (excluding superficial bladder cancer or non-melanoma skin cancer).
- Pregnant or breastfeeding.

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Patient Characteristics

	400 mg defactinib BID
Patients, n	10
Sex	
Male	8 (80.0%)
Female	2 (20.0%)
Median age, years (range)	71 (55-83)
Histology	
Epithelial	4 (40.0%)
Biphasic	2 (20.0%)
Sarcomatoid	4 (40.0%)
ECOG PFS	
0	7 (70.0%)
1	3 (30.0%)

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Adverse Events

Adverse Event	400 mg defactinib BID (n=10)
Bilirubin Increased	4 (40.0%)
Nausea	2 (20.0%)
Diarrhea	2 (20.0%)
Constipation	2 (20.0%)
Dyspnoea	2 (20.0%)
Back Pain	2 (20.0%)
Headache	2 (20.0%)
Adominal Pain Upper	2 (20.0%)
Hypertension	2 (20.0%)

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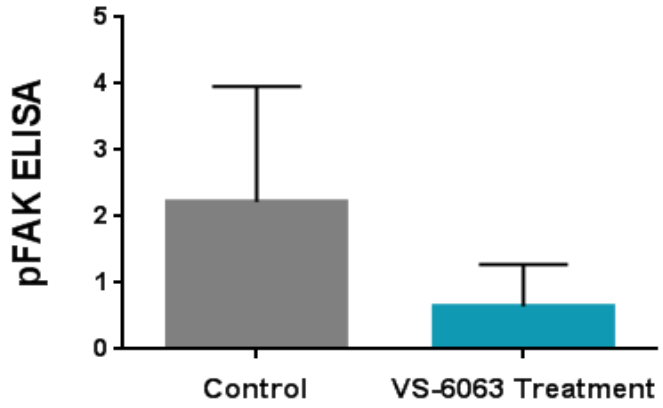
VS-6063 (defactinib) inhibits FAK activity in mesothelioma biopsies



- VS-6063 treatment at Day12 [Core Needle Biopsy] was compared with Control [Surgical Biopsy at >30 days after VS-6063]
- Mean pFAK (Y397) reduced by 70% in the patients evaluated to date

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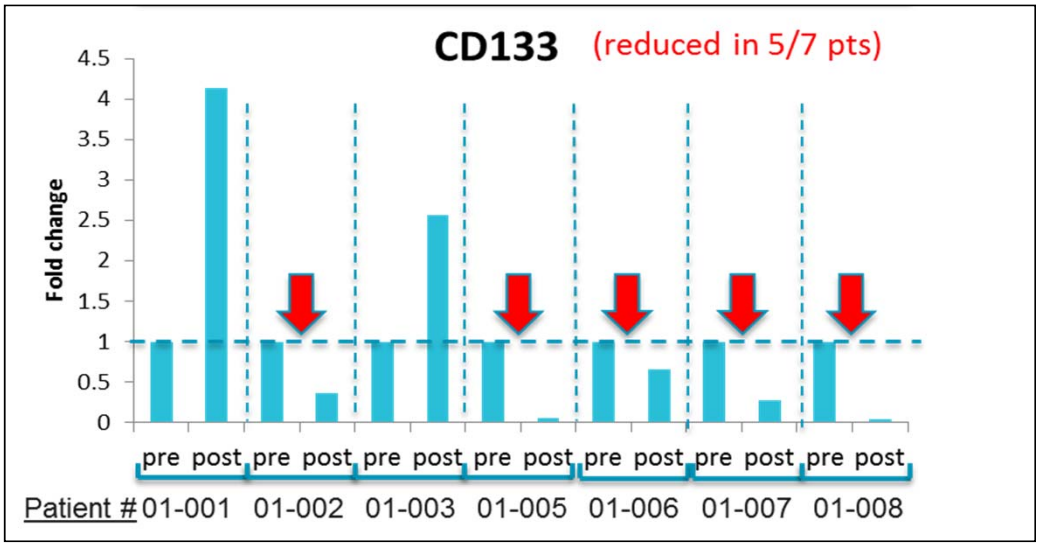
VS-6063-203: Tumor CSC RNA Changes in Malignant Mesothelioma



- **CD133 is reduced during VS-6063 treatment (post = Day 12) in 5 of 7 patient tumors**
- **Other CSC markers (CXCR2, SOX2, and POSTN) are also reduced during VS-6063 treatment**
- **These CSC markers, including CD133, are increased following pemetrexed-cisplatin chemotherapy (Paul Baas, iMIG presentation)**

