#CT143

# Phase I study of the combination of a RAF-MEK inhibitor CH5126766 and FAK inhibitor defactinib in an intermittent dosing schedule with expansions in *KRAS* mutant cancers

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# Conflict of Interest

**Personal financial interests - honoraria received:**

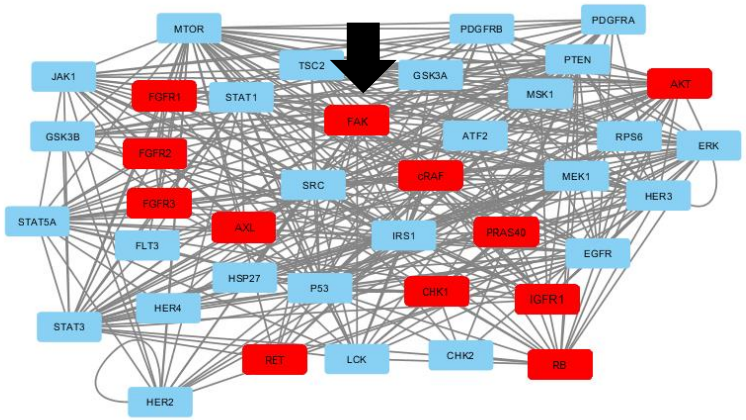
*Astellas, Novartis, Karus Therapeutics, Phoenix Solutions, Eli Lilly, Astex, Vernalis, Boehringer-Ingelheim, Janssen*

**Institutional financial interests – funding for Phase I investigator-initiated trials:**

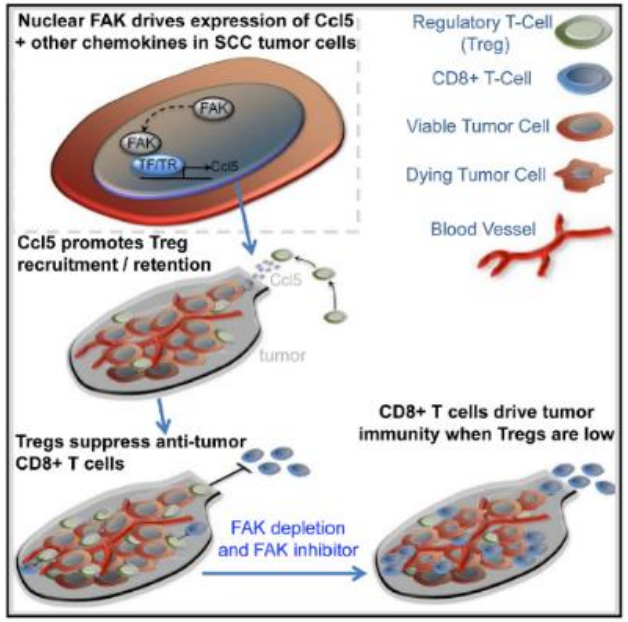
*Onyx Pharmaceuticals, BTG International, Chugai, AstraZeneca, Verastem*

**Employment:** *I am an employee of the Institute of Cancer Research, which is involved in the development of PI3K, HSP90, HDAC, AKT, ROCK, RAF, CHK1 and HSF1 inhibitors.*

