

Volrustomig as single-agent first-line therapy for unresectable pleural mesothelioma: Substudy 5 of the eVOLVE-02 phase 2 study

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Plain language summary

Why are we performing this research?

- Pleural mesothelioma is an aggressive cancer that mainly affects the lining of the lungs and is often linked to previous asbestos exposure. Pleural mesothelioma may develop gradually over time, and symptoms typically appear several decades after exposure to asbestos and other mineral fibers. This means that pleural mesothelioma is often not diagnosed until it has reached an advanced stage when the tumor cannot be completely removed with surgery.
- Although newer treatments such as immunotherapy have improved survival, outcomes remain poor and better treatment options are still needed.
- Volrustomig is a new drug designed to target two proteins, PD-1 and CTLA-4, activating a type of immune cell called T cells to attack cancer cells.

How are we performing this research?

In this study, participants will receive volrustomig as their first treatment. The study will assess how well the treatment works and how safe it is in patients whose cancer cannot be completely removed with surgery (referred to as *unresectable* disease) and who have not received previous drug treatment that affects the whole body (known as *systemic therapy*). Doctors will monitor how the tumor responds to treatment using scans and will assess safety through clinical evaluations and laboratory tests.

Who will participate in this study?

Approximately 75 adults with newly diagnosed pleural mesothelioma that is not suitable for surgery will take part in this study. To be eligible, participants must not have received previous systemic treatment for pleural mesothelioma and must meet specific medical eligibility criteria.

Where can I access more information?

This is an ongoing substudy of the global eVOLVE-02 study and no results are available yet. More information about the eVOLVE-02 study can be found at clinicaltrials.gov/study/NCT06535607. You may also speak to your doctor about clinical studies.

Volrustomig and rationale

- Volrustomig (MEDI5752) is a monovalent, dual checkpoint inhibitor, bispecific, humanized IgG1 monoclonal antibody that has been engineered to achieve coordinated and targeted PD-1 and CTLA-4 blockade on the same T cell (**Figure**), with increased CTLA-4 blockade on PD-1-positive activated T cells compared to PD-1-negative resting T cells.^{12,13}
 - Activated T cells express >10x more PD-1 than CTLA-4 on the cell surface; volrustomig uses PD-1 as an anchor leading to enhanced CTLA-4 blockade *in vitro*.¹²
- The bispecific structure of volrustomig may provide advantages compared to the administration of separate antibodies against PD-1 and CTLA-4 through cooperative binding of both targets on the same activated T cell,¹² including:
 - Preferential localization and accumulation on PD-1-positive activated T cells in the tumor microenvironment, when compared with a combination of monoclonal antibodies targeting PD-1 and CTLA-4.¹²
 - Greater levels of peripheral T-cell activation than seen with approved PD-(L)1 + CTLA-4 combinations.¹³
- Volrustomig in combination with chemotherapy is being evaluated as 1L treatment in patients with unresectable PM in the ongoing phase 3 eVOLVE-Meso trial (NCT06097728).¹⁴
- Volrustomig + carboplatin + pemetrexed has shown promising efficacy with manageable tolerability in 1L NSCLC,¹⁵ and volrustomig monotherapy has shown encouraging efficacy and manageable safety in the first-in-human phase 1 study (NCT03530397) of patients with solid tumors.^{13,16,17}
- Building upon these findings, the phase 2 eVOLVE-02 (NCT06535607) study is evaluating volrustomig as monotherapy or in combination with anticancer agents in patients with advanced/metastatic solid tumors and is currently recruiting.
 - Four substudies are ongoing in patients with cervical cancer (substudy 1), head and neck squamous cell carcinoma (substudies 2 and 3) or PM (substudy 5); substudy 4 in patients with esophageal squamous cell carcinoma is not yet recruiting.
- Substudy 5 of eVOLVE-02, described here, will evaluate the safety and efficacy of volrustomig as monotherapy in patients with untreated unresectable PM.

Figure: Structure of volrustomig, a monovalent, dual checkpoint inhibitor, bispecific antibody^{12,13}

Anti-PD-1

Anti-CTLA-4

eVOLVE-02 (NCT06535607) phase 2 study: Substudy 5

- Substudy 5 is an open-label, single-arm study:

Study population:

- Newly diagnosed unresectable PM with known histology (epithelioid or non-epithelioid)
- WHO/ECOG PS 0–1
- Measurable disease per mRECIST v1.1 (pleural lesions) and/or RECIST v1.1 (metastatic non-pleural lesions)

N≈75

Volrustomig (IV)

until disease progression, unacceptable toxicity, consent withdrawal, or maximum treatment duration is reached

Primary endpoint:

• ORR

Secondary endpoints include:

- PFS, OS, DoR, TTR, DCR
- Safety and tolerability
- PK and immunogenicity

- Tumor assessments:** every 6 weeks (±7 days) from the start of study intervention until Week 48, and every 12 weeks (±7 days) thereafter until radiological disease progression, with a confirmation scan performed ≥4 weeks after initial progression, if applicable.
- Survival assessments:** every 8 weeks (±2 weeks) after the 90-day follow-up visit until 3 years after the start of study intervention, and every 12 weeks (±2 weeks) thereafter until end of study or death.

