Phase 1b Study of AMG 757, a Half-Life Extended Bispecific T-Cell Engager (HLE BiTE®) Immuno-Oncology Therapy Targeting DLL3, In De Novo Or Treatment-Emergent Neuroendocrine Prostate Cancer (NEPC)

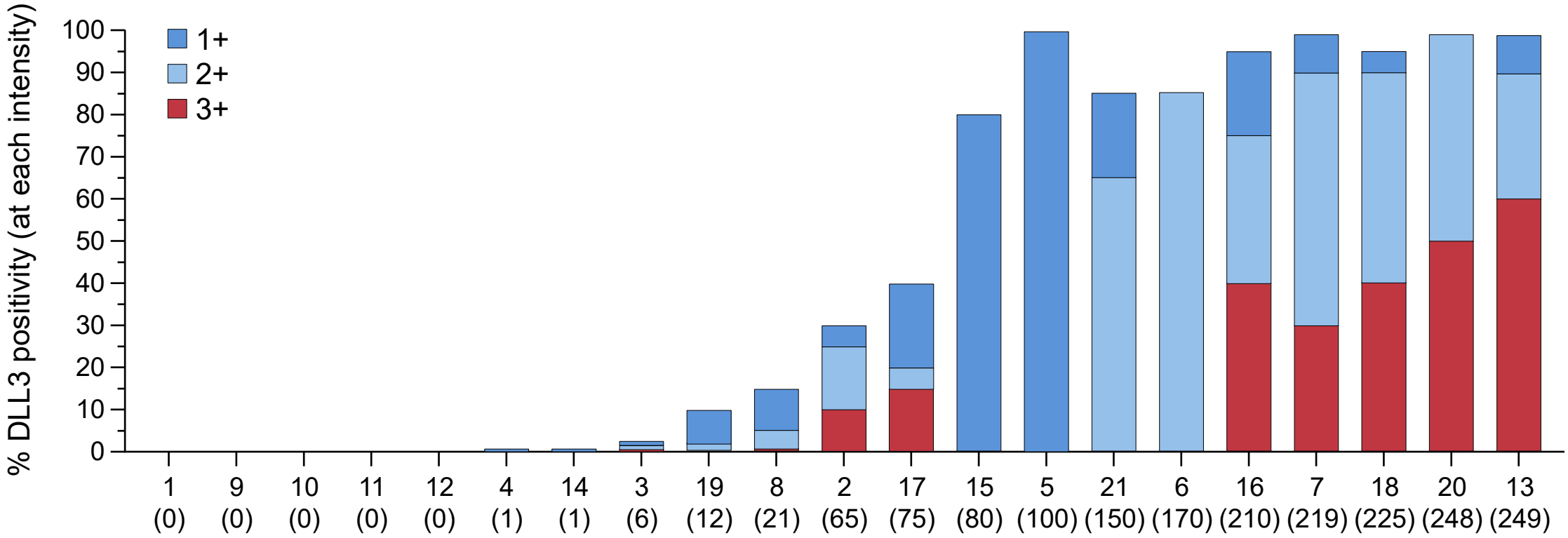
Background

- De novo neuroendocrine prostate cancer (NEPC) is a rare aggressive variant form of prostate cancer with poor prognosis and no standard treatment approach[1,2]
  - Treatment-emergent NEPC is usually characterized by histological transformation from adenocarcinoma to a high-grade neuroendocrine tumor, and may develop in 15%–20% of patients with metastatic castration-resistant prostate cancer (mCRPC)[2]
- Delta-like ligand 3 (DLL3), an inhibitory Notch ligand, has been shown to be highly expressed on NEPC tumors (~77%) and minimally expressed on normal tissue, making it a compelling therapeutic target[3,4]

1. Wang HT, et al. *J Clin Oncol*. 2014;32:3383-3390.
2. Aggarwal R, et al. *J Clin Oncol*. 2018;36:2492-2503.
3. Tsai H, et al. *BMC Cancer*. 2017;17:759.
4. Puca L, et al. *Sci Transl Med*. 2019;11:eaav0891.