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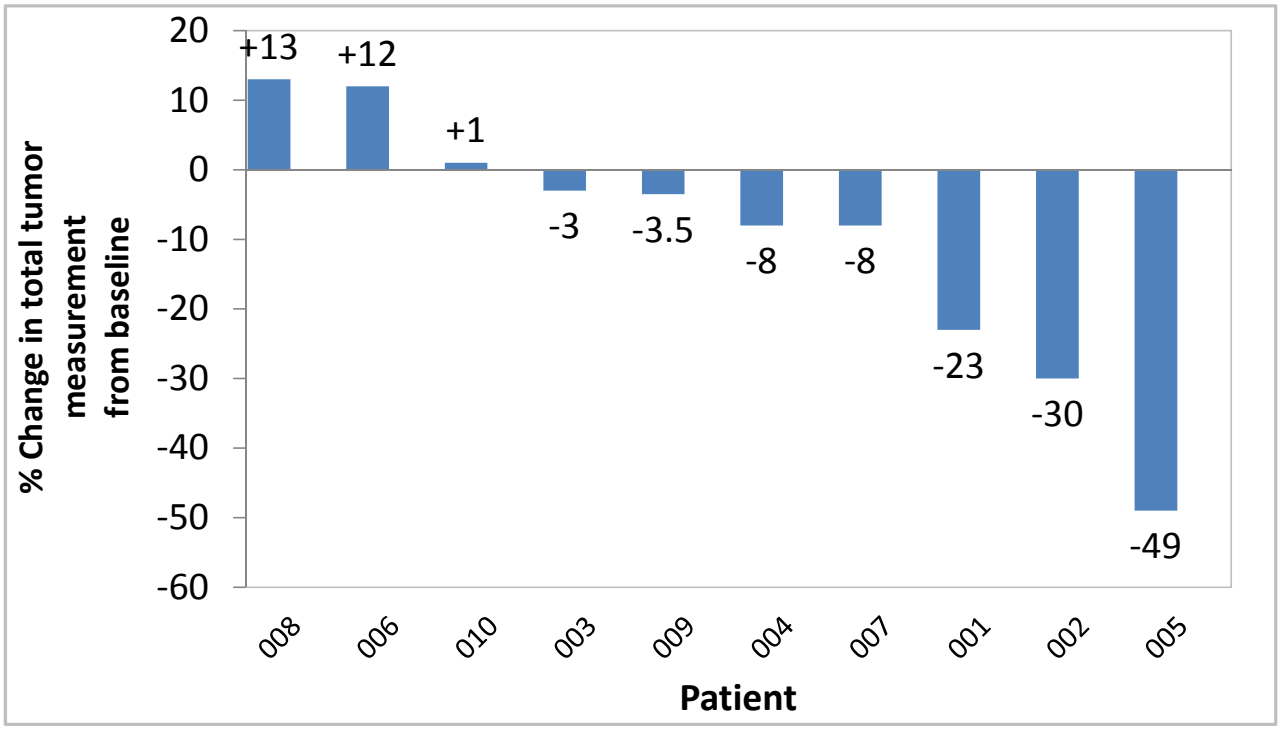
VS-6063-203: Encouraging Early Signal After 12 Days of Treatment



