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\(^3,4\)

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

<table>
<thead>
<tr>
<th>Adenocarcinoma with neuroendocrine components (Gleason score 5+5)</th>
<th>Small cell carcinoma of the prostate</th>
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<tbody>
<tr>
<td>% Positive Cells</td>
<td>% Positive Cells</td>
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<tr>
<td>80</td>
<td>90</td>
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<tr>
<td>Intensity/H-Score*</td>
<td>Intensity/H-Score*</td>
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<td>65</td>
<td>150</td>
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*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
AMG 757 engages endogenous T cells and NEPC cells

- **Anti-CD3**
- **Anti-DLL3**
- **Fc domain (to extend half-life)**

**T-cell activation**

**Serial lysis of NEPC cells**

**T-cell proliferation**

**Tumor cell apoptosis**

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 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

Owonikoko et al. ASCO 2021
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 consists of two parts: dose exploration and dose expansion

NEPC, neuroendocrine prostate cancer.
Figure 4. Phase 1b AMG 757 in NEPC Study Design

**Part 1: Dose Exploration**

- **N~20**
  - AMG 757
  - Cohort 4
    - N=3–4
  - Cohort 3
    - N=3–4
  - Cohort 2
    - N=3–4
  - Cohort 1
    - N=3–4

**Part 2: Dose Expansion**

- **N~40**
  - AMG 757

**Screening (up to 28 days)**

**Enrollment**

- End of Treatment†
- Safety Follow-up‡
- Long-term Follow-up§
- MTD/RP2D

†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
• 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
Acknowledgments

• Amgen

• Clinical Co-Investigators:
  – Ana Aparicio, MD Anderson
  – Shahneen Sandhu, Peter MacCallum Cancer Centre
  – Axel Heidenreich, University of Cologne

• UCSF collaborators
  – Jonathan Chou
  – Larry Fong