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# CRESTONE: Initial Efficacy and Safety of Seribantumab in Solid Tumors Harboring NRG1 Fusions

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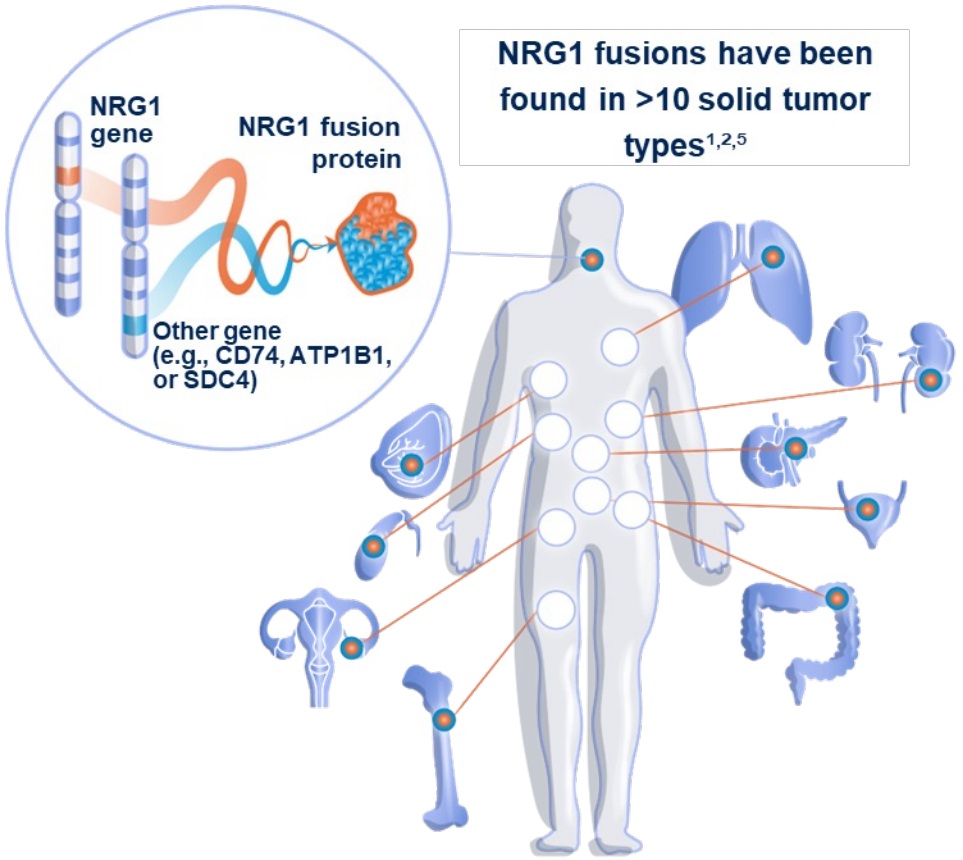
# NRG1 Gene Fusions in Solid Tumors

- NRG1 gene fusions are:
  - Rare genomic alterations resulting from the fusion of NRG1 with a partner gene[1]
  - NRG1 fusion proteins bind to and activate HER3[1]
  - Often mutually exclusive of other known oncogenic alterations[2–4]
  - Found in 0.2% of all solid tumors;
    - Enrichment has been observed in KRAS wild-type PDAC and invasive mucinous adenocarcinoma of the lung[3–6]
- Due to the large intronic regions of the gene fusion, RNA-based sequencing is the gold standard for detecting NRG1 fusions[6–8]
- Patients with tumors harboring an NRG1 fusion have poor outcomes with standard therapies, including chemotherapy and immunotherapy[3,9]
- There are currently no approved targeted therapies for tumors harboring NRG1 fusions[6,10]

