

ST316, a First-in-Class β -Catenin Antagonist, Demonstrates Safety and Efficacy in Metastatic Colorectal Cancer (mCRC)

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Poster # CT156

Addressing CRC with ST316

- Aberrant activation of the Wnt/ β -catenin signaling pathway is a critical driver of tumor initiation and progression in colorectal cancer (CRC)
- β -catenin has an essential physiologic role in intestinal stem cell renewal and bone homeostasis, creating challenges for therapeutic antagonism
- BCL9/9L is a co-activator that recruits and retains β -catenin in the nucleus, and recruits Pygo to the enhanceosome transcription complex to enhance Wnt/ β -catenin transcriptional activity
- BCL9/9L is essential for oncogenic signaling but dispensable for physiologic β -catenin functions
- ST316 is a first-in-class antagonist of the interaction between β -catenin and BCL9, a complex responsible for driving oncogene expression and immune exclusion in multiple cancers

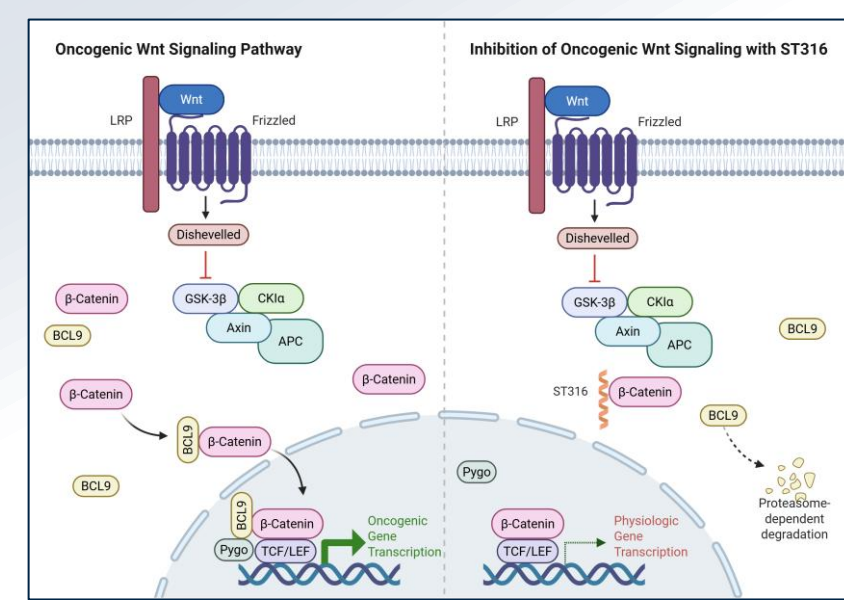


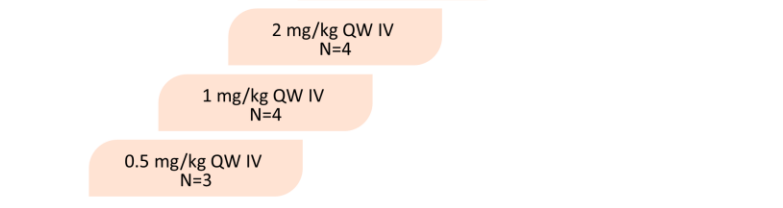
Figure 1. ST316 Disrupts Oncogenic Wnt/ β -catenin Signaling

Study Design

Figure 2. Phase 1/2 Study Design to Investigate ST316 Safety, Pharmacokinetics, Pharmacodynamics and Efficacy in Selected Advanced Unresectable and Metastatic Solid Tumors

Phase 1 Dose Escalation - Monotherapy (Completed)

- POPULATION**
Relapsed/refractory solid tumor types selected based on prevalence of abnormalities of the Wnt/ β -catenin signaling pathway*
- OBJECTIVES**
- Safety, PK, PD
 - Identify RP2D
- DESIGN**
- 3 + 3
 - Monotherapy
 - 1x/weekly IV



* Phase 1 tumor types: Colorectal, NSCLC, Ovarian, Synovial Sarcoma, Cholangiocarcinoma, HCC, Pancreatic, Melanoma, Breast

Phase 2 Dose Expansion - Combination (Ongoing)