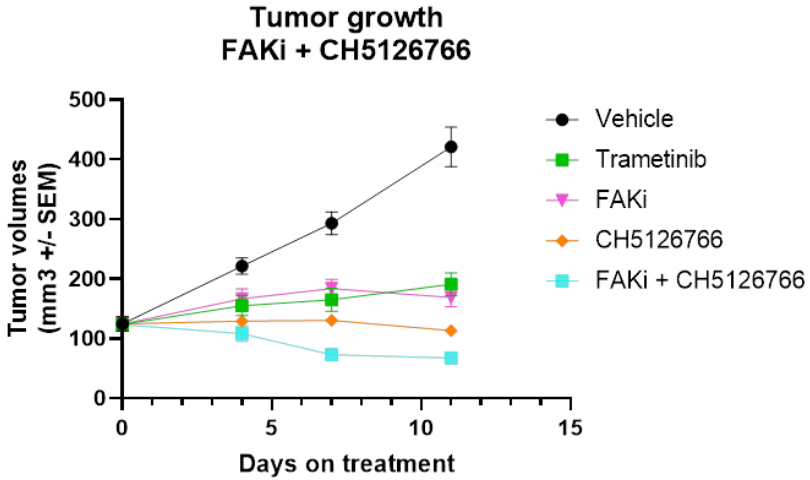
# Rationale for study




Rewiring of signal transduction following MEK inhibition



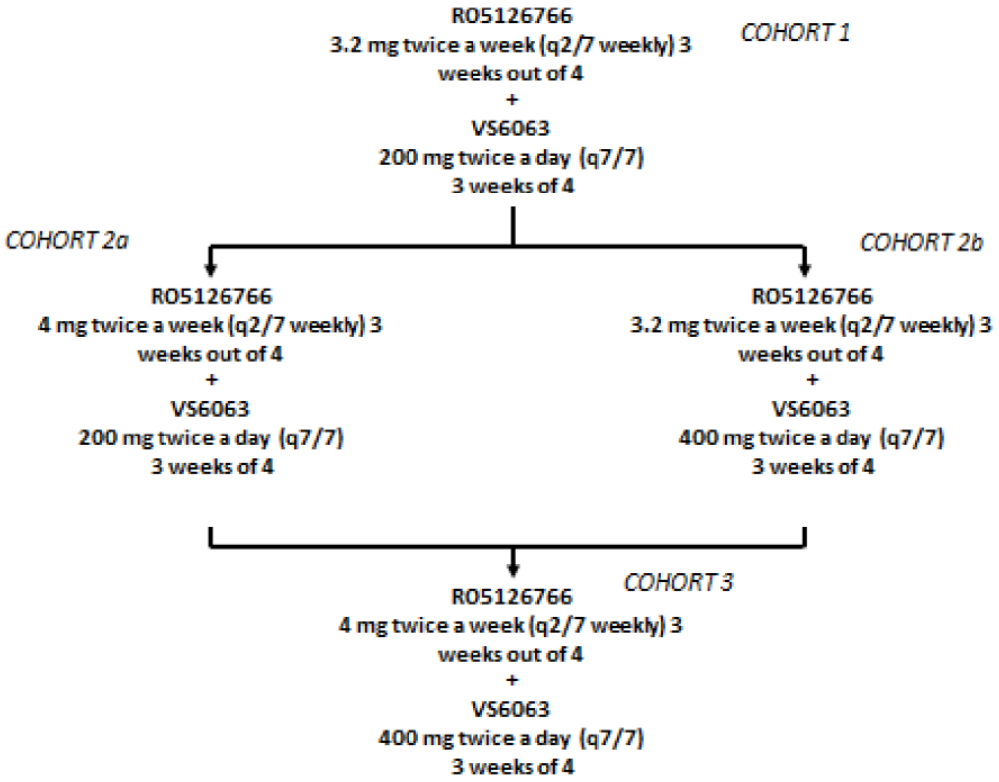

FAK inhibition reduces T reg populations




Preclinical experimental models show regression

***Serrels A Cell 2015, 163:160-173***

# Design




Post R2PD Expansions in LGSOC (20), *KRAS* mutated NSCLC (20), *KRAS* mutated CRC (10)

# Safety

| Adverse event details | Escalation | | | | | | Total (n=12) |
|---|---|---|---|---|---|---|---|
| | RO 3.2mg VS 200mg (n=3) | | RO 4mg VS 200mg (n=6) | | RO 3.2mg VS 400mg (n=3) | | |
| | G.1 - G.2 | G.3 - G.4 | G.1 - G.2 | G.3 - G.4 | G.1 - G.2 | G.3 - G.4 | |
| Rash | 2 | | 6 | | 3 | | 11 |
| CK elevation | 2 | | 2 | 1 | 1 | | 6 |
| Nausea | 1 | | 3 | | 2 | | 6 |
| Hyperbilirubinemia | 1 | 1 | 1 | 1 | 1 | | 5 |
| Diarrhoea | 2 | | 1 | | 2 | | 5 |
| Visual disturbance | | | 2 | | 2 | | 4 |
| Vomiting | 1 | | 2 | | | | 3 |
| Paronychia | 1 | | 1 | | 1 | | 3 |
| AST elevation | | | 1 | | 1 | | 2 |
| Fatigue | | | 2 | | | | 2 |
| ALT elevation | | | 1 | | 1 | | 2 |
| Anaemia | | 1 | | | 1 | | 2 |
| Alopecia | | | 2 | | | | 2 |
| Thrombocytopenia | | | 2 | | | | 2 |
| Skin infection | | | 1 | | 1 | | 2 |
| Fever | | | | | 1 | | 1 |
| Conjunctivitis | 1 | | | | | | 1 |
| Mouth soreness | | | 1 | | | | 1 |
| Face pain | | | | | 1 | | 1 |
| Total: | 11 | 2 | 28 | 2 | 18 | 0 | 61 |

Recommended phase 2 dose is CH5126766 3.2 mg twice a week (Mon-Thu) + 200 mg of defactinib twice a day, both given 3 weeks out of 4 in 28 day cycles.

