100P

RS-0139, a novel tumor-targeted docetaxel nanomedicine, with potent anti-tumor activity in a broad spectrum of tumor cell lines and xenograft models

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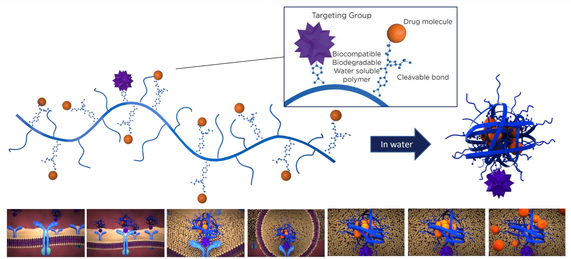
BACKGROUND

- Sagitta™ platform technology is discovered to reduce toxicity while maximizing the efficacy of cytotoxic drugs.
- Sagitta™ Bir, a water-soluble polymeric carrier, allows covalent binding of multiple active substances and targeting moieties to the polymer backbone.
- RS-0139 is the first drug candidate developed with this platform.

Structure of Sagitta™ Bir



METHODS

- RS-0139 is a tumor-targeted, docetaxel-releasing prodrug. The active molecule (DTX) is covalently bound to the polymer backbone via a short peptide releasing only upon entry to the cell via endocytosis. The carrier is also equipped with a targeting peptide which shows high affinity to $\alpha_v\beta_3$, $\alpha_v\beta_5$, and $\alpha_v\beta_6$ integrin receptors highly expressed on the tumor cell.
- A comprehensive set of in vivo studies are conducted to assess potential anti-tumor activity of RS-0139

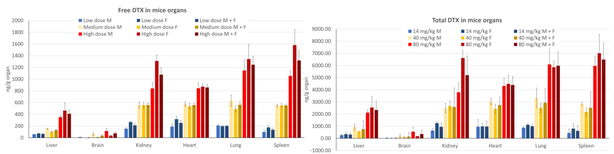
RESULTS

Physical properties of RS-0139 such as enhanced aqueous solubility provide an advantage over the currently used taxanes. Also, the pharmacokinetic profile is not only improved in terms of half-life and AUC but also is demonstrated to be translatable across species. In preclinical studies, the enzymatically cleavable covalent conjugation of DTX enabled sustained release, reducing adverse effects due to limited circulating free DTX. Hence, RS-0139 showed superior tolerability in healthy mice, rats, and rabbits compared to DTX. Besides, the dosing frequency was reduced due to the 5-fold increase in the half-life. Preclinical data strongly supported the clinical translation of this novel nanomedicine for the treatment of solid tumors. The Phase I clinical trial is ongoing on NSCLC patients.

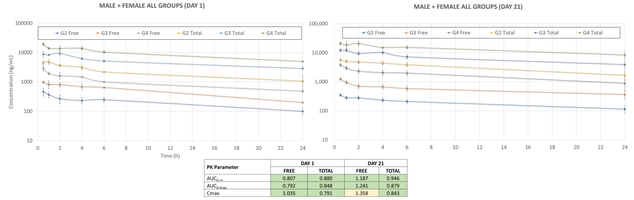
The EC50 value for docetaxel was lower than for both untargeted RS-0139 and RS-0139 at all tested cell lines, as expected.

Item	Cell Line	EC_{50} (M)		
		Docetaxel	Untargeted RS-0139	RS-0139
1	A549	7.9×10^{-9}	3.8×10^{-8}	1.9×10^{-8}
2	SKOV-3	1.7×10^{-8}	1.5×10^{-7}	1.4×10^{-7}
3	MDA-MB-231	4.5×10^{-8}	1.4×10^{-6}	8.0×10^{-7}

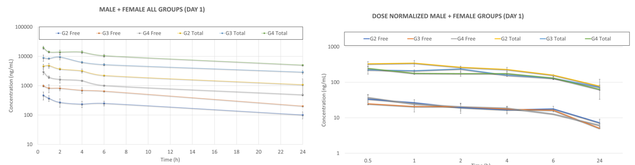
Biodistribution in all organs are proportional to dose; No statistically significant unexpected change in accumulation was observed.



No accumulation was observed between day 1 and day 21 pharmacokinetic parameters. AUC and Cmax are dose proportional for Sagitta® released and total API.



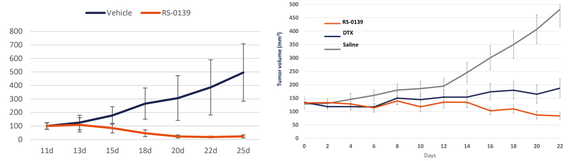
PK Parameter	DAY 1		DAY 21	
	FREE	TOTAL	FREE	TOTAL
AUC_{inf}	0.807	0.880	1.187	0.946
AUC_{0-last}	0.792	0.848	1.241	0.879
Cmax	1.035	0.791	1.358	0.843



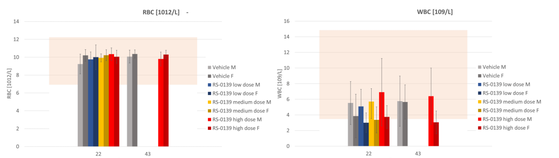
DAY 1	FREE DRUG							
Group	Dose	Fold Increase	AUC_{inf} (ng/mL.min)	Fold Increase	C_{max} (ng/mL)	Fold Increase	$t_{1/2,\beta}$ (h)	
M+F G2	LOW	1.00	7.0	1.00	468.6	1.00	14.0	
M+F G3	MEDIUM	2.86	18.9	2.71	989.2	2.11	12.1	
M+F G4	HIGH	2.00	27.9	1.47	2,990.4	3.02	12.9	

DAY 1	TOTAL DRUG							
Group	Dose	Fold Increase	AUC_{inf} (ng/mL.min)	Fold Increase	C_{max} (ng/mL)	Fold Increase	$t_{1/2,\beta}$ (h)	
M+F G2	LOW	1.00	72.1	1.00	4,834.5	1.00	13.2	
M+F G3	MEDIUM	2.86	182.3	2.53	9,491.1	1.96	15.3	
M+F G4	HIGH	2.00	334.0	1.83	19,642.9	2.07	14.7	

The superior anti-tumor activity of RS-0139 in 22RV1 prostate cancer xenograft model & SKOV3 ovarian cancer xenograft model



Dose increase does not affect the hemogram significantly



CONCLUSION

- **Tumor cell expression of the integrins is correlated with disease progression in various tumor types such as breast, pancreatic, prostate, non-small cell lung cancers and glioblastoma.**
- **Preclinical studies demonstrate promising results for NSCL, breast and prostate cancers.**

FOR FURTHER INFORMATION

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