Abstract CT229

CRESTONE: A Phase 2 study of seribantumab in adult patients with neuregulin-1 (NRG1) fusion positive locally advanced or metastatic solid tumors

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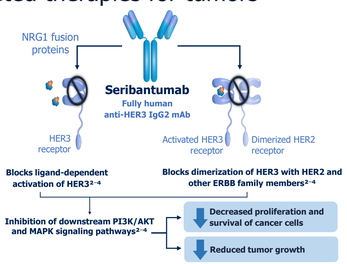
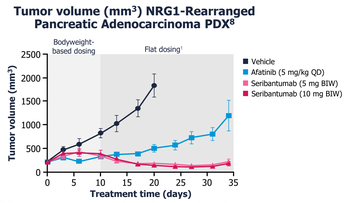
INTRODUCTION

- NRG1 fusions represent a rare and potentially actionable oncogenic alteration found in ~0.2% of solid tumors[1]
- Patients (pts) with tumors harboring an NRG1 fusion have poor outcomes with standard therapies, including chemotherapy and immunotherapy[1,2]. There are currently no approved targeted therapies for tumors harboring NRG1 fusions[3,4]
- Seribantumab is a fully human anti-HER3 IgG2 monoclonal antibody that blocks NRG1 binding to HER3 thus inhibiting the PI3K/AKT and MAPK downstream signaling pathways[5-8]



- Seribantumab has shown significant anti-tumor activity in PDX models and in pts with solid tumors harboring NRG1 fusions[8,9]



- CRESTONE (NCT04383210) is a multi-center, global Phase 2 study of seribantumab in adult pts with solid tumors harboring NRG1 fusions
- Here, we present updated efficacy results for pts in Cohort 1 (n=30) dosed at 3 g IV QW. Safety data are evaluated for pts enrolled in Cohort 1 and exploratory Cohorts 2 and 3 (n=51). Data presented represent data cut off of 02 Dec 2022

METHODS

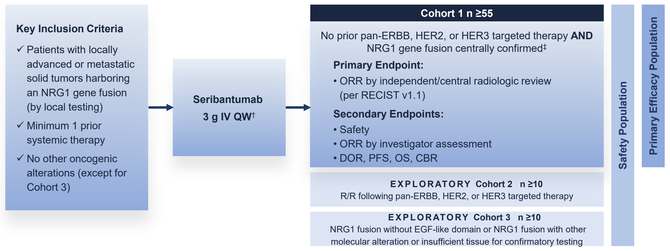


Figure 1. CRESTONE Phase 2 study design

[†]Animals were initially treated with seribantumab at 5 mg/kg or 10 mg/kg. Around days 5–10, dosing was changed to flat dosing and seribantumab was given at 5 mg BIW or 10 mg BIW for the remainder of treatment; [†]A safety run-in phase evaluated seribantumab as induction, consolidation, and maintenance dosing; [‡]Pts are enrolled and treated based on local NRG1 fusion testing result with post-enrollment confirmation by central RNA-based NGS assay; [¶]Includes pts in Cohort 1 who received the optimized RP2D of seribantumab 3 g QW including pts in the safety run-in who received seribantumab 3 g QW beyond induction/reinduction per SAP; [#]Includes all pts who received at least 1 dose of seribantumab at any dose level in all cohorts; [§]1 each of colon, endometrial, esophagus, head and neck, and ovary; [‖]BAG4, FUT10, GADD45GIP1, IL1RL2, ITGB1, NOTCH2, POMK, PTN, RNF169, TMPRSS3; [^]Required for Cohort 1 only post-enrollment; [^^]Central RNA-based NGS assay pending/quality not sufficient for testing/results not available;*Defined in the study protocol and SAP as Cohort 1 pts with centrally confirmed NRG1 fusion status who received seribantumab at 3g QW dosing regimen (starting with Protocol Version 3.0 and later), with investigator assessed response per RECISTv1.1. Pts in the safety-run in (enrolled under Protocol Version 2.0 or earlier) are included if they received seribantumab at 3 g QW beyond induction/reinduction; 8 pts (5 with NSCLC) are not evaluable for response at time of data cut off: 1 patient recently enrolled / not yet to first scan; 1 patient without post-baseline scan reported in EDC; 6 pts with pending/unknown central NRG1 fusion status All responses are confirmed ≥4 weeks per RECIST v1.1.

