A Phase 2 Study of Magrolimab Combination Therapy in Patients with Recurrent or Metastatic Head and Neck Squamous-Cell Carcinