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Disclosure

- I am an employee and stockholder of Verastem Inc.
- I will be discussing investigational drugs
Targeting cancer stem cells for a durable clinical response

- CSCs are cells that **self-renew, generate the heterogeneous tumor**, and are associated with **drug resistance and recurrence**
- CSC presence in minimally residual disease results in **tumor progression, invasion, and metastasis**

Days

Tumor Volume

Conventional chemotherapy

Initial tumor

Conventional Chemo

Recruing tumor

Tumor reduction but CSCs survive

Durable clinical response

Anti-CSC agent + conventional chemo (concurrent or sequential)

Tumor reduction and elimination of CSCs

Initial tumor

Chemo

Days

CSC Agent

Tumor Volume

Conventional chemotherapy

Initial tumor

Conventional Chemo

Recruing tumor

Tumor reduction but CSCs survive

Durable clinical response

Anti-CSC agent + conventional chemo (concurrent or sequential)

Tumor reduction and elimination of CSCs

Initial tumor

Chemo

Days

CSC Agent
PI3K/mTOR inhibitor (VS-5584) and FAK inhibitor (VS-4718) biochemical activities

VS-6063:  
- FAK Enzymatic IC$_{50}$ = 21 nM  
- FAK Cellular EC$_{50}$ = 18 nM

VS-4718:  
- FAK Enzymatic IC$_{50}$ = 42 nM  
- FAK Cellular EC$_{50}$ = 31 nM

VS-5584:  
- PI3K isoform IC$_{50}$ (nM)
  - Alpha: 3.4  
  - Beta: 2.6  
  - Delta: 21  
  - Gamma: 3.0  
  - IC$_{50}$ (nM)

Integrins

RTKs

PI3K

FAK

p130Cas

Elimination of CSCs
FAK and PI3K/mTOR inhibitors preferentially target CSCs in vitro

**FAK inhibitor**
- **VS-6063 treatment**
- **SUM159 cell line**

**PI3K/mTOR inhibitor**
- **VS-5584 treatment**
- **SUM159 cell line**
CSC markers in SCLC

CD87 is a prognostic marker in SCLC (Li et al., 2014)

CD87+ cells are enriched by chemotherapy and reduced with CSC agents

Riboflavin uptake & intracellular autofluorescence identifies epithelial CSCs (Lorenzo et al. 2014)

Autofluorescent cells are more greatly reduced by CSC agents than by standard chemotherapy
In vivo reduction of CSCs in SCLC

NCI-H841 SCLC xenograft model

Control → Cisplatin / Etoposide → CSC Agent → Cis/Etop -> CSC Agent → Liberase → Harvest tumor → Viable cells → Re-implantation in limiting dilutions

PI3K/mTOR inhibitor (VS-5584)

- Control
- Cis/Eto
- VS-5584 (P=0.01)
- Cis/Eto/VS-5584 (P=0.0009)

FAK inhibitor (VS-4718)

- Control
- Cis/Eto
- VS-4718 (P=0.25)
- Cis/Eto/VS-4718 (P=0.001)
PI3K/mTOR inhibitor efficacy in front line and maintenance chemotherapy

Modeling front line + maintenance:
Concurrent treatment with chemotherapy
(NCI-H69 SCLC xenograft model)

Modeling maintenance:
Sequential treatment after chemotherapy
(SCLC PDX xenograft model #052)
FAK inhibitor efficacy in maintenance chemotherapy

SCLC PDX xenograft model #501

SCLC PDX xenograft model #052

Debulking

Cisplatin/Etoposide

Vehicle

Cisplatin/Etoposide → VS-4718

Debulking

Cisplatin/Etoposide

Vehicle

Cisplatin/Etoposide → VS-4718
Summary & conclusions

- Verastem clinical candidates are inhibitors of PI3K/mTOR (VS-5584) and FAK (VS-4718, VS-6063)
- The Cancer Stem Cell population in SCLC in vivo models are inhibited by VS-5584 and VS-4718
- CSC markers CD87 and Riboflavin are reduced by treatment with VS-4718 and VS-5584 in vitro
- CSC agents VS-5584 and VS-4718 delay tumor progression in maintenance therapy models
- These studies provide a compelling rationale for SCLC clinical trials with VS-5584 and FAK inhibitors