Overcoming the proliferation rate paradox: Clinical evaluation of a continuous dosing scheme of the novel oral Eg5 inhibitor 4SC-205.

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Introduction

- 4SC-205 is an orally available, anti-mitotic small molecule (MW 448.5 Da).
- The compound potently inhibits human kinesin Eg5 (KIC50) with an IC50 ~ 3nM and > 3,000 fold selectivity towards other kinases.
- 4SC-205 demonstrates excellent preclinical efficacy in a diverse set of solid tumour models in vitro and in vivo.

Preclinical Data

- 4SC-205 is a highly potent and selective inhibitor of human Eg5 kinase
- 4SC-205 demonstrates potent anti-proliferative effects on cancer cell lines

Preclinical in vitro Data

- 4SC-205 inhibits tumour growth in subcutaneous xenograft models in a dose dependent manner

Preclinical Data — AEGIS Study

- Open label, dose escalation trial of oral 4SC-205 in patients with advanced solid tumours
- Study objectives were analysis of safety and tolerability, determination of the maximum tolerated dose (MTD) and pharmacokinetics of 4SC-205.
- 59 patients were enrolled in four different dosing schemes.

Safety

- MoA of 4SC-205 was demonstrated in skin biopsies.
- pH3 as marker of mitotic arrest (N=26)
- Febrile neutropenia
- Thrombocytopenia
- Neutropenia
- Lymphopenia
- Dehydration
- Stomatitis

Biomarker Response

- Median time on treatment [d] N = 46 N = 13
- Median of patients who went into follow-up
- No objective response according to RECIST was observed

Clinical Data

- 4 of 6 patients (67%) in the 20mg once daily dosing cohort showed stable disease compared to other dosing schedules.
- Patients at 20mg once daily dosing could be treated 4 times longer compared to 50mg once weekly dosing.
- Several dosing schemes were evaluated in 59 patients in the AEGIS study, with 4SC-205 demonstrated in skin biopsies.

Conclusions

- To be of our knowledge 4SC-205 is the only oral available Eg5 inhibitor in clinical development allowing for once daily dosing.
- Preclinical evidence and literature data suggested that anti-mitotic therapies, and Eg5 inhibition in particular, need continuous exposure to guarantee sufficient target coverage.
- Several dosing schemes were evaluated in 59 patients in the AEGIS study, with once daily dosing amongst others.
- Patients at 20mg once daily dosing could be treated 4 times longer compared to other dosing schedules.
- pH3 biomarker response demonstrates intended mode-of-action at once daily dosing.
- 20mg once daily dosing represents the recommended Phase II dose (RP2D).

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References:


Posters:

- Dose escalation study of the novel oral Eg5 inhibitor 4SC-205 in patients with advanced solid tumours (www.proqinase.com).