**Note PET/CT performed to guide biopsy and tumor response assessed using RECIST modified for mesothelioma*

**Unlocked, in-progress data as of Aug 2014*

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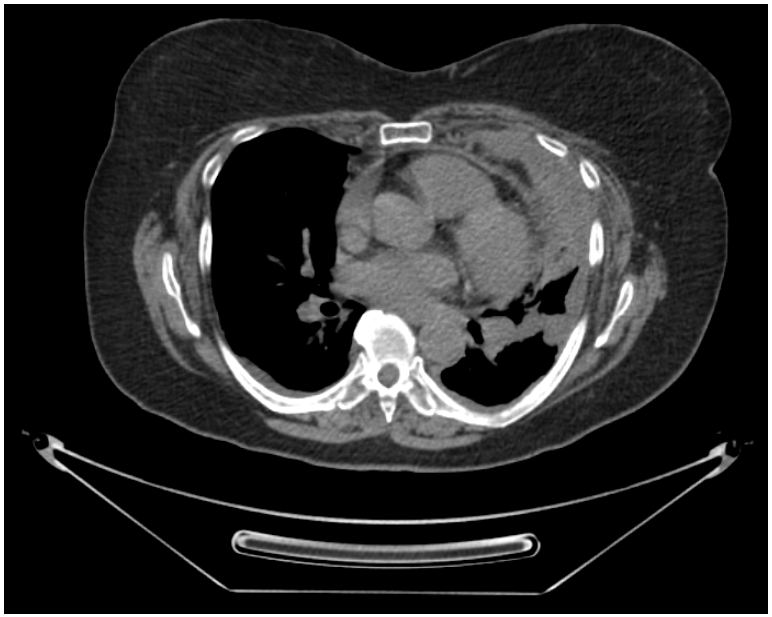
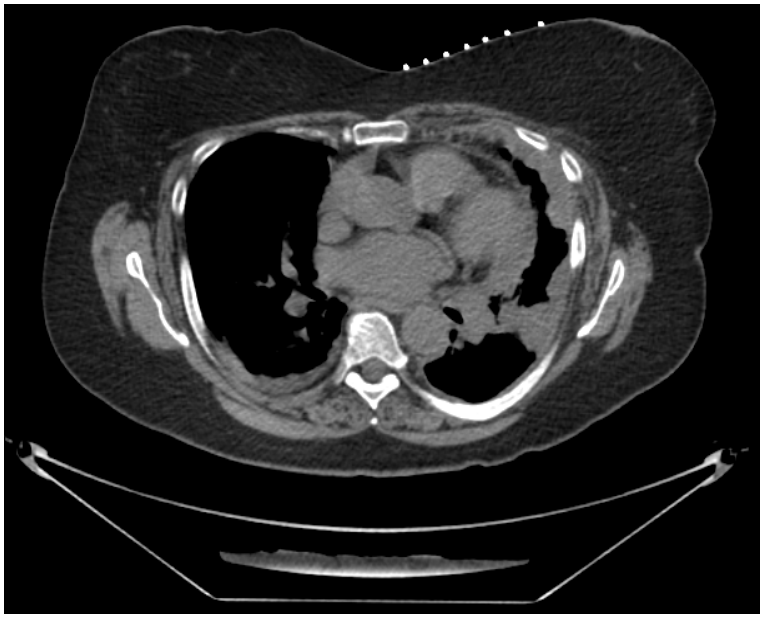
Radiographic image of patient response



Pre-treatment



Post-treatment

Patient: 01-005 (Epithelial MPM)

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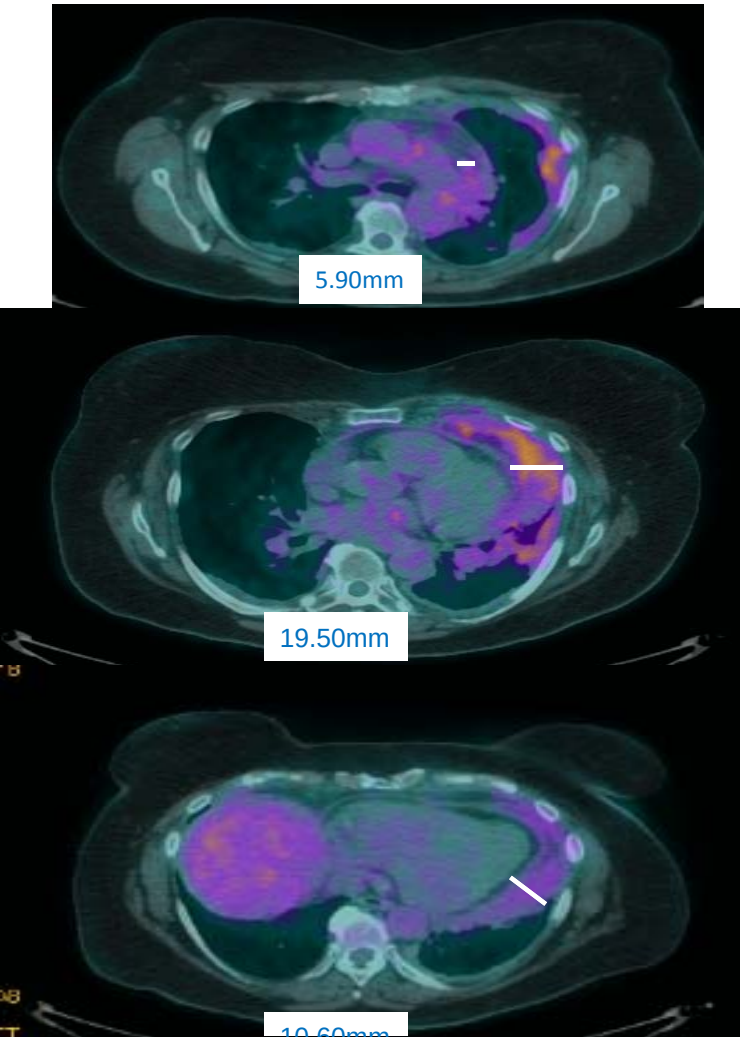
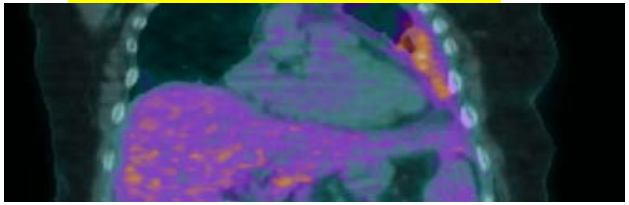
01-005