DLL3 is Prevalent in 76% of NEPC Tumor Samples

- 16 of 21 NEPC tumors (76%) stained positive for DLL3, with a median (range) *H*-score of 90 (1–249)
  - Median % DLL3 positive tumor cells: 83%

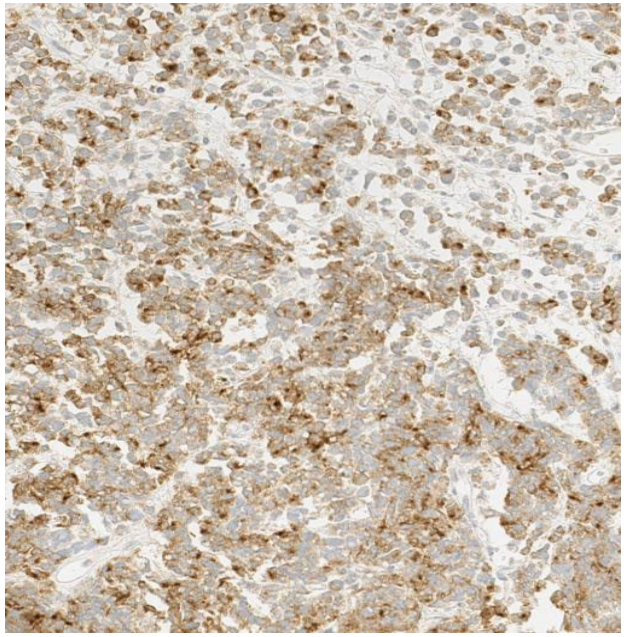


H-score, provides a semiquantitative assessment of DLL3 and combines percentage of cells expressing DLL3 (0–100) and the intensity of the signal range (0–3, with 0=no to 3=strong straining), giving a possible *H*-score range of 0–300

NEPC Tissues Express DLL3 mRNA and Protein

- DLL3 expression was observed in NEPC tumor and tissue sections immunostained with an anti-DLL3 antibody

Adenocarcinoma with neuroendocrine components (Gleason score 5+5)	
% Positive Cells	Intensity/H-Score*
80	**65**



Small cell carcinoma of the prostate	
% Positive Cells	Intensity/H-Score*
90	**150**