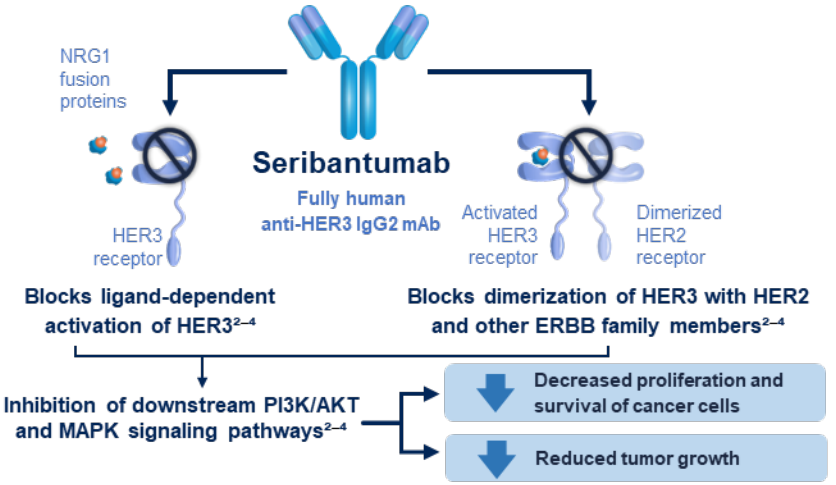


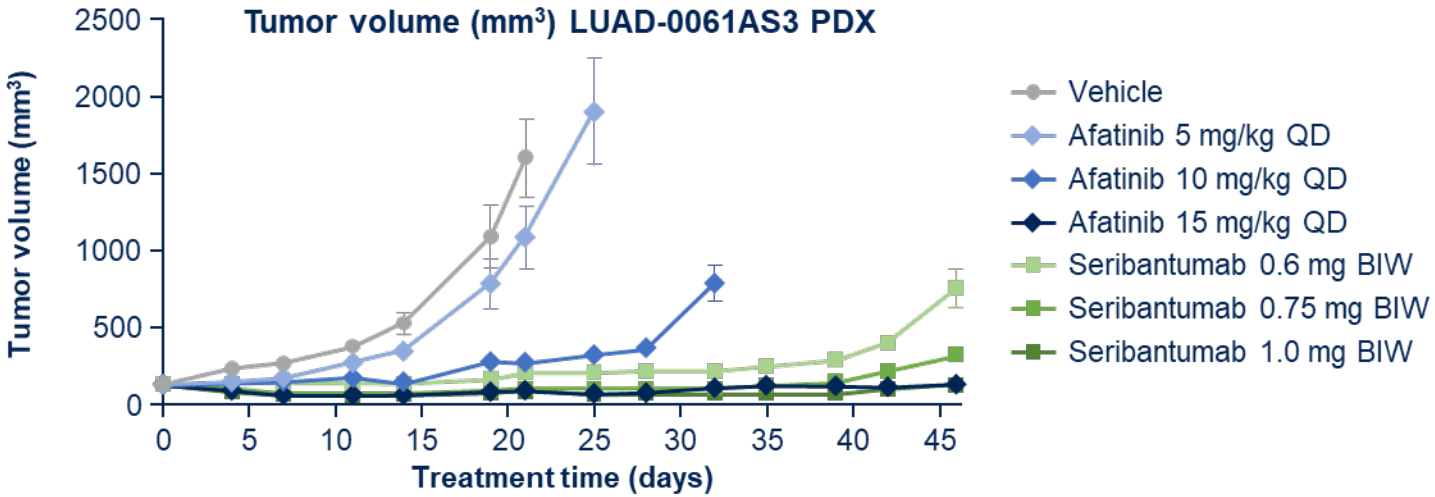

NRG1, neuregulin-1; PDAC, pancreatic ductal adenocarcinoma

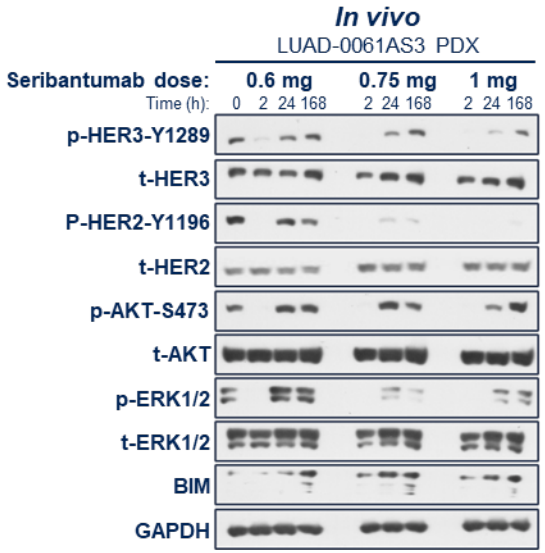
**Sources:** 1. Jonna S et al. *Clin Cancer Res*. 2019;25:4966–4972; 2. Drilon A et al. *Cancer Discov*. 2018;8:686–695; 3. Chang JC et al. *Clin Cancer Res*. 2021;27:4066–4076; 4. Jones MR et al. *Clin Cancer Res*. 2019;25:4674–4681; 5. Jonna S et al. *J Clin Oncol*. 2020;38(15_suppl):3113–3113; 6. Laskin J et al. *Ann Oncol*. 2020;31:1693–1703; 7. Russo A et al. *Precis Cancer Med*. 2020;3:14; 8. Liu S. *Lung Cancer*. 2021;158:25–28; 9. Drilon A et al. *J Clin Oncol*. 2021;39:2791–2802; 10. Lyu H et al. *Acta Pharm Sin B*. 2018;8:503–510.

# Seribantumab Inhibits NRG1 Fusion Tumor Growth

- Seribantumab is a fully human anti-HER3 IgG2 monoclonal antibody[1,2]
  - Competes with NRG1 to bind to HER3[2,4]
  - Prevents dimerization and phosphorylation of HER3 with other HER family members[2–4]
  - Inhibits downstream PI3K/AKT and MAPK/ERK pathways to inhibit tumor cell growth and proliferation[2–4]
- Seribantumab inhibited tumor growth and induced tumor regression in preclinical models at clinically achievable concentrations[4]




Seribantumab is under investigation in a clinical trial and has not been approved by the FDA for any indication
LUAD, lung adenocarcinoma; PDX, patient-derived xenograft

**Sources:** 1. Schoeberl B et al. *Sci Signal*. 2009;77:1–14; 2. Schoeberl B et al. *Cancer Res*. 2010;70:2485–2494; 3. Schoeberl B et al. *NPJ Syst Biol Appl*. 2017;3:16034; 4. Odinstov I et al. *Clin Cancer Res*. 2021;27:3154–3166.