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; CR, complete response; CBR, clinical benefit rate; DOR, duration of response; ICI, immune checkpoint inhibitor; NE, not evaluable for RECIST response/pending scan data; NSCLC, non-small cell lung cancer; NRG1, neuregulin 1; ORR, objective response rate; PDX, patient-derived xenograft; PFS, progression free survival; PR, partial response; PS, performance status; R/R, relapse/refractory; SAP, statistical analysis plan; SD, stable disease.

RESULTS

Table 1. Patient Demographics

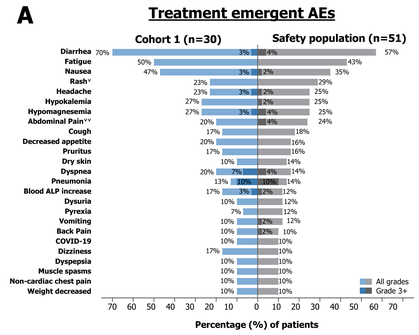
Demographic	Cohort 1[¶] (N=30)	NSCLC Cohort 1[¶] (N=23)	Safety Population[#] (N=51)
Age			
Median (range)	60.5 (38.0, 80.0)	61.0 (39.0, 80.0)	62.0 (19.0, 84.0)
Sex; n (%)			
Female	20 (67)	16 (70)	34 (67)
Male	10 (33)	7 (30)	17 (33)
Race; n (%)			
American Indian or Alaska Native	1 (3)	1 (4)	1 (2)
Asian	3 (10)	2 (9)	8 (16)
Black or African American	4 (13)	3 (13)	5 (10)
White	22 (73)	17 (74)	36 (71)
Other	0	0	1 (2)
ECOG PS; n (%) [Δ]			
0	10 (33)	7 (30)	22 (43)
1	17 (57)	14 (61)	25 (49)
2	3 (10)	2 (9)	3 (6)

[Δ] ECOG PS data for 1 patient in the Safety Population missing at time of data cut off
Note: Percentages may not add up to 100% due to rounding

Table 2. Baseline Disease Characteristics

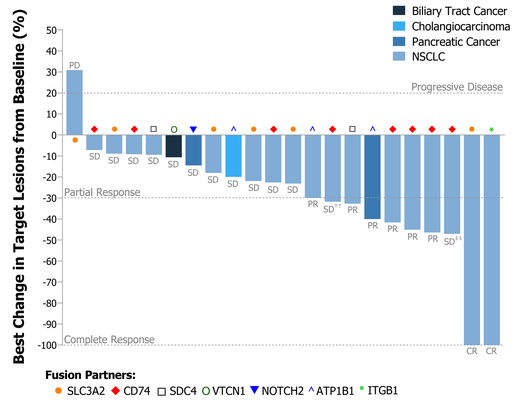
Disease Characteristic	Cohort 1[¶] (N=30)	NSCLC Cohort 1[¶] (N=23)	Safety Population[#] (N=51)
Primary Tumor Type; n (%)			
Biliary Tract/Cholangiocarcinoma	4 (13)	-	6 (12)
Breast	0	-	4 (8)
NSCLC	23 (77)	23 (100)	30 (59)
Pancreas	2 (7)	-	6 (12)
Other[§]	1 (3)	-	5 (10)
NRG1 Fusion Partners; n (%)			
AGRN	0	0	2 (4)
APP	1 (3)	0	3 (6)
ATP1B1	3 (10)	1 (4)	4 (8)
CD74	9 (30)	9 (39)	15 (29)
RBPMS	1 (3)	0	2 (4)
SDC4	2 (7)	2 (9)	2 (4)
SLC3A2	8 (27)	8 (35)	9 (18)
VAMP2	2 (7)	2 (9)	2 (4)
VTCN1	1 (3)	0	2 (4)
Other[‖]	3 (10)	1 (4)	10 (20)
Central NRG1 Fusion Status[^]; n (%)			
Confirmed	24 (80)	20 (87)	
Unconfirmed	0	0	
Unknown[^^]	6 (20)	3 (13)	
Prior Systemic Therapies; n (%)			
Median (range)	1.0 (1.0, 5.0)	1.0 (1.0, 3.0)	2.0 (1.0, 7.0)
Prior platinum	-	23 (100)	-
Prior ICI	-	17 (74)	-

