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Furthering the clinical development of navicixizumab in advanced epithelial ovarian cancer patients with a population pharmacokinetic model and exploratory exposure-safety-efficacy response analyses.

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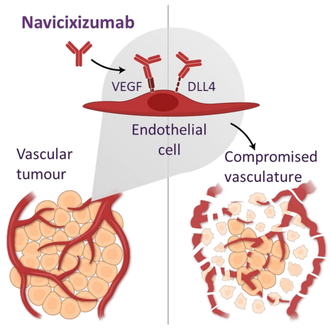
BACKGROUND

Navicixizumab: Strategically Designed for Efficacy and Safety

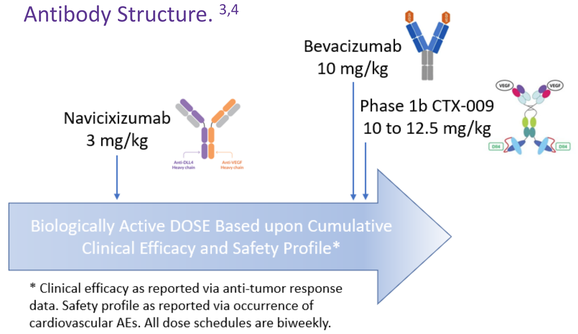
- Navicixizumab is a first-in-class, bispecific, anti-angiogenic antibody to vascular endothelial growth factor (VEGF) and delta-like ligand 4 (DLL4) in the Notch pathway[1]
- Designed to overcome VEGF resistance and more potent than targeting either DLL4 or VEGF alone[2]
- Designed to retain potent antitumor effects while reducing risks associated with DLL4 inhibition
- Designed to downregulate DDL4-Notch signaling in tumors and both Notch and VEGF pathways in angiogenesis



Clinical Experience with Navicixizumab:

- Phase 1a Study B83-001 in patients with solid tumors (n= 66)
  - Dose escalation (0.5, 1.0, 2.5, 3.5, 5.0, 7.5, 10, or 12.5 mg/kg Q3W) and dose expansion (7.5 mg/kg Q3W)
- Phase 1b B83-002 in ovarian cancer patients (n=44)
  - Dose escalation (3, 4 mg/kg Q2W plus weekly paclitaxel)
  - Dose expansion (3 mg/kg Q2W plus weekly paclitaxel)
- Phase 1b B83-003 in colorectal cancer patients (n=15)
  - Dose escalation (3, 4 mg/kg Q2W plus Q2W Folinic acid, fluorouracil, and irinotecan (FOLFIRI) or Folinic acid, fluorouracil, and oxaliplatin (FOLFOX)
  - Dose expansion (3 mg/kg Q2W plus Q2W FOLFIRI or FOLFOX)

Navicixizumab is Biologically Active at Lower Doses Relative to Bevacizumab and Other DLL4/VEGF Bispecific Antibodies in Clinical Development Regardless of Stoichiometric Binding Capabilities or Antibody Structure. [3,4]



* Clinical efficacy as reported via anti-tumor response data. Safety profile as reported via occurrence of cardiovascular AEs. All dose schedules are biweekly.

OBJECTIVES OF THE ANALYSIS

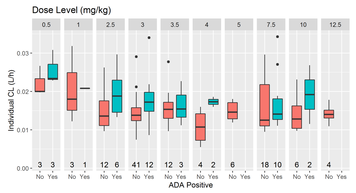
- Develop a population pharmacokinetic model using data from all 3 clinical trials conducted with navicixizumab
  - Covariates included anti-drug antibody (ADA) status, gender, race, type of tumor, tumor stage, weight
- Explore the relationships between navicixizumab exposures and key safety measures
  - Included evaluating changes in mean arterial pressure as an indicator of hypertension
  - Covariates included tumor stage, type, gender, weight, ADA, age, concurrent chemotherapy, ethnicity and rate
- Explore the relationships between navicixizumab exposures and key efficacy measures
  - Included evaluating changes in peak tricuspid velocity as an indicator for risk of pulmonary hypertension
- Explore relationships between disease characteristics and treatment response using regression analysis