- POPULATION**
- Colorectal cancer (2L MSS CRC)
 - Potential to assess additional Wnt/ β -catenin-driven indications
- OBJECTIVES**
- Confirm safety
 - Explore PD
 - Assess efficacy
- DESIGN**
- 2L CRC
 - ST316 + FOLFIRI + Bevacizumab (N=15)

Baseline characteristic	ST316 + FOLFIRI + bevacizumab (n=15)
Sex (%)	8 (53.3%) Male 7 (46.7%) Female
Age, median (range)	54 (22-74)
Liver metastases, n (%)	10 (66.7%)
Mutations, n (%)	10 (66.7%)
APC	1 (6.7%)
KRAS	9 (60%)
NRAS	3 (20%)
MSS	15 (100%)
Prior treatments, n (%)	15 (100%)
Chemo	8 (53.3%)
Bevacizumab	

Safety

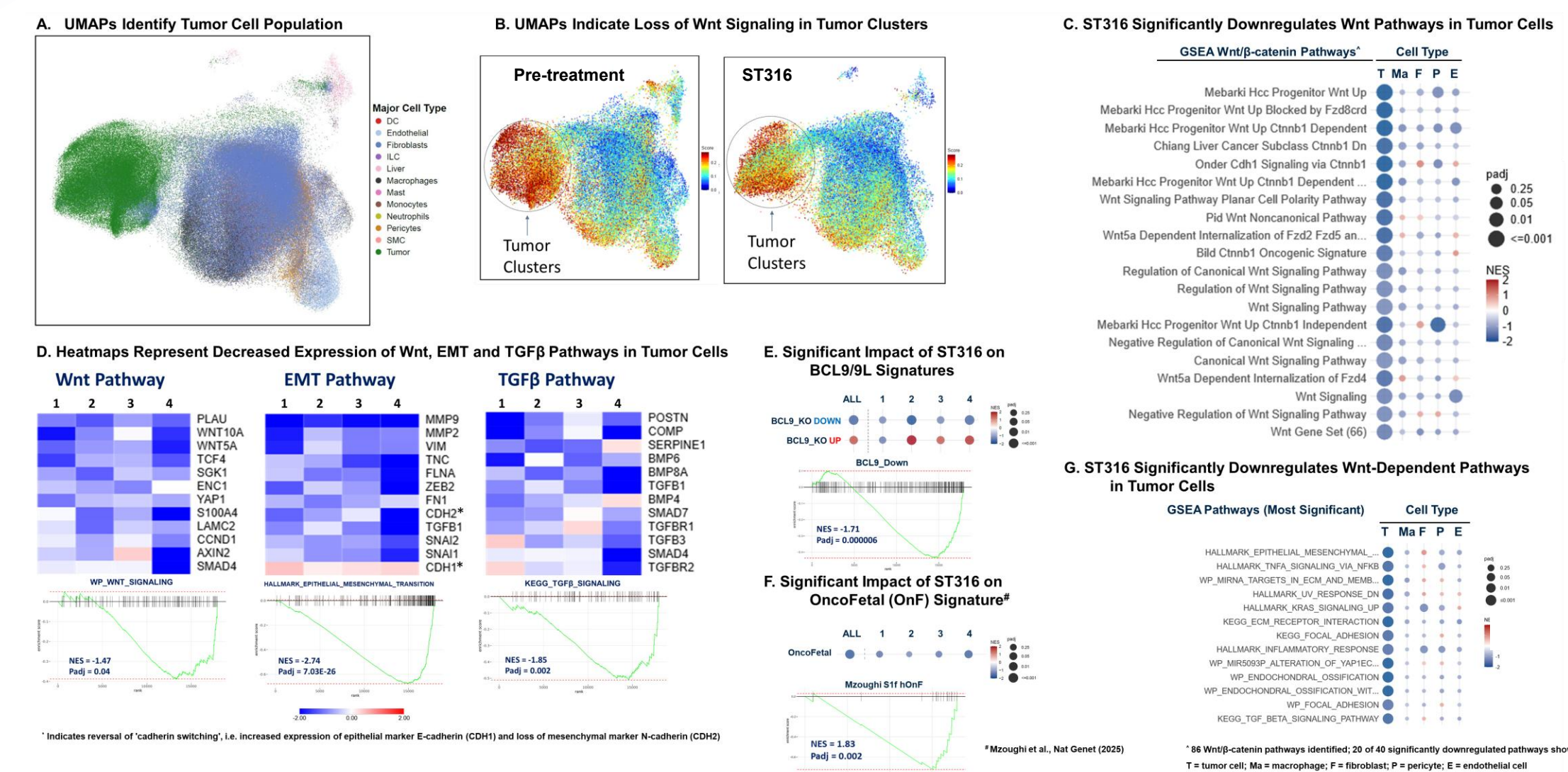
Table 1. Most common treatment emergent adverse events (AEs) reported in >20% on patients.