# Pharmacokinetics

## CH5126766

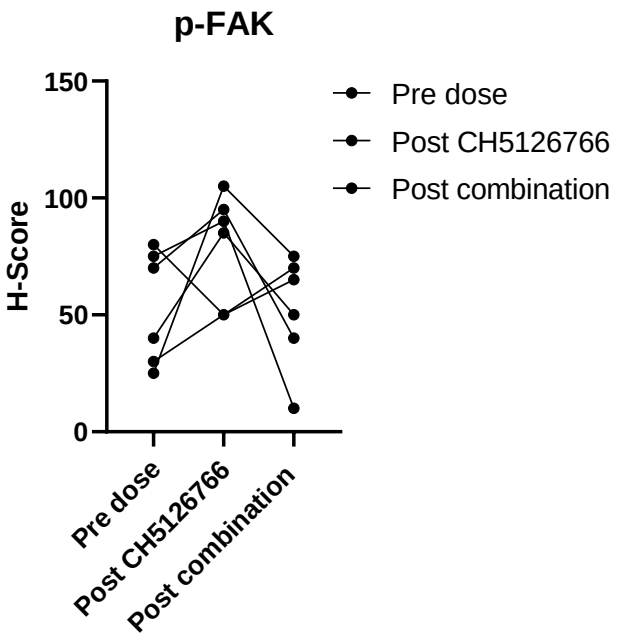
| Cohort | Dose (mg) | N | Subject | $AUC_{0-24h}$ (h*ng/mL) | $C_{max}$ (ng/mL) |
|---|---|---|---|---|---|
| 1 | 3.2 (with 200mg VS) | 3 | Mean | 6179 | 354 |
| | | | CV% | 32.1 | 30.4 |
| 2a | 4 (with 200mg VS) | 5 | Mean | 5353 | 289 |
| | | | CV% | 15.8 | 16.0 |
| 2b | 3.2 (with 400mg VS) | 1 | FRA101-007 | 3302 | 229 |

## Defactinib

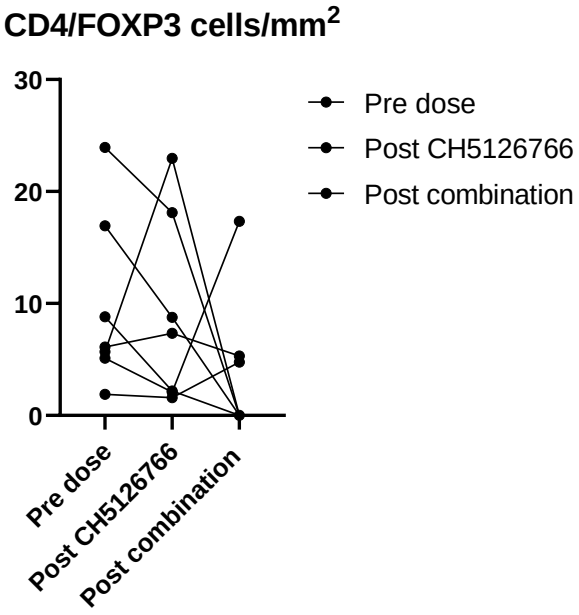
| Cohort | Dose (mg) | N | Subject | AUClast (h*ng/mL) | Cmax (ng/mL) |
|---|---|---|---|---|---|
| 1 | 200 (with 3.2mg RO) | 3 | Mean | 2071 | 273 |
| | | | CV% | 103 | 80 |
| 2a | 200 (with 4mg RO) | 5 | Mean | 2252 | 318 |
| | | | CV% | 124 | 117 |
| 2b | 400 (with 3.2mg RO) | 3 | Mean | 2807 | 360 |
| | | | CV% | 31 | 32 |