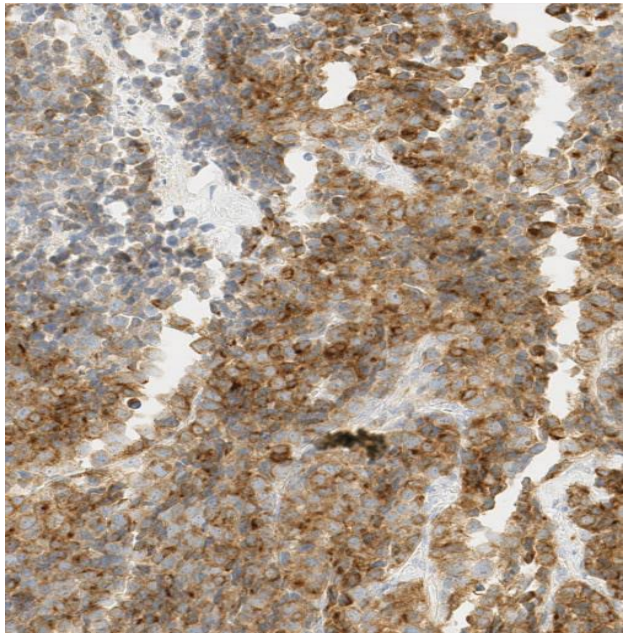


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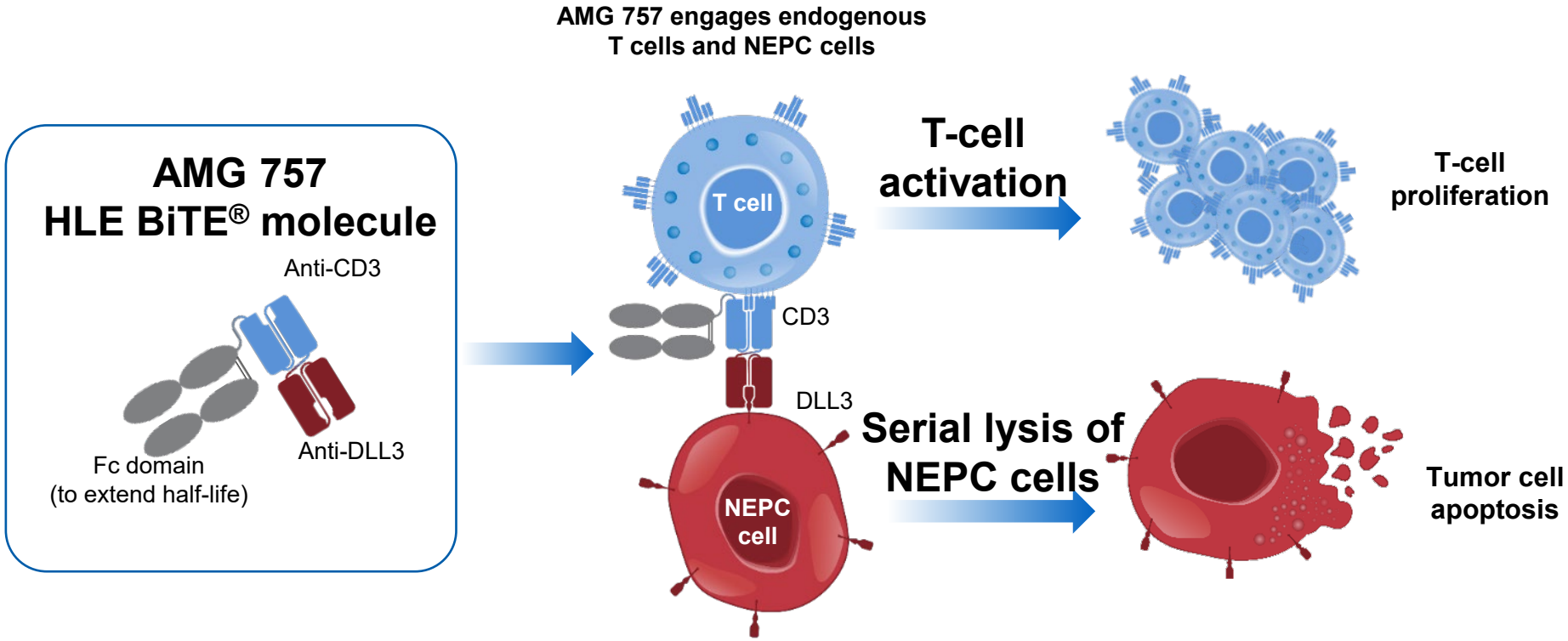
Figure 3. AMG 757: A HLE BiTE® Therapy Targeting DLL3

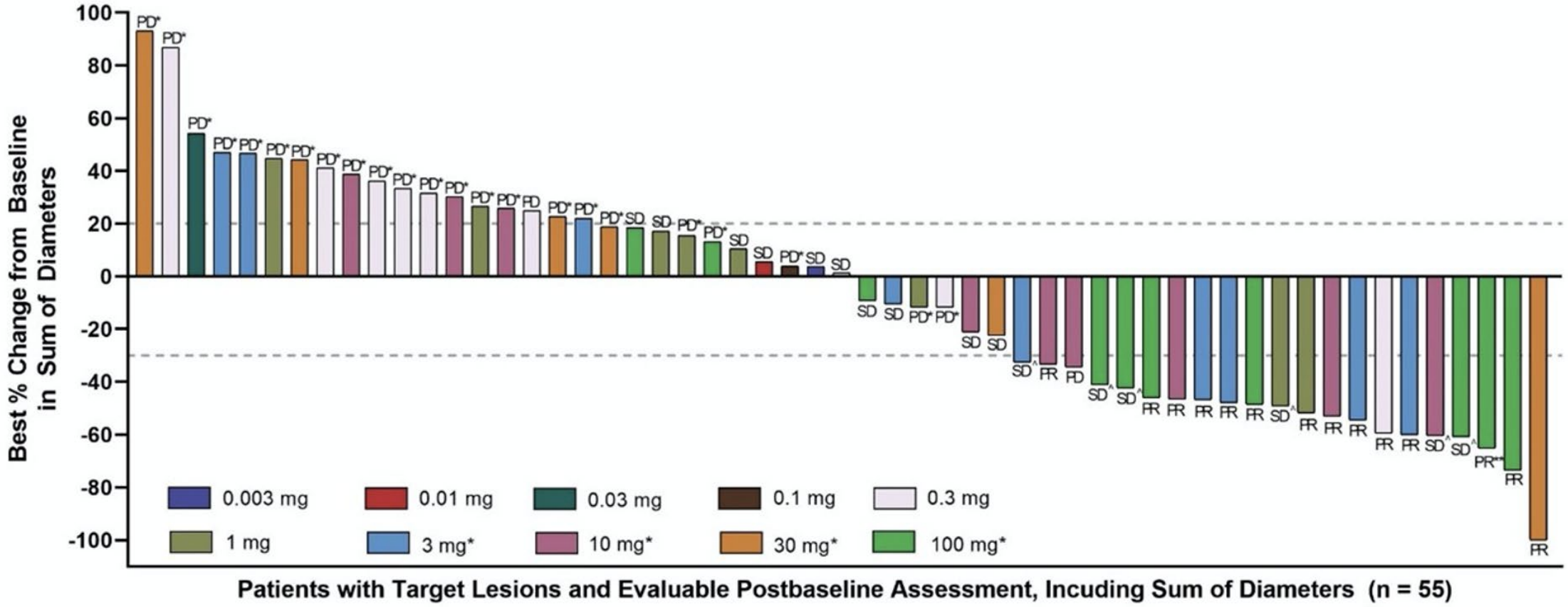


CD, cluster of differentiation; DLL3, delta-like ligand 3; Fc, fragment crystallizable domain; HLE BiTE, half-life extended bispecific T-cell engager; NEPC, neuroendocrine prostate cancer.

AMG 757: HLE BiTE Therapy Targeting DLL3

- AMG 757 is a HLE BiTE® immuno-oncology therapy designed to redirect cytotoxic T cells to tumor cells by binding to DLL3 on cancer cells and CD3 on T cells
- AMG 757 induces T-cell dependent lysis of DLL3-neuroendocrine tumor cell lines, including NEPC cells
- Pre-clinical activity of AMG 757 in NEPC patient-derived models
- Preliminary results of an ongoing first-in-human study suggest that AMG 757 is safe and has anti-tumor activity in patients with small cell lung cancer (SCLC; NCT03319940)

AMG 757 Demonstrates Encouraging Activity in Small Cell Lung Cancer



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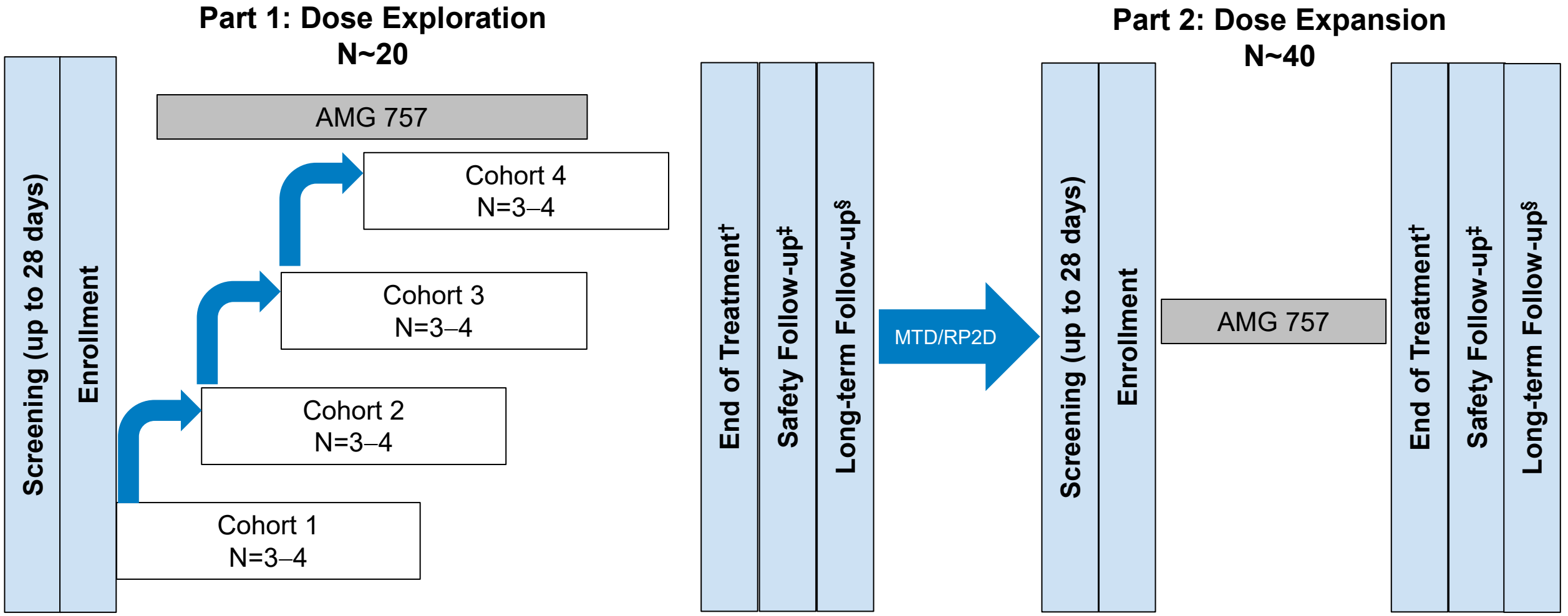
Study Overview