# CRESTONE: A Phase 2 Study of the Anti-HER3 mAb Seribantumab in Solid Tumors with NRG1 Fusions

**Key Inclusion Criteria**

- ✓ Patients with locally advanced or metastatic solid tumors harboring an NRG1 gene fusion (by local testing)
- ✓ Minimum 1 prior systemic therapy
- ✓ No other oncogenic alterations (except for Cohort 3)

NCT04383210

**Seribantumab**
**3g IV QW†**

**Cohort 1 n ≥55**

No prior pan-ERBB, HER2, or HER3 targeted therapy **AND** NRG1 gene fusion centrally confirmed‡

**Primary Endpoint:**

- ORR by independent/central radiologic review (per RECIST v1.1)

**Secondary Endpoints:**

- Safety
- ORR by investigator assessment
- DOR, PFS, OS, CBR (CR, PR, SD, ≥24 weeks)

**EXPLORATORY Cohort 2 n ≥10**
R/R following pan-ERBB, HER2, or HER3 targeted therapy

**EXPLORATORY Cohort 3 n ≥10**
NRG1 fusion without EGF-like domain or NRG1 fusion with other molecular alteration or insufficient tissue for confirmatory testing

Safety Population

Primary Efficacy Population

†A safety run-in phase evaluated seribantumab as induction, consolidation, and maintenance dosing; seribantumab 3g QW selected as the optimized RP2D for patients with solid tumors harboring an NRG1 fusion. Patients from the safety run-in who transitioned to 3g QW after induction/reinduction will be included in the primary efficacy analysis per the SAP;
‡Patients are enrolled and treated based on local NRG1 fusion testing result with post-enrollment confirmation by central RNA-based NGS assay.



PRESENTED BY:
Daniel R. Carrizosa, MD

# Patient Demographics and Disease Characteristics

| Demographic | Cohort 1† (N=15) | Safety Population‡ (N=35) |
|---|---|---|
| **Age** | | |
| Median (range) | 61 (44, 76) | 65 (19, 76) |
| **Sex; n (%)** | | |
| Female | 10 (67) | 24 (69) |
| Male | 5 (33) | 11 (31) |
| **Race; n (%)** | | |
| American Indian or Alaska Native | 1 (7) | 1 (3) |
| Asian | 2 (13) | 7 (20) |
| Black or African American | 2 (13) | 3 (9) |
| White | 10 (67) | 23 (66) |
| Other | 0 | 1 (3) |
| **ECOG PS; n (%)** | | |
| 0 | 5 (33) | 18 (51) |
| 1 | 10 (67) | 17 (49) |
| 2 | 0 | 0 |

| Disease Characteristic | Cohort 1† (N=15) | Safety Population‡ (N=35) |
|---|---|---|
| **Primary Tumor Type; n (%)** | | |
| Biliary Tract/cholangiocarcinoma | 0 | 2 (6) |
| Breast | 0 | 4 (11) |
| NSCLC | 14 (93) | 20 (57) |
| Pancreas | 1 (7) | 5 (14) |
| Other§ | 0 | 4 (11) |
| **NRG1 Fusion Partners; n (%)** | | |
| ATP1B1 | 1 (7) | 2 (6) |
| CD74 | 6 (40) | 11 (31) |
| SDC4 | 2 (13) | 2 (6) |
| SLC3A2 | 5 (33) | 6 (17) |
| AGRN | 0 | 2 (6) |
| APP | 0 | 2 (6) |
| Other‖ | 1 (7) | 10 (29) |
| **Central NRG1 Fusion Status^; n (%)** | | |
| Confirmed | 14 (93) | |
| Unconfirmed | 0 | ^ |
| Unknown^^ | 1 (7) | |
| **Prior Systemic Therapies** | | |
| Median (range) | 1 (1, 5) | 2 (1, 6) |

†Includes patients in Cohort 1 who received the optimized RP2D of seribantumab 3g QW including patients in the safety run-in who received seribantumab 3g QW beyond induction/reinduction; ‡Includes all patients who received at least 1 dose of seribantumab in all cohorts; §Colon, endometrial, esophagus, and head and neck; ‖BAG4, FUT10, IL1RL2, ITGB1, POMK, PTN, RBPMS, RNF169, TMPRSS3, VTCN1; ^Required for Cohort 1 only post-enrollment; ^^Central RNA-based NGS assay pending/quality not sufficient for testing/results not available.
Note: Percentages may not add up to 100% due to rounding

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# Safety Summary of Seribantumab Monotherapy

## Adverse events reported in ≥15% of patients

| | Treatment-emergent AEs (N=35); n (%) | | | | Treatment-related AEs (N = 35); n (%) | | | |
|---|---|---|---|---|---|---|---|---|
| **Preferred Term** | **Any Grade** | **Grade 1** | **Grade 2** | **Grade ≥ 3†** | **Any Grade** | **Grade 1** | **Grade 2** | **Grade ≥ 3‡** |
| Patients with ≥1 AE | 35 (100) | 8 (23) | 10 (29) | 17 (49) | 30 (86) | 17 (49) | 11 (31) | 2 (6) |
| Diarrhea | 17 (49) | 11 (31) | 4 (11) | 2 (6) | 14 (40) | 10 (29) | 3 (9) | 1 (3) |
| Fatigue | 14 (40) | 7 (20) | 7 (20) | 0 | 10 (29) | 5 (14) | 5 (14) | 0 |
| Rash§ | 11 (31) | 9 (26) | 2 (6) | 0 | 9 (26) | 7 (20) | 2 (6) | 0 |
| Hypokalemia | 10 (29) | 6 (17) | 3 (9) | 1 (3) | 3 (9) | 3 (9) | 0 | 0 |
| Nausea | 10 (29) | 7 (20) | 1 (3) | 2 (6) | 6 (17) | 5 (14) | 1 (3) | 0 |
| Abdominal pain‖ | 8 (23) | 4 (11) | 2 (6) | 2 (6) | 3 (9) | 1 (3) | 2 (6) | 0 |
| Decreased appetite | 8 (23) | 4 (11) | 3 (9) | 0 | 3 (9) | 1 (3) | 2 (6) | 0 |
| Headache | 8 (23) | 7 (20) | 1 (3) | 0 | 1 (3) | 1 (3) | 0 | 0 |
| Hypomagnesemia | 8 (23) | 6 (17) | 1 (3) | 0 | 2 (6) | 2 (6) | 0 | 0 |
| Cough | 7 (20) | 5 (14) | 2 (6) | 0 | 1 (3) | 1 (3) | 0 | 0 |
| Anemia^ | 6 (17) | 4 (11) | 1 (3) | 1 (3) | 1 (3) | 1 (3) | 0 | 0 |
| Dysuria | 6 (17) | 6 (17) | 0 | 0 | 0 | 0 | 0 | 0 |

- Safety profile of 35 patients with tumors harboring NRG1 fusions who received at least 1 dose of seribantumab in the CRESTONE study
  - One DLT (Grade 2 fatigue resulting in dose reduction by the Investigator in the safety run-in)
  - 27 (77%) patients received the optimized RP2D of seribantumab 3g QW
- Majority (80%) of TRAEs were Grade 1 or 2
- Two (6%) patients received dose reductions for AEs per the Investigator
  - One patient for Grade 1 ALT increase
  - One patient for Grade 2 fatigue
- No patients discontinued seribantumab for AEs

†2 Grade 5 TEAEs (unrelated to seribantumab) of lung infection (n=1 patient) and malignant neoplasm progression (n=1 patient); ‡No Grade 4 or 5 TRAEs reported; 2 Grade 3 TRAEs of diarrhea (n=1 patient) and vomiting (n=1 patient); §Includes preferred term (PT) of rash and maculo-papular rash; ‖Includes PT of abdominal pain, abdominal pain upper, abdominal distention; ^Includes PT of anemia and iron deficiency anemia.

AE, adverse event; ALT, alanine transaminase; DLT, dose-limiting toxicity; TRAE, treatment-related adverse event

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# Clinical Activity of Seribantumab in Tumors Harboring NRG1 Fusions

| Investigator-assessed (INV) Response, % | Cohort 1 Primary Efficacy Population† (n=12‡) | Cohort 1 - NSCLC Primary Efficacy Population† (n=11‡) |
|---|---|---|
| **Objective response rate; n (%)** | **4 (33)** | **4 (36)** |
| **Complete response; n (%)** | **2 (17)** | **2 (18)** |
| **Partial response; n (%)** | **2 (17)** | **2 (18)** |
| Stable disease; n (%) | 7 (58) | 6 (55) |
| Progressive disease; n (%) | 1 (8) | 1 (9) |
| Disease control rate; n (%) | 11 (92) | 10 (91) |

†Defined in the study protocol and Statistical Analysis Plan as Cohort 1 patients with centrally confirmed NRG1 fusion status who received at least 1 dose of seribantumab at 3g QW dosing regimen (starting with Protocol Version 3.0 and later). Patients in the safety-run in (enrolled under Protocol Version 2.0 or earlier) are included if they received seribantumab at 3g QW beyond induction/reinduction;
‡3 patients are not included for efficacy analysis 2 patients are not for evaluable response (1 patient recently enrolled and not yet eligible for post-baseline scan; 1 patient died due to sepsis, unrelated to disease progression or seribantumab and no post-baseline tumor measurements recorded) AND 1 patient with unknown central NRG1 fusion status as of visit cut-off date.

All responses are confirmed ≥4 weeks per RECIST v1.1. All patients have tumors harboring NRG1 fusion by local testing
Note: Percentages may not add up to 100% due to rounding

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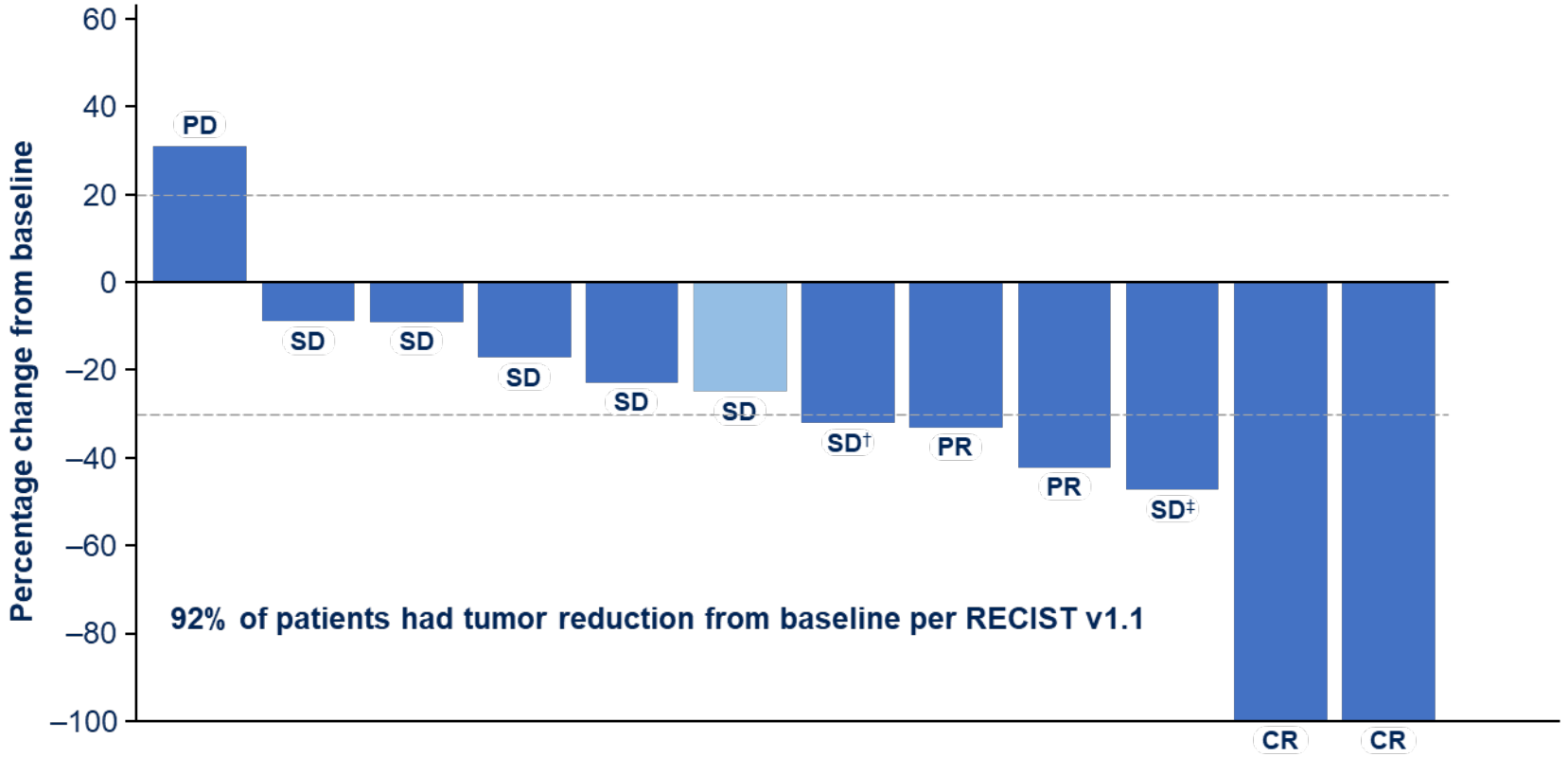
# Efficacy of Seribantumab in Tumors Harboring NRG1 Fusions




| Confirmed INV-ORR | |
|---|---|
| Overall | 33% (4/12) |
| NSCLC | 36% (4/11) |

**Primary tumor type:**
- Lung/NSCLC
- Pancreas

†Unconfirmed PR, unable to be confirmed as subsequent scans showed patient in SD;
‡Unconfirmed PR, patient 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.
INV-ORR, investigator-assessed objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1
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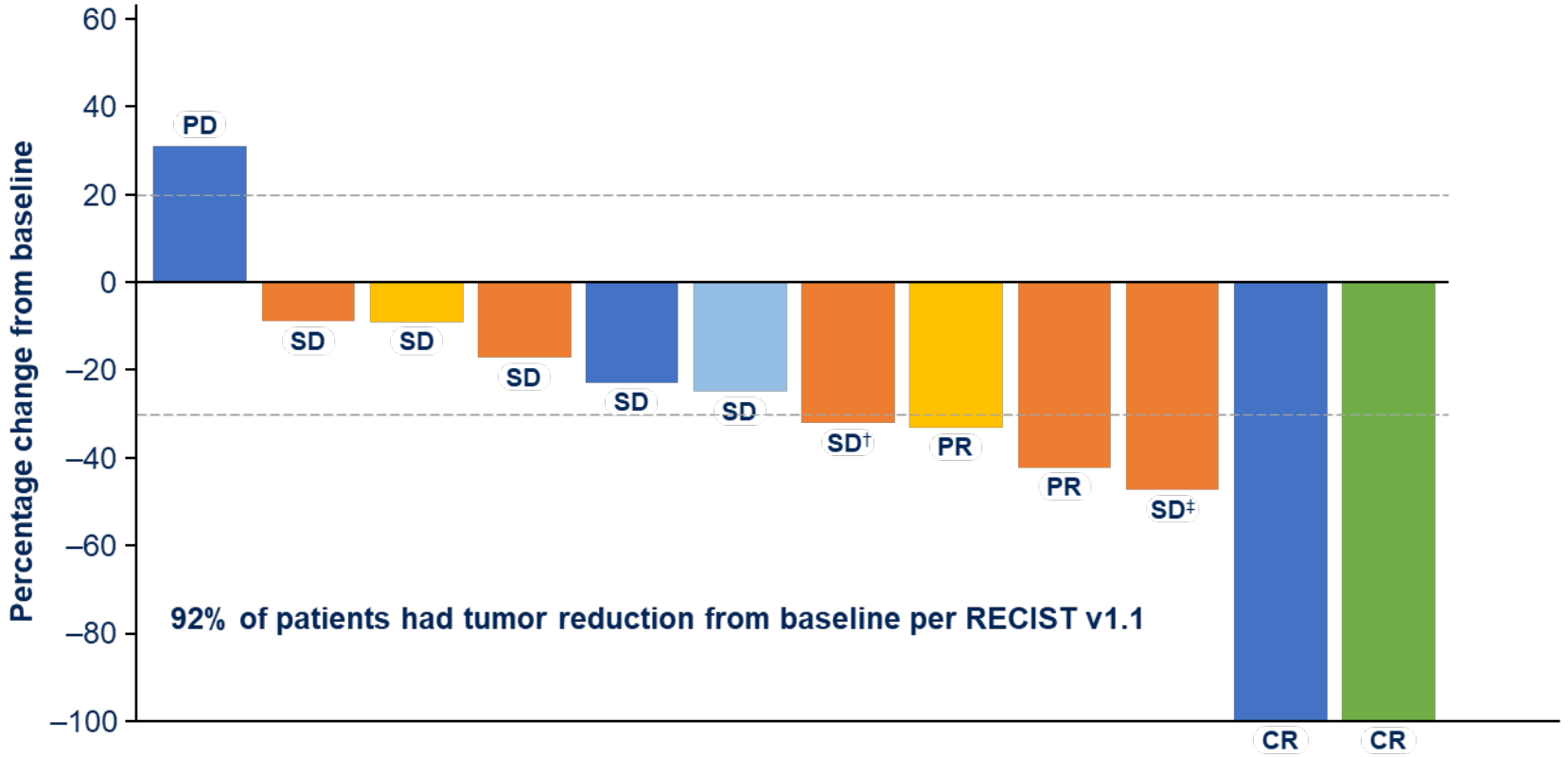
# Efficacy of Seribantumab in Tumors Harboring NRG1 Fusions Regardless of Fusion Partner