Pharmacokinetic profile similar to what is seen in single agent studies

# Pharmacodynamics

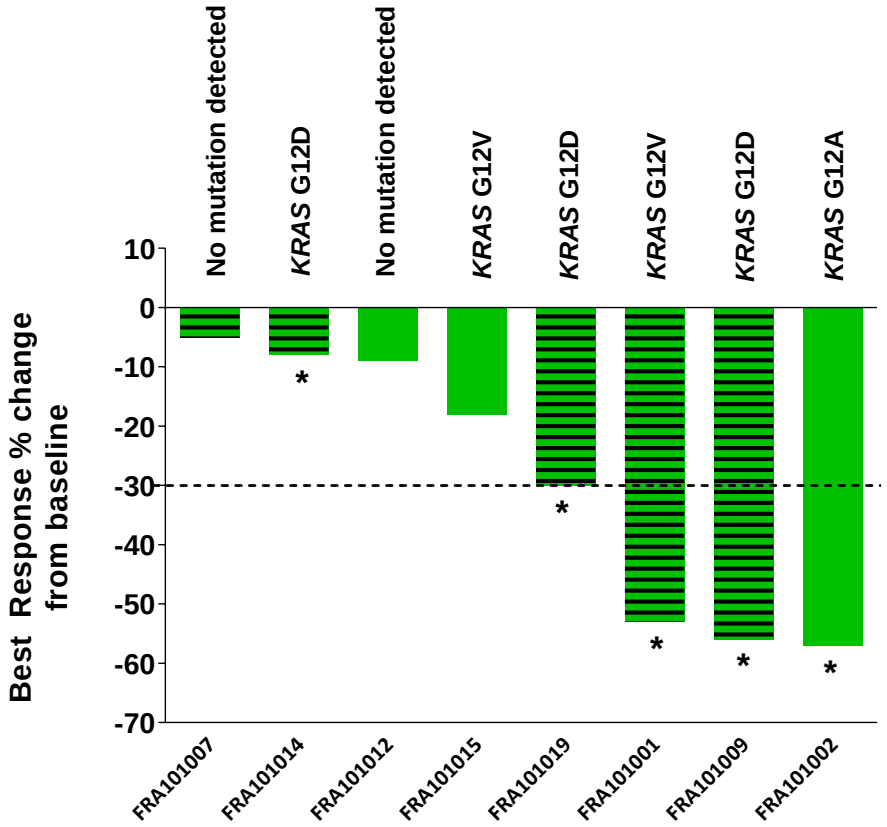


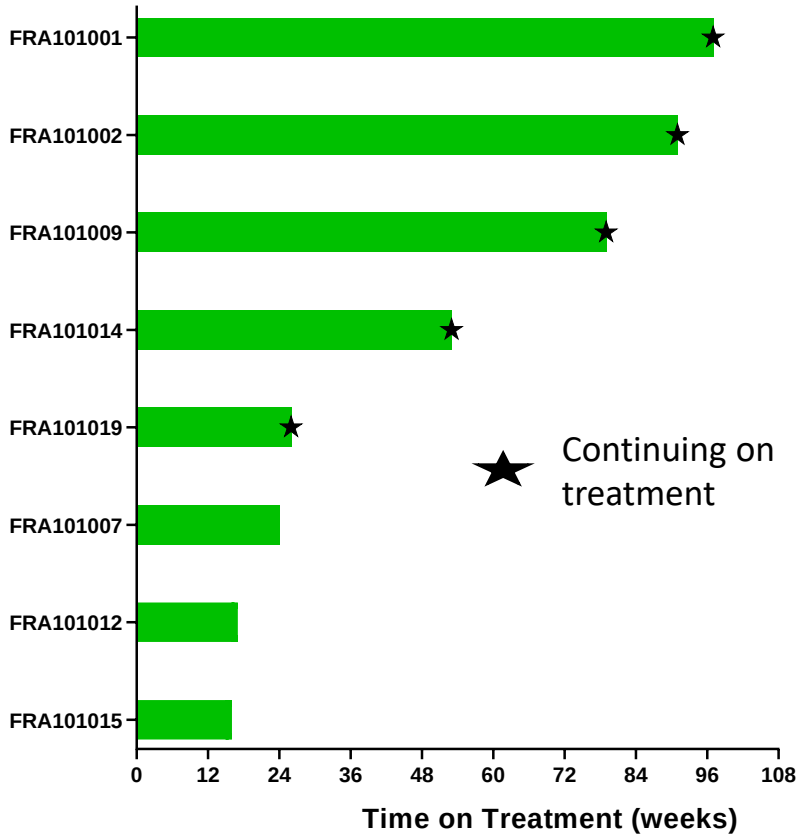

Induction of p-FAK following single dose of CH5126766 which is reduced following institution of combination therapy