Epithelial MPM

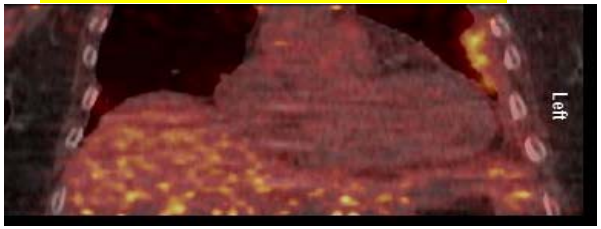
Pretreatment PETCT



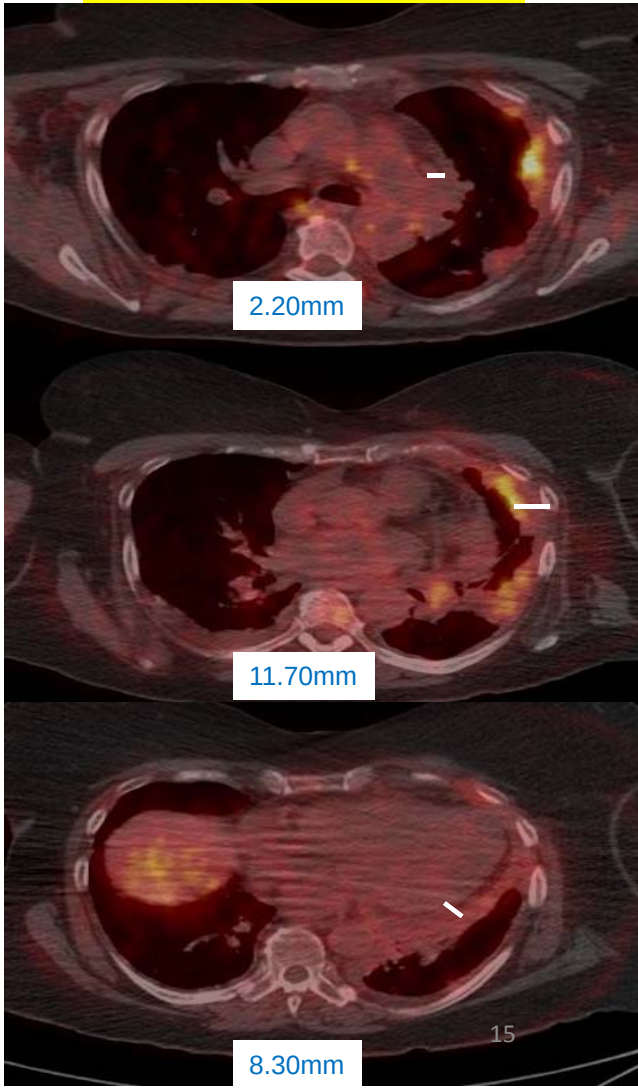
Pretreatment PETCT



Post treatment PETCT



Post treatment PETCT



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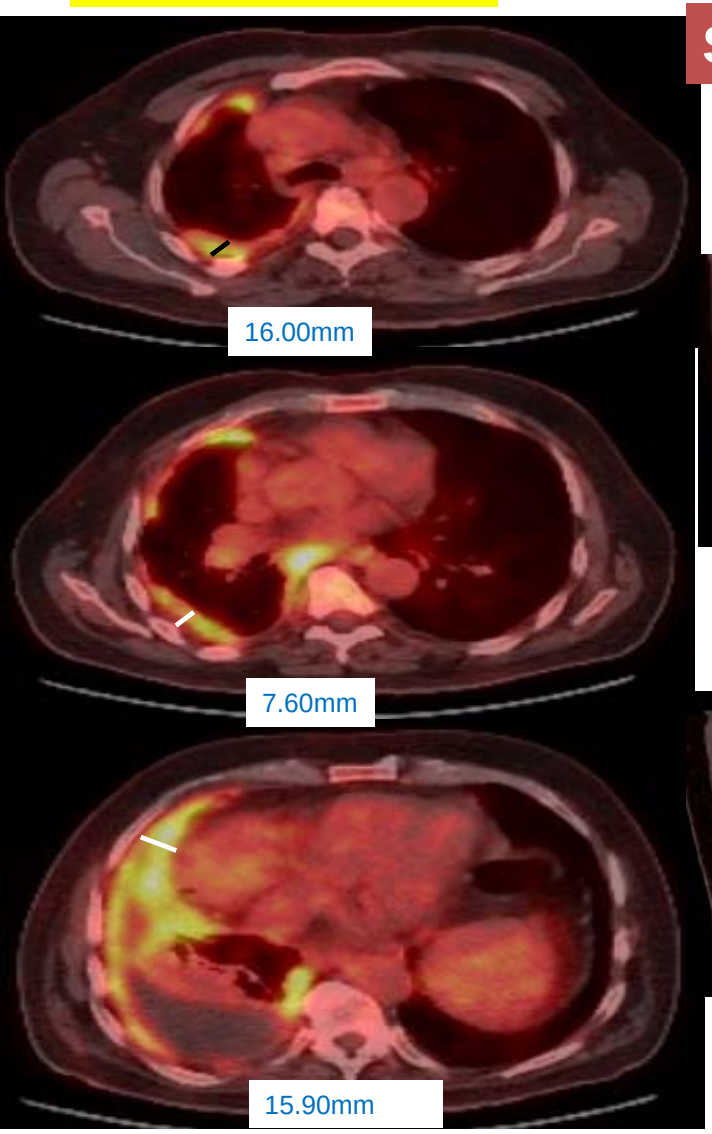
Pre-treatment PETCT

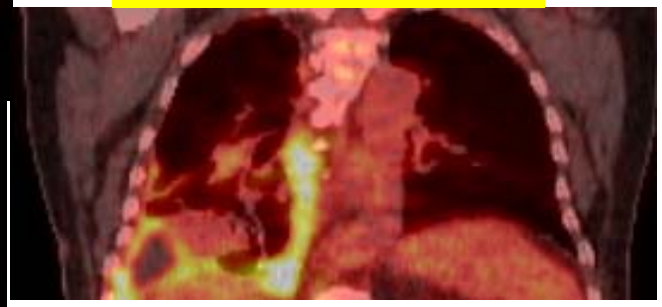
01-001

Sarcomatoid MPM

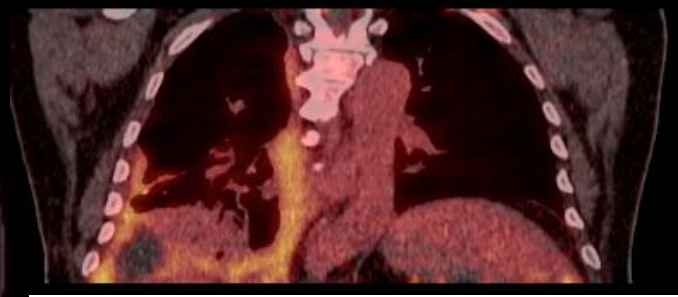
Post treatment PETCT

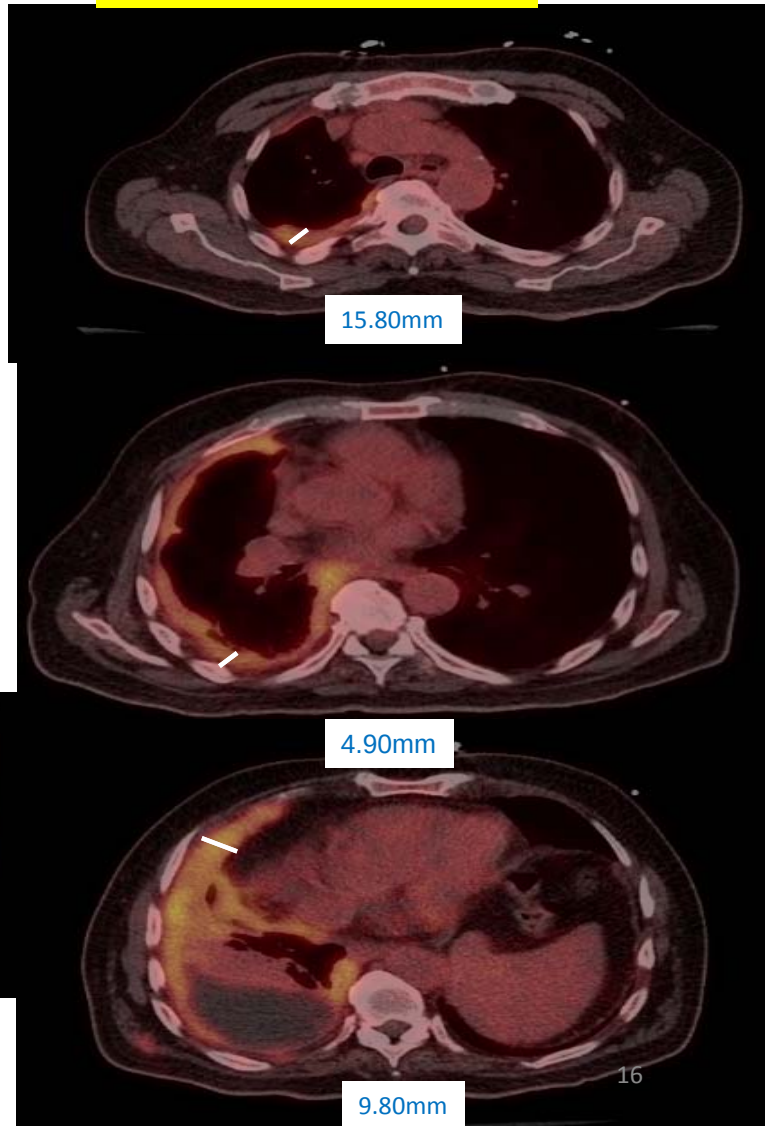


Pretreatment PETCT