| Confirmed INV-ORR | |
|---|---|
| Overall | 33% (4/12) |
| NSCLC | 36% (4/11) |

**NRG1 fusion partner:**
- SLC3A2
- CD74
- SDC4
- ATP1B1
- ITGB1

†Unconfirmed PR, unable to be confirmed as subsequent scans showed patient in SD;
‡Unconfirmed PR, patient 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.
INV-ORR, investigator-assessed objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1
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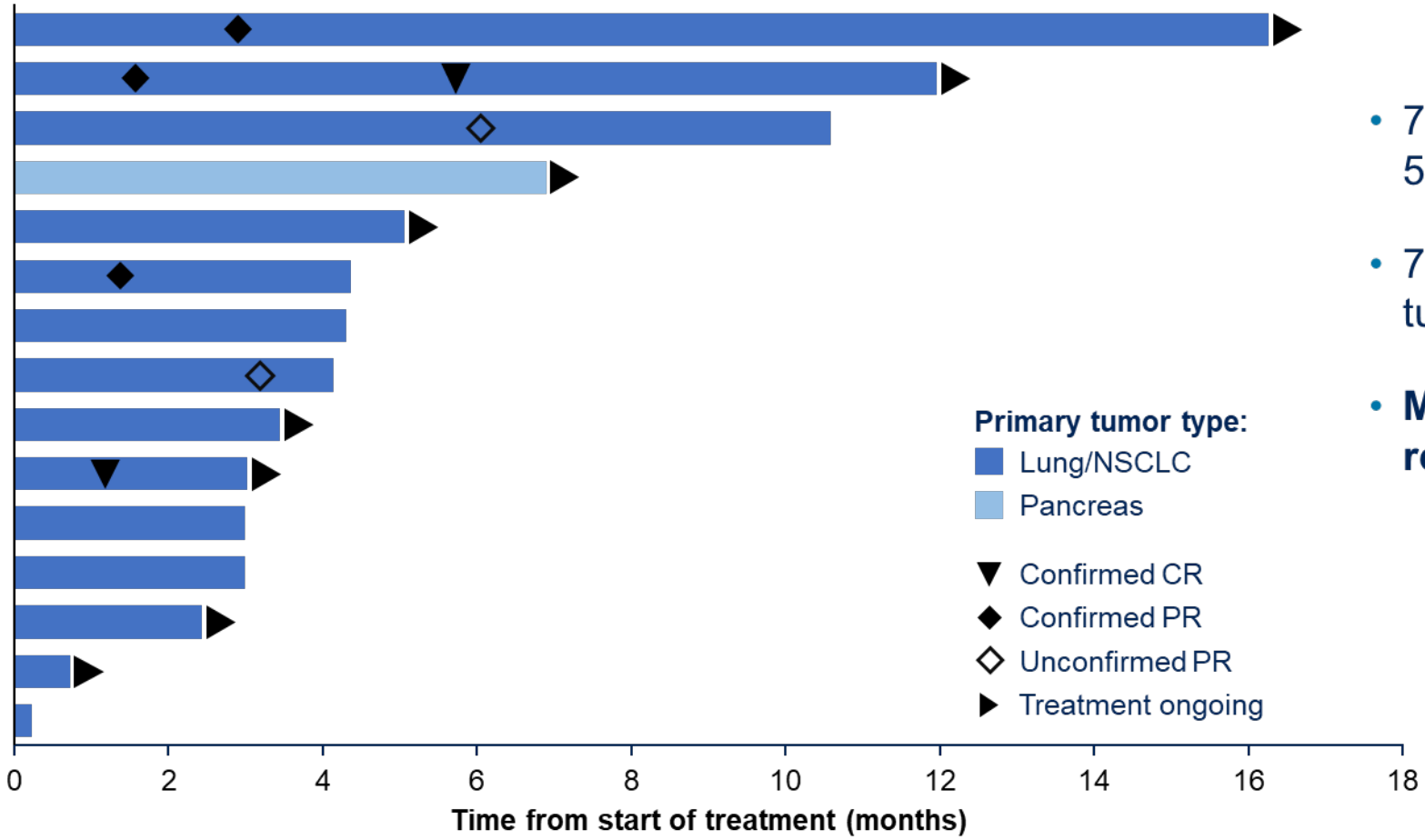
# Duration of Seribantumab Therapy in Tumors Harboring NRG1 Fusions