Reduction in numbers of regulatory T cells in tumour following defactinib

# Efficacy – Low Grade Serous Ovarian Cancer



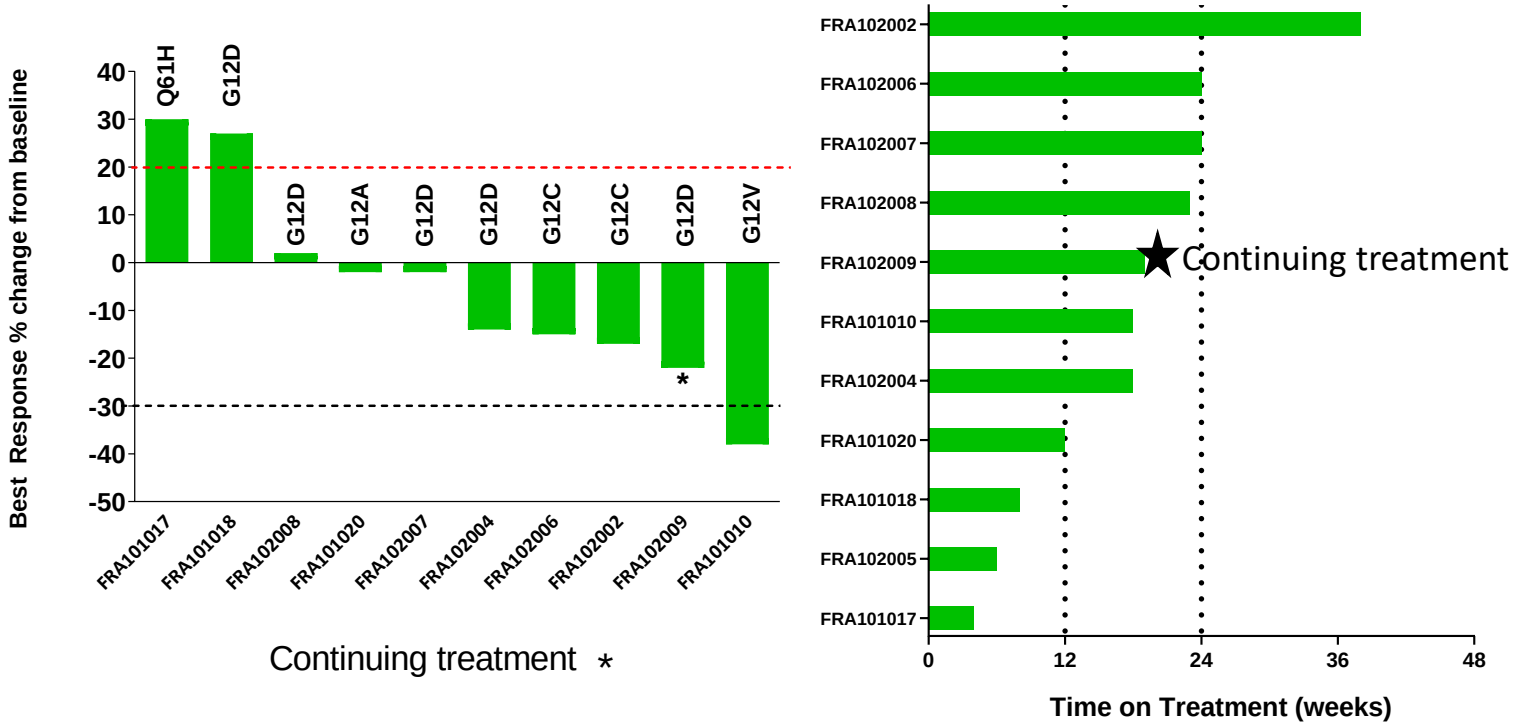

Continuing on treatment *

Previous MEK inhibitor treatment

- Response rates in *KRAS* mutated LGOSC 67% (4/6) and 50% (4/8) for all LGSOC compared to efficacy in current literature; <10 % chemotherapy, 13% Letrozole and 26% for trametinib
- Responses durable and in patients who have prior MEK inhibitor therapy

*Nov 2019 data cut off used*

# Efficacy *KRAS*$^{M}$ NSCLC




- Reduction in tumour size in non G12C *KRAS* mutated cancers
- Patients with NSCLC and *KRAS* mutations enrolled. 3/10 patients received treatment for 24 weeks

*Nov 2019 data cut off used*

# Conclusions

- The recommended dose of CH5126766 is 3.2 mg Mon-Thu in combination with defactinib 200 mg BD, both drugs delivered 3 weeks out of 4
- Proof of concept pharmacodynamics changes and PK similar to single agent studies
- Promising efficacy in LGSOC and studies in *RAS* mutant tumours ongoing

*We would like to patients and families and funders*

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