TEAS>20%	Escalation - ST316 Monotherapy (n=23)				Expansion - Combination ST316 + Bevacizumab + FOLFIRI (n=15)			
	All Grades		Grade \geq 3		All Grades		Grade \geq 3	
	n	n%	n	n%	n	n%	n	n%
Abdominal Pain	11	47.8%	1	4.3%	1	6.7%	0	0
ALT increase	6	26.1%	3	13%	14	93.3%	9	60%
AST increase	6	26.1%	2	8.7%	14	93.3%	5	33.3%
Constipation	2	8.7%	0	0	8	53.3%	0	0
Decreased appetite	8	34.8%	0	0	1	6.7%	0	0
Fatigue	12	52.2%	2	8.7%	12	80.0%	0	0
Nausea	7	30.4%	0	0	10	66.7%	0	0
Reduced neutrophil count	0	0	0	0	8	53.3%	8	53.3%
Vomiting	5	21.7%	0	0	1	6.7%	0	0
Stomatitis	0	0	0	0	6	40%	0	0
Diarrhea	2	8.7%	0	0	8	53.3%	2	13.3%
Anemia	5	21.7%	2	8.7%	1	6.7%	1	0
Pyrexia	6	26.1%	0	0	0	0	0	0
Weight decrease	6	26.1%	0	0	0	0	0	0
Constipation	2	8.7%	0	0	8	53.3%	0	0
Cough	5	21.7%	0	0	4	26.7%	0	0
Vision Blurred	0	0	0	0	4	26.7%	0	0

- Favorable ST316 safety profile as monotherapy (n=23) and in combination with FOLFIRI + Bevacizumab in 2L CRC patients (n=15)
- Majority of AEs are grade 1-2 and resolved
- Liver enzyme elevations were observed with higher incidence in the combination cohort