FINAL PHARMACOKINETIC MODEL

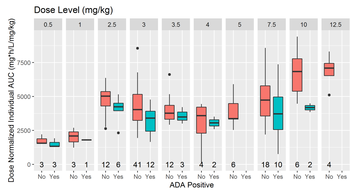
Final Parameter Estimate			Inter-Individual & Residual Variability			
Parameter	Population Mean	%RSE	Final Estimate	%RSE	Magnitude	Error Model
CL: Central Clearance (L/h)	0.0142	3.21	0.0815	14.8	29.1 %CV	Exponential
CL: 0.5 mg/kg Dose Level Effect	1.61	6.61				
CL: 1 mg/kg Dose Level Effect	1.40	16.2				
CL: Exponent of (WTKGT/75) for CL	0.506	21.3				
CL: Fold-Change in CL for ADA positive	1.17	6.98				
VC: Central Volume (L)	3.14	2.37	0.0259	16.7	16.2 %CV	Exponential
VC: Exponent of (WTKGT/75) for VC	0.641	11.2				
VC: Fold-Change in VC for GI Tumors	1.18	3.53				
Q: Distribution Clearance (L/h)	0.0261	8.06				
VP: Peripheral Volume (L)	1.73	6.90	0.123	40.1	36.2 %CV	Exponential
Study 001 Constant CV RV component			0.0446	13.3	21.1 %CV	Constant CV
Study 002 Constant CV RV component			0.0651	28.5	25.5 %CV	Constant CV
Study 003 Constant CV RV component			0.0315	26.3	17.7 %CV	Constant CV
Minimum Value of the Objective Function: 29445.666						

- Two-compartment model adequately fit the data
- Significant covariates included:
  - Weight – higher weight correlates with higher clearance and central volume of distribution
  - ADA positive patients – 17% higher clearance
  - GI Tumor patients – 18% higher central volume of distribution
  - 0.5 mg/kg dose patients– 61% higher clearance
  - 1.0 mg/kg dose patients – 40% higher clearance
- Generally, dose proportional at 2.5 mg/kg and above

Anti-drug Positive Patients do not Have Clinically Relevant Differences in Clearance.

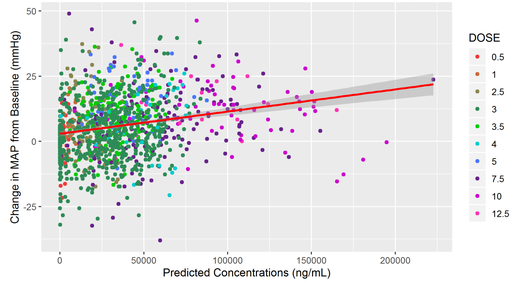


Navicixizumab Pharmacokinetics are Mostly Dose Proportional from 2.5 mg/kg and Higher.



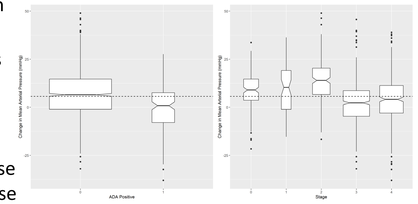
RELATATIONSHIP BETWEEN NAVICIXIZUMAB EXPOSURE AND BLOOD PRESSURE

Mean Arterial Blood Pressure Changes Relative to Baseline are Navicixizumab Concentration-dependent.



- Stage 3 and 4 patients and ADA positive patients have significantly lower changes in mean arterial pressure
  - Likely due to higher clearance in both groups
  - Better safety profile in these patients
- The highest mean arterial pressures should be clinically manageable and do not limit dose levels for navicixizumab
  - Note that therapeutically-relative dose levels are within the 3 to 4 mg/kg dose range

Comparatively Lower Changes in Mean Arterial Pressure are Observed in ADA Positive and Stage 3 and Stage 4 Patients.