Post treatment PETCT





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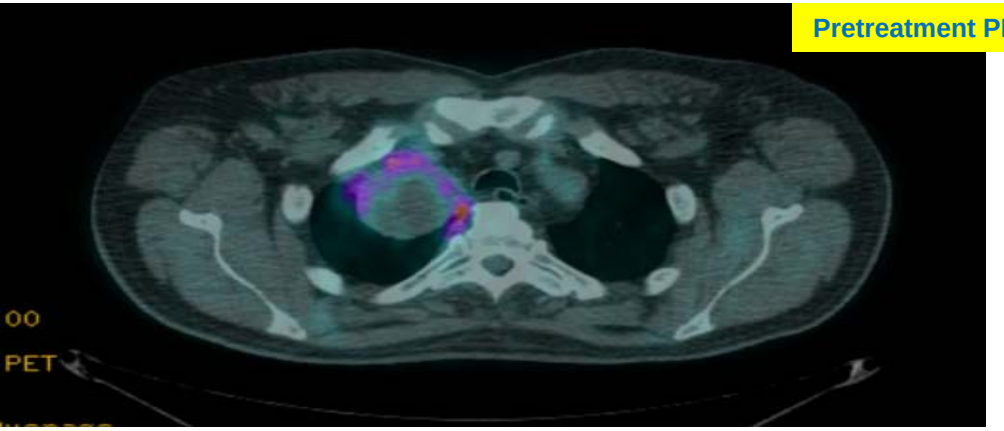
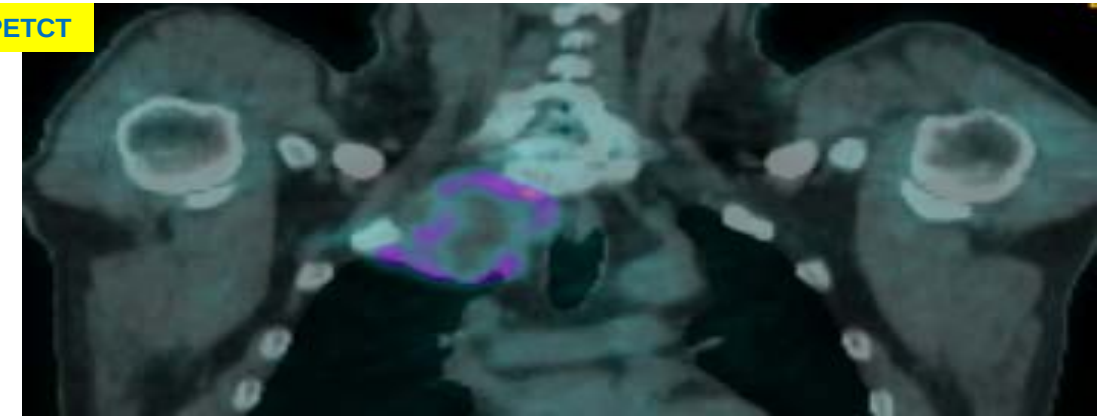
Pretreatment PETCT