- NCT04702737 is an open-label, phase 1b study evaluating AMG 757 monotherapy in patients with metastatic NEPC that is de novo or treatment-emergent
  - The study consist of two parts: dose exploration and dose expansion

NEPC, neuroendocrine prostate cancer.

Figure 4. Phase 1b AMG 757 in NEPC Study Design



†Within 14 days after the last dose; ‡approximately 35±5 days after the end of the last dose; §every 3 months up to 3 years from the first dose for all patients who have not withdrawn consent
MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

Key Eligibility Criteria

- Adult ≥18 years of age
- Metastatic de novo or treatment-emergent NEPC
  - Histological diagnosis of small cell NEPC, histologic evidence of prostate cancer with neuroendocrine differentiation by IHC, and/or ≥2 alterations in Tp53, RB1, and/or PTEN by immunohistochemistry or genomic analyses of baseline tumor tissue or circulating tumor DNA, **with**
  - Adequate organ function, and no untreated/symptomatic brain metastases
- Progressed on at least 1 line of prior systemic treatment
- Measurable disease per RECIST 1.1 criteria with PCWG3 modifications
- Eastern Cooperative Oncology Group performance status of ≤ 2

NEPC, neuroendocrine prostate cancer; PCWG3, Prostate Cancer Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors.

Objectives

- **Primary Objectives**
  - Evaluate the safety and tolerability of AMG 757 monotherapy
  - Determine the maximum tolerated dose or recommended phase 2 dose of AMG 757
- **Secondary Objectives**
  - Evaluate antitumor activity (ie, objective response, duration of response, progression-free survival, overall response) of AMG 757
  - Characterize the pharmacokinetics of AMG 757
- **Correlative Analyses:**
  - Association between baseline tumor genomic and RNA expression profile with clinical outcomes including DLL3
  - Association between intra-tumoral and peripheral immune cell subsets with outcomes
  - 5-hydromethylcytosine (5-hmc) profiling of serial ctDNA samples

Conclusion

- The differential expression profile of DLL3 on NEPC tumors versus normal tissue makes it a compelling therapeutic target
- Limited standard of care treatment options currently available for this high risk aggressive subset of prostate cancer
- AMG 757 is a HLE BiTE® immuno-oncology therapy designed to engage CD3-positive T cells to DLL3-positive tumor cells and induce T cell activation and proliferation and T cell–dependent tumor lysis
- AMG 757 demonstrates encouraging preliminary activity in SCLC, with confirmed objective response rate of 20% in a heavily pre-treated population
- NCT04702737, a phase 1b study evaluating AMG 757 in patients with NEPC, is planning to open to accrual in 2H 2021

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