Small molecule in combination with Immune Checkpoint therapies
Positive immunomodulation by specific VEGFR3 inhibition

Project Overview

Drug concept: Develop a small molecule for cancer immunotherapy that targets immunosuppressive cell trafficking to increase ICT response rate

Target class: EVT801 is a specific inhibitor of the tyrosine kinase VEGFR3

Target status: Drug candidate / 1 year from phase I

Targeted indication: Combination with immune checkpoint therapies for non-responding patients

Administration: Oral administration

Drug candidate profile:

VEGFR3 / FLT4

EVT801 is highly selective
Sorafenib

Activitb

Supportive in vivo activity:
- Full tumour control on DEN-induced tumour model
- Intermediate tumour control on VEGFR3 tumours with VEGFR3-TME

Immuno-modulatory effects that we are seeking:
Optimal potential to synergize with immune check point inhibitors

- Elevated CD8+ T cell responses
- Nanomolar activity on functional cellular assays
- Selectivity: 30 fold less potent on VEGFR2 which is the only off-target
- Anti-tumour activity in preclinical development
- Therapeutic index above 10 in rat and monkey studies pending

Abstract

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Clinical Translation: biomarkers of stratification and activity

Patient stratification:
VEGFR3 is expressed on 40-80% of the tumor microenvironment
Specific cohorts are under investigation

Biomarkers of activity in tumor:
Signaling pathway

Biomarkers of activity in blood:
Collaboration with University Cancer institute of Toulouse for specific markers in patients receiving ICT

Conclusion

Sustained tumour blood vessel normalization
Decrease of tumour-induced immunosuppression
- Decrease of angiogenesis
- Less Necrotic and Hypoxic tumours
- Increase of T cell: MDSCs ratio
- Tumour
- Decrease of CD4+ T cells
- Decrease of CD8+ PD-L1+ cells
- Increase of M1 macrophages

Enhancement of antitumor immunity and activity on tumor microenvironment:
Potential to induce durable clinical responses

Efficacy
- Nanomolar activity on functional cellular assays
- Strong anticancer effects in clinically relevant models
- Greater efficacy expected in human (lower IC50 and clearance)

Selectivity
- > 10 fold less potent on VEGFR2 which is the only off-target

Safety
- In vitro safety profile of EVT801 is compatible with progression into preclinical development
- Therapeutic index above 10 according rat DRF and monkey MD
- 4-week rat and monkey studies pending

EVT801 has the potential to enlarge patient population sensitive to immune check point inhibitors

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