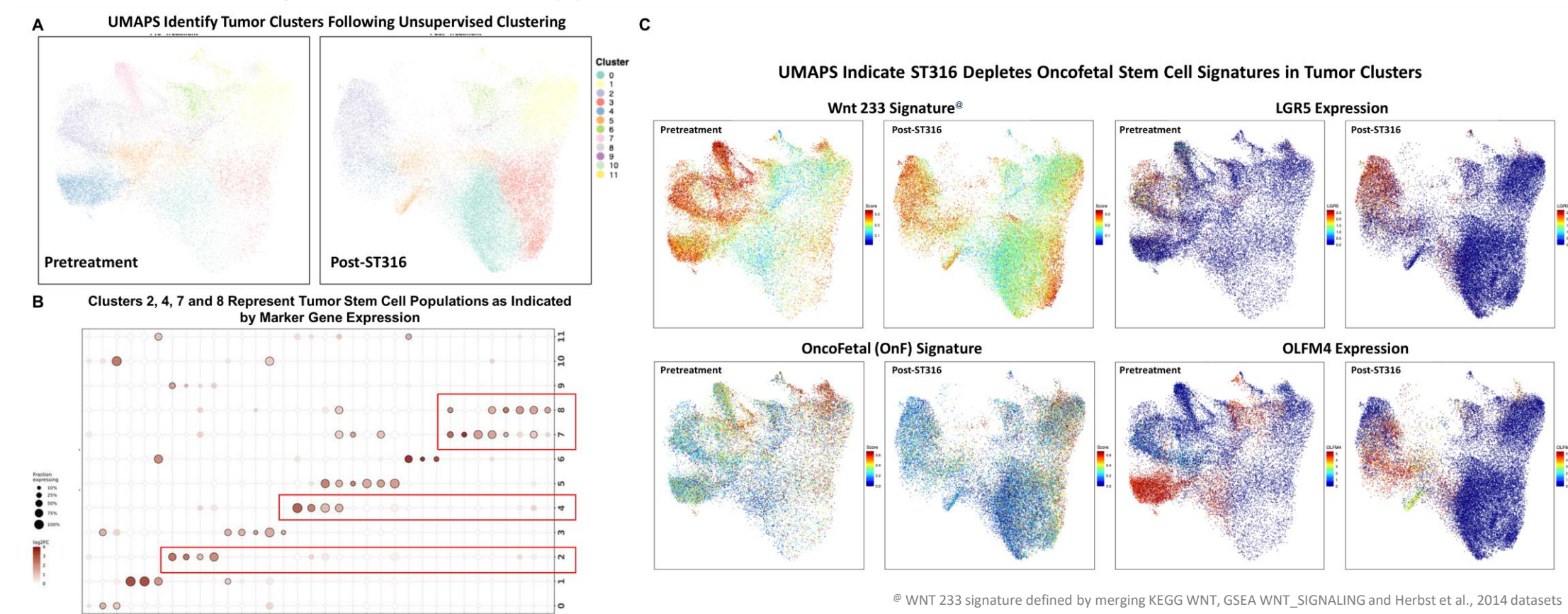
Spatial Transcriptomics

Figure 3. Supervised Clustering Indicates Significant Downregulation of Wnt and Wnt-Related Epithelial-to-Mesenchymal Transition (EMT) and TGF β Pathways in Tumor Cells Following ST316 Monotherapy



- Data represents supervised clustering of spatial transcriptomics data from Phase 1 (n=4; matched pre- and post-ST316)
- UMAP projections identify tumor cells (Panel A) and indicate selectively reduced Wnt signatures in the tumor cluster following ST316 monotherapy (Panel B)
- Tumor cells display significant downregulation following ST316 monotherapy in 40 of 86 Wnt/ β -catenin-related pathways identified in GSEA, with minimal impact in non-tumor cells (Panel C; top 20 most significant Wnt pathways shown)
- Heatmaps indicate reduced expression of Wnt, EMT and TGF β pathway genes following ST316 monotherapy (Panel D; data shown by individual patient)
- Significant changes in BCL9/9L and oncofetal signatures (Panels E and F). Data shown by individual patient
- Top significantly impacted GSEA pathways includes downregulation of Wnt-dependent EMT and TGF β pathways in tumor cells (Panel G)

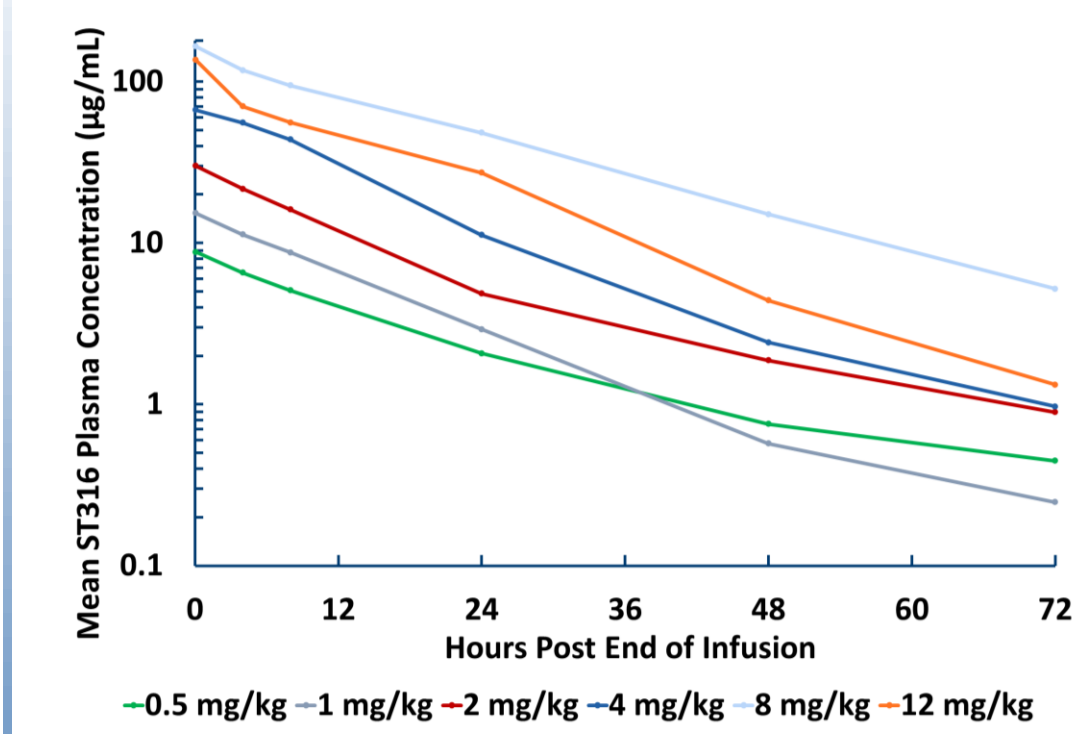
Figure 4. Unsupervised Clustering of Tumor Cells Identifies Loss of Clusters Displaying Cancer Stem Cell Features Following ST316 Monotherapy