Key inclusion criteria

- Age ≥18 years.
- WHO/ECOG PS of 0 or 1.
- Histologically confirmed diagnosis of PM with known histology (epithelioid or non-epithelioid).
- Advanced unresectable disease that cannot be treated with curative surgery (with or without chemotherapy).
- Measurable disease per mRECIST 1.1 (pleural lesions) and/or RECIST v1.1 (metastatic non-pleural lesions).
- Adequate organ and bone marrow function at baseline.
- Life expectancy ≥12 weeks.

Key exclusion criteria

- Any prior systemic therapy for PM.
- History of another primary malignancy.
- Active or prior documented autoimmune or inflammatory disorders.
- Untreated or progressive CNS metastatic disease.
- Cardiac conditions including cardiomyopathy, heart failure, uncontrolled hypertension, unstable angina pectoris and cardiac arrhythmia.
- Severe or uncontrolled systemic diseases including ongoing or active infection, ILD, serious chronic GI conditions associated with diarrhea, psychiatric illness/social situations and active bleeding diseases.
- Evidence of infection including active tuberculosis, HIV infection that is not well controlled, active hepatitis A, and active or uncontrolled hepatitis B or hepatitis C.
- Any concurrent chemotherapy, radiotherapy, investigational, biologic, or hormonal therapy for cancer treatment.
- Prior exposure to immune-mediated therapy including other anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies.

Background

- Pleural mesothelioma (PM) is a rare, aggressive, and difficult-to-treat cancer, often linked to previous asbestos exposure.¹
 - Most patients with PM generally present with advanced disease, and even in early stages, curative intent surgery to achieve margin-negative resection is often not possible.^{2,3} Overall, approximately 75–80% are diagnosed with unresectable disease.^{3,4}
 - The median survival for untreated PM is approximately 4–12 months^{5–7} with fewer than 5% of patients surviving to 5 years.⁷
- Until recently, 1L SoC for unresectable PM was pemetrexed plus platinum (± bevacizumab); it has since evolved to include immune checkpoint therapy.^{2,8}
 - Phase 3 studies have demonstrated significant improvements in survival outcomes for patients receiving anti-PD-1 therapies in combination either with an anti-CTLA-4 therapy or with chemotherapy, versus chemotherapy alone; the greater benefit has been observed in non-epithelioid disease, which may inform preferred treatment by histology.^{9–11}
 - Recommended 1L treatment for unresectable PM includes nivolumab + ipilimumab or pembrolizumab with pemetrexed and platinum-based chemotherapy, regardless of histology, while pemetrexed plus platinum (± bevacizumab) also remains a preferred option.^{2,6,8}
- There is still significant unmet need given the ongoing poor prognosis; further study is needed to optimize dual checkpoint approaches across histologic subtypes and refine regimen selection.

Study status

- Enrollment is planned at sites in 8 countries/regions.
- Currently recruiting; approximately 75 participants will be recruited.

Poster

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Abbreviations

1L, first line; CNS, central nervous system; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HIV, human immunodeficiency virus; IgG1, Immunoglobulin G1; ILD, interstitial lung disease; IV, intravenous; mRECIST, modified RECIST; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand-1; PFS, progression-free survival; PK, pharmacokinetics; PM, pleural mesothelioma; RECIST, Response Evaluation Criteria in Solid Tumors; SoC, standard of care; TTR, time to response; WHO, World Health Organization.

Acknowledgements

This study is sponsored by AstraZeneca. Medical writing support, under the direction of the authors, was provided by Ifigeneia Mavragani, PhD, of Ashfield MedComms (London, UK), an Inizio company, and funded by AstraZeneca.

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Disclosures

Michael Offin reports consulting roles/honorarium with Novartis, Jazz, Pfizer, Servier, Vivace, Targeted Oncology, DAVA Oncology, Cardinal Health, OnLive, MJH, American Society for Radiation Oncology; grant support from the Druckenmiller Foundation, Department of Defense, and LUNgevity Foundation; uncompensated scientific advisory board member for the Mesothelioma Applied Research Foundation and elected Member of the IASLO Rare Tumor Committee.

References

1. Roca E, et al. *Curr Oncol* 2024;31:4968–83.

2. Kindler HL, et al. *J Clin Oncol* 2018;36:1343–73.

3. Taioli E, et al. *PLoS One* 2015;10:e0145039.

4. Saddoughi SA, et al. *Ann Thorac Surg* 2018;105:432–7.

5. Bou-Samra P, et al. *Cancer Med* 2023;12:12208–20.

6. Cedres S, et al. *Cancers (Basel)* 2023;15:5787.

7. Schumann SO, et al. *J Thorac Dis* 2021;13:2510–23.

8. Popat S, et al. *Ann Oncol* 2022;33:129–42.

9. Baas P, et al. *Lancet* 2021;397:375–86.

10. Peters S, et al. *Ann Oncol* 2022;33:488–99.

11. Chu QS, et al. *J Clin Oncol* 2023;41(Suppl 17):LBA8505.

12. Dovedi SJ, et al. *Cancer Discov* 2021;11:1100–17.

13. Tran B, et al. *Clin Cancer Res* 2026;32:2850–64.

14. Scherpereel A, et al. *J Thorac Oncol* 2024;19(10 Suppl):S281.

15. Ahn M-J, et al. *Ann Oncol* 2022;33(Suppl 7):S1423.

16. Albiges L, et al. *J Clin Oncol* 2022;40(Suppl 16):107.

17. Voss MH, et al. *Ann Oncol* 2023;34(Suppl 2):S1012.