- 75% of **responding** patients and 53% of **all** patients remain on treatment
- 75% of **responses** occurred by first tumor assessment (Week 6 ± 2 weeks)
- **Median DOR has not yet been reached** (range: 1.4–11.5 months)

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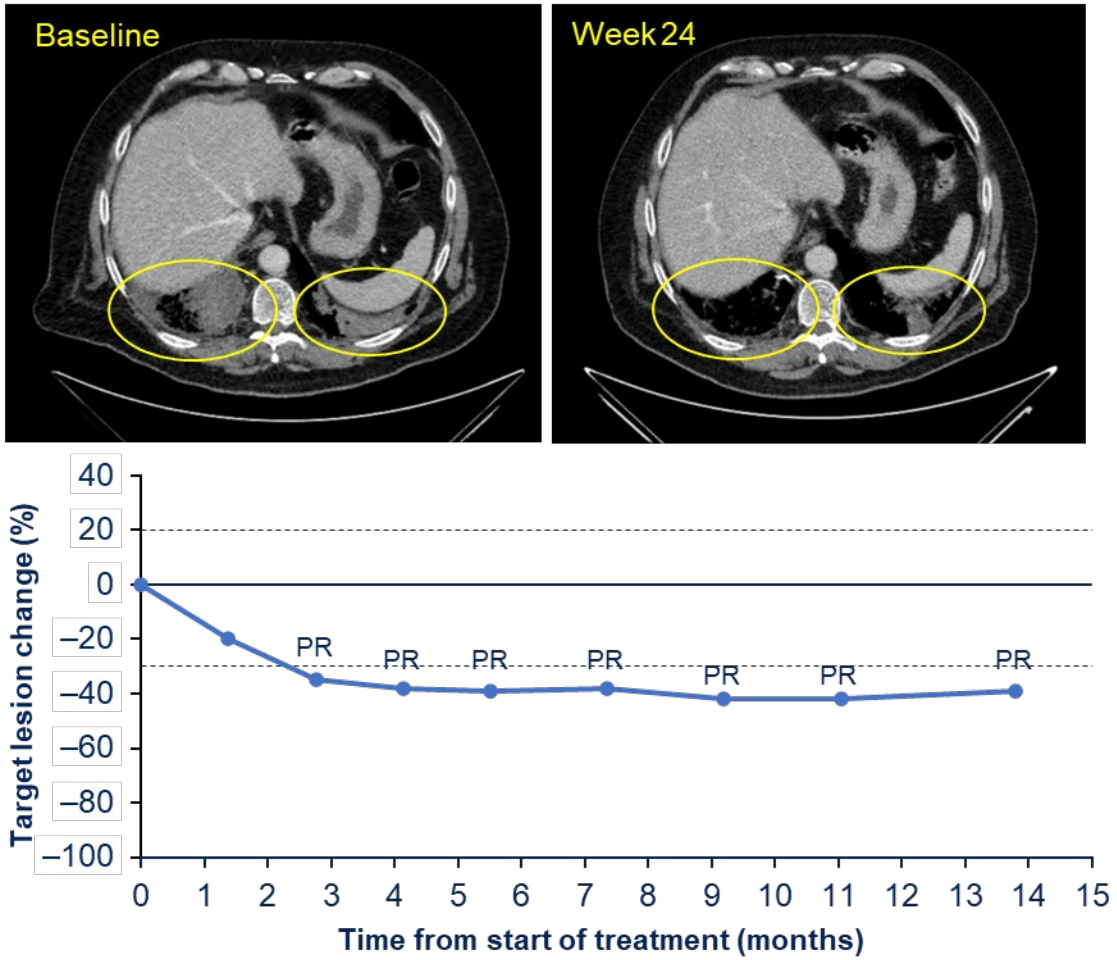
# Durable Response in CD74-NRG1 NSCLC




- 70-year-old male with NSCLC adenocarcinoma
- Three prior lines including platinum-based chemotherapy, immunotherapy (IO), and investigational therapy (IO and targeted agent)
- PR (35% tumor reduction) at Week 12; maximum tumor reduction of 42%
- Duration of response 11.5 months (ongoing)
- Seribantumab treatment ongoing for 16.0 months
  - Initiated seribantumab treatment under safety run-in
  - Transitioned to seribantumab 3g QW after induction/consolidation