- UMAP projections represent unsupervised clustering of tumor cells from 3 CRC patients from Phase 1 (matched pre- and post-ST316; Panel A)
- Clusters 2, 4, 7 and 8 display tumor stem cell markers (Panel B). Loss of Wnt/ β -catenin signatures observed in tumor stem cells following ST316 monotherapy exposure (Panel C; Wnt 233 Signature)
- ST316 monotherapy led to elimination of clusters 7 and 8 (Panel A) which are enriched in markers of the oncofetal (OnF) stem cell signature (Panel C)
 - OnF stem cells arise from non-curative chemotherapy and display fetal conversion and high metastatic capacity
 - OnF cells display resistance to FOLFIRI, supporting combination strategies incorporating ST316 with FOLFIRI in CRC

Pharmacokinetics

Figure 5. ST316 Displays Dose-Proportional Increases in Exposure with Increasing Dose From 0.5 to 8 mg/kg in Phase 1 Dose Escalation (n=3-4 per cohort; n=23 total)

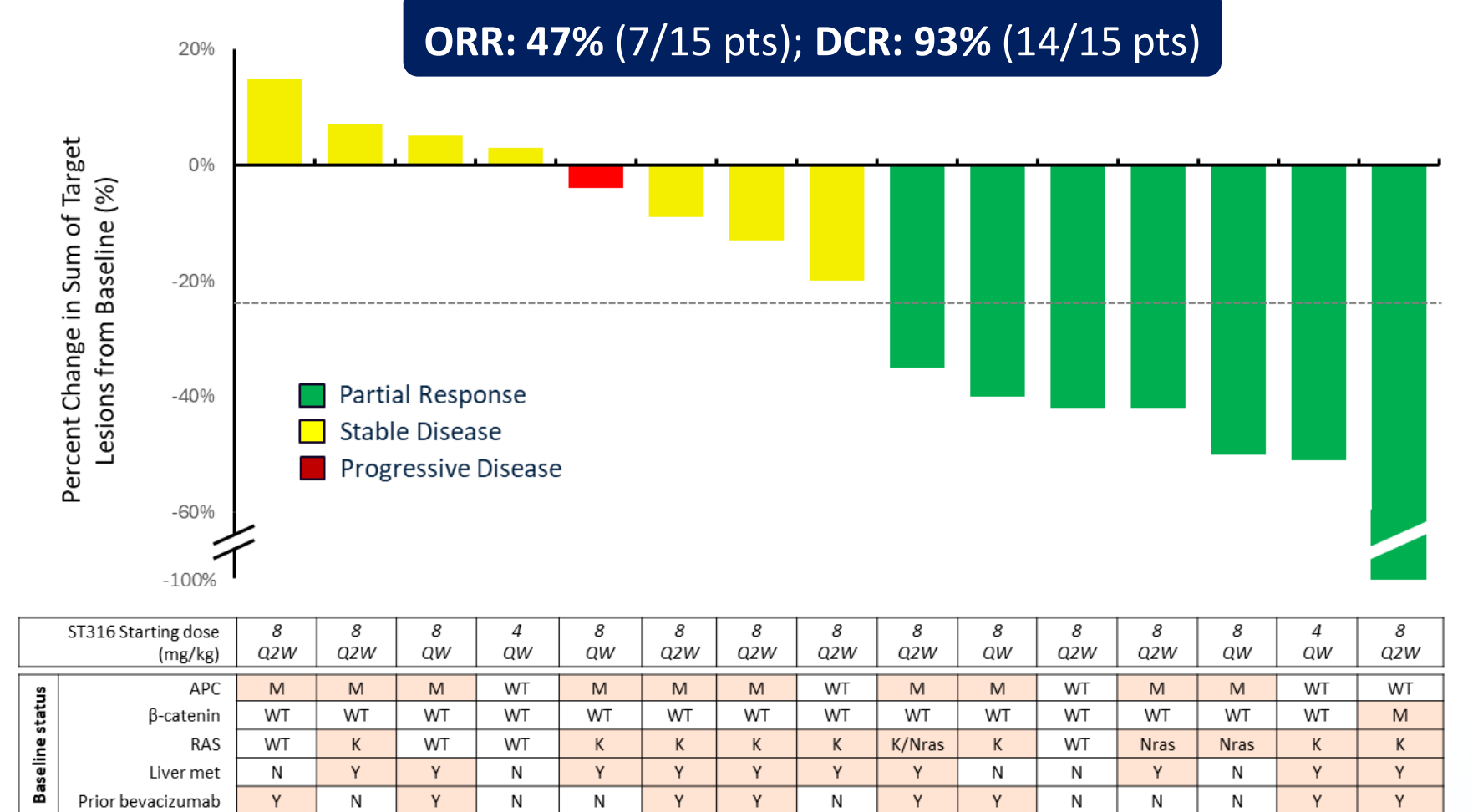


- No significant accumulation or loss of ST316 observed after repeated dosing
- 0.5 mg/kg dose level meets efficacious exposures identified in non-clinical studies

Dose (mg/kg)	C _{max} (ug/ml)	AUC _{0-12h} (hr*ug/ml)	C _{min} Ratio	AUC _{0-12h} Ratio
0.5	8.8	159.1	-	-
1	15.3	237.7	1.74	1.5
2	30.1	461.6	3.42	2.9
4	69.9	1085	7.95	6.8
8	165.3	3130	18.8	19.7
12	136.0	1774	15.5	11.2

Efficacy

Figure 6. ST316 Displays Potent Efficacy in 2L CRC When Administered in Combination With FOLFIRI + Bevacizumab



Conclusions

- ST316 monotherapy evaluated in Phase 1 Dose Escalation
 - Well tolerated, with no DLT or related SAEs observed
 - Potent on-target pharmacodynamic effects
 - Broad reduction of Wnt/ β -catenin signatures in tumor cells but not in adjacent normal cells; similar significant impact on Wnt-dependent EMT and TGF β pathways
 - Elimination of tumor stem cell populations associated with chemoresistance and metastasis
 - Pharmacokinetics are dose-proportional and achieve predicted efficacious exposures
- ST316 in combination with FOLFIRI + Bevacizumab evaluated in Phase 2 Dose Expansion
 - Efficacy demonstrated with 47% ORR; compares favorably to historical studies evaluating combination of anti-VEGF biologic and chemotherapy in 2L CRC (ORR range: 5 – 23%)[#]
- Data supports further evaluation of ST316 in combination with FOLFIRI and bevacizumab in 2L CRC in a randomized Phase 2 study
- Sapience plans to explore ST316 monotherapy in a clinical study in familial adenomatous polyposis (FAP), a rare, inherited condition driven by APC mutations that typically develops into CRC

[#] Iwamoto et al, Ann Oncol 2015 (EAGLE Study); Van Cutsem et al, JCO 2012 (VELOUR Study); Tabernero et al, Lancet Oncol 2015 (RAISE Study); Bennouna et al, Lancet Oncol 2013 (ML18147 Study); Masi et al, Ann Oncol 2015 (BEBYP Study); Giantonio et al, JCO 2007 (E3200 Study)