ADA Positive = 1, ADA negative = 0 — Tumor Stage

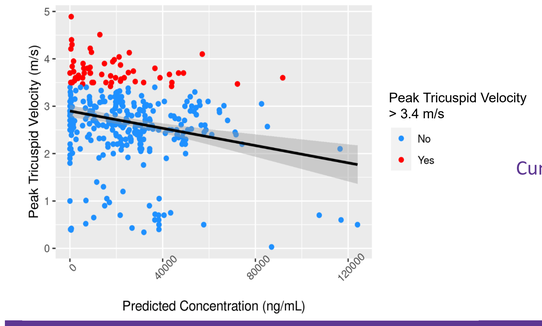
RELATATIONSHIP BETWEEN NAVICIXIZUMAB EXPOSURE AND PEAK TRICUSPID VELOCITY

- Peak tricuspid velocity data were used to evaluate the relationship between navicixizumab exposure and the risk of pulmonary hypertension
- Overall incidence of peak tricuspid velocities >3.4 ms is ~ 30%, regardless of dose level
- No individual covariates are predictors of pulmonary hypertension
- Elevated peak tricuspid velocity is significantly correlated with cumulative exposures, specifically AUC and dose
- Use of the 3 mg/kg dose level allows for prolonged pharmacodynamic effect, supporting longer treatment durations

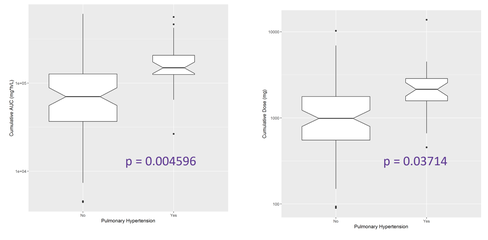
No Relationship Between Incidence of Peak Tricuspid Velocity >3.4 m/s by Navicixizumab Dose Level.

Cohort Dose Level (mg/kg)	PTV >3.4 m/s (n)	Total Patients (n)	Incidence (%)
0.5	0	3	0
1	0	3	0
2.5	3	12	25
3	14	42	33.3
3.5	2	11	18.2
4	2	4	50
5	0	4	0
7.5	4	11	36.4
10	1	5	20
12.5	1	3	33.3

Peak Tricuspid Velocity is not Related to Acute Navicixizumab Concentration.



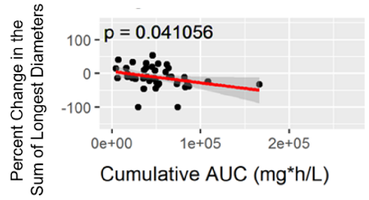
Cumulative Navicixizumab Exposure is Related to Peak Tricuspid Velocity >3.4 m/s.



RELATATIONSHIP BETWEEN NAVICIXIZUMAB EXPOSURE AND DEPTH OF RESPONSE

- A single measurement for each individual taken closest to 8 weeks after start of therapy was selected
- Both covariates of female reproductive tumors and stage 3 and 4 tumors demonstrated a significant relationship between cumulative AUC and depth of response
  - Higher cumulative AUC correlates with increased tumor reduction

Stage 3 and 4 Female Reproductive Cancer Patients had the More Favorable Efficacy Profile; Driven by Cumulative Exposure.



SUMMARY

- Navicixizumab clearance was generally dose proportional at 2.5 mg/kg and above
- Decreases in exposure among ADA positive patients are not applicable at clinically relevant doses
- Mean arterial pressure decreases with stage 3 and 4 patients and ADA positive patients, supporting a favorable adverse event profile in this population
- Increased peak tricuspid velocity is driven by cumulative AUC and dose
- Stage 3 and 4 female reproductive tumor patients have a favorable efficacy profile that is driven by cumulative AUC

REFERENCES

1. Jimeno A, et al. *Invest New Drugs* 2019;37:461-472; 2. Yen W-C, et al. *Mol Can Ther* 2015;14:C164; 3. Moore et al. J Clin Oncol 2022 (in press) 4.Compass Therapeutics (2022, Jan) Compass Corporate Presentation. compasstherapeutics.com