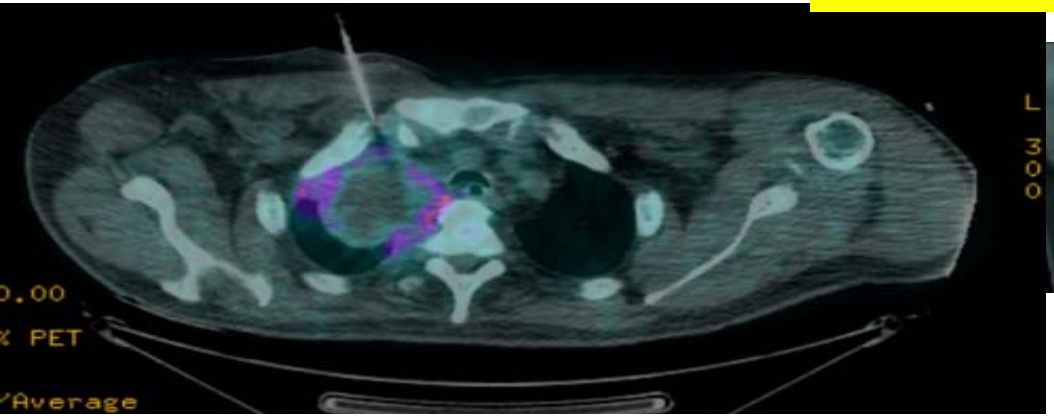


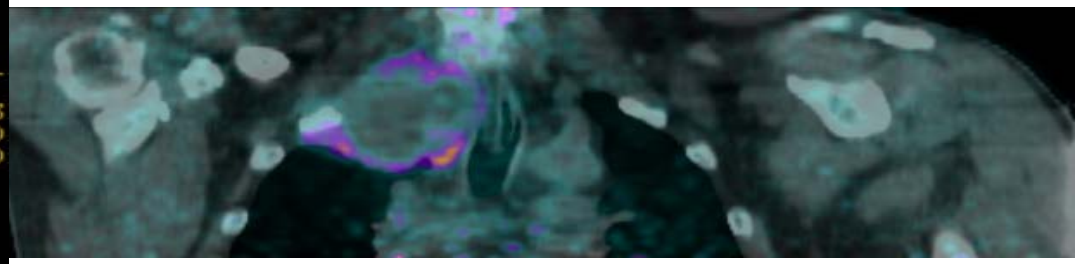


Sarcomatoid MPM

01-004

Post treatment PETCT





Summary of Preliminary VS-6063-203 Study Data

- Defactinib was well tolerated with no apparent negative impact on surgical outcome
- Defactinib inhibits FAK activity
- Defactinib inhibits multiple CSC markers
- Intriguing signs of tumor reduction observed after 12 days of dosing following defactinib treatment
- Next steps
  - Increase of treatment period from 12 days to 35 days with surgery 7 days post-last dose.
  - Enrollment of an additional 10-15 subjects
  - Further analysis of additional stem cell markers and genomic profiling (DNA/RNA)

- Window studies prior to surgery are a viable opportunity to explore the biological activity of novel drugs in mesothelioma.