- Overall, 41 pts (80%) reported at least one TRAE
- There were no treatment-related death on study
- 4 pts (8%) experienced dose reduction due to TRAE
- 3 pts (6%) experienced dose interruption due to TRAE
- No pts discontinued seribantumab due to TRAE



[γ] Includes preferred term (PT) of rash and maculo-papular rash; [γγ]Includes PT of abdominal pain, abdominal pain upper, abdominal distention

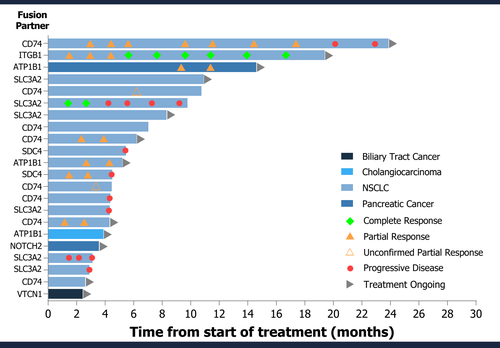
Figure 2. Treatment emergent AEs (A) and treatment related AEs (B) in pts receiving seribantumab monotherapy. Adverse events reported in ≥10% of pts



- Of the 30 pts in Cohort 1, 22 are evaluable for primary efficacy*
- Confirmed responses in pancreatic and NSCLC including 2 CRs regardless of NRG1 fusion partner
- INV-ORR 36% and DCR 95% (overall)
- INV-ORR 39% (NSCLC) and DCR 94%

[††] Unconfirmed PR, unable to be confirmed as subsequent scans showed pt in SD; [‡‡] Unconfirmed PR, pt died due to lung infection (history of COVID-19 infection) before confirmatory scan was able to be completed, no evidence of clinical disease progression at time of death.

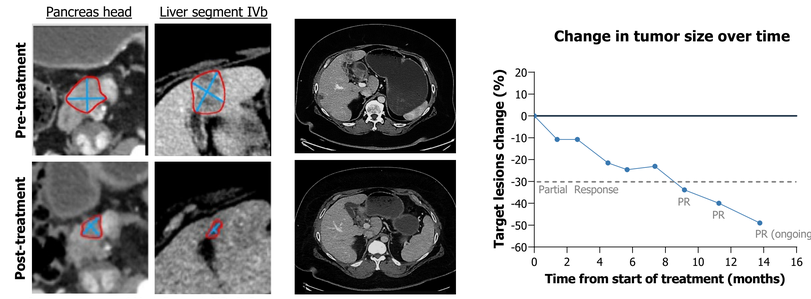
Figure 2. Best overall response and percent tumor reduction in Cohort 1



- 62.5% of responding pts remain in response and on treatment
- 54.5% of all pts remain on treatment
- Median time to response: 6.8 weeks (range: 4.3 – 39.3 weeks)
- Median DOR has not been reached (range: 1.4 – 17.2 months)

Figure 3. Duration of seribantumab treatment in Cohort 1

- 44-year-old man diagnosed with Stage IV pancreatic adenocarcinoma with multiple metastases to the liver
  - Four prior lines of therapy including gemcitabine/paclitaxel (1L), 5FU/liposomal irinotecan (2L), gemcitabine/paclitaxel (3L), and FOLFOX (4L)
  - Confirmed PR with maximal tumor reduction of 49%
  - Duration of response 4.6 months (ongoing)
  - Time on treatment 14.6 months (ongoing)



Images courtesy of Mark Burkard, MD, PhD

Figure 4. Response in a patient with ATP1B1-NRG1 pancreatic cancer

CONCLUSIONS

- This study enrolled diverse tumor types with a variety of NRG1 fusion partners
- Seribantumab administered 3 g IV QW induced deep and durable benefit for patients with previously treated solid tumors harboring NRG1 fusions
  - INV-ORR: 36% (overall); 39% (NSCLC) including 2 CRs
- Seribantumab was generally well tolerated, and the safety profile was consistent with observations from previous studies evaluating seribantumab[10-13]
- These data support seribantumab, a HER3 directed IgG2 mAb, as a potential treatment option for patients with solid tumors harboring NRG1 fusions

ACKNOWLEDGMENTS

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