Images courtesy of Tejas Patil, MD; University of Colorado
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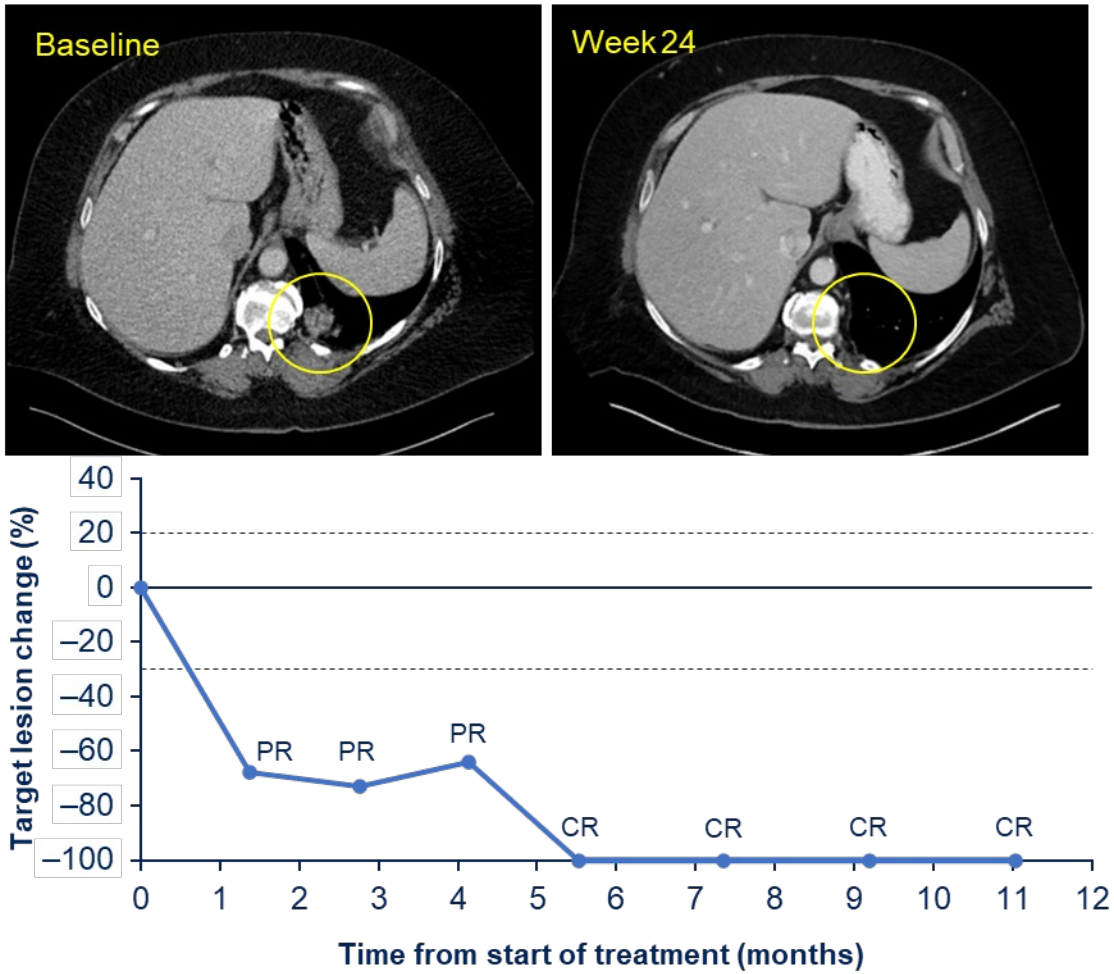
# Deep and Durable Response in ITGB1-NRG1 NSCLC




- 60-year-old female with NSCLC adenocarcinoma
- Three prior lines including platinum-based chemotherapy and immunotherapy
- PR (68% tumor reduction) at Week 6
- Deepening of response to CR at Week 24
- Duration of response 9.7 months
  - CR ongoing for 5.6 months
- Treatment ongoing for 11.7 months

Images courtesy of Daniel R. Carrizosa, MD; Levine Cancer Institute
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# Conclusions

- Initial data support the ability of seribantumab to produce deep and durable benefit for patients with previously treated solid tumors harboring NRG1 fusions
  - INV-ORR: 33% (2 PRs, 2 CRs); NSCLC INV-ORR: 36% (2 PRs, 2 CRs)
  - Durable ongoing responses with DOR of 9.7 and 11.5 months
  - Disease control rate of 92%
- Seribantumab was generally well tolerated, and the safety profile was consistent with observations from previous studies evaluating seribantumab[1–4]
  - Majority of AEs were Grade 1 or 2
  - No AEs led to discontinuation of seribantumab treatment
- These data support the continued evaluation of seribantumab in the ongoing Phase 2 CRESTONE (NCT04383210) study as a potential new standard of care for patients with solid tumors harboring NRG1 fusions
  - Comprehensive genomic profiling, particularly RNA-based NGS, will be important to identify patients with gene fusions

INV-ORR, investigator-assessed objective response rate

**Sources:** 1. Denlinger C et al. *Invest New Drugs*. 2021;39:1604–1612; 2. Liu JF et al. *J Clin Oncol*. 2016;20;34:4345–4353; 3. Cleary JM et al. *Invest New Drugs*. 2017;35:68–78; 4. Sequist LV et al. *Oncologist*. 2019;24:1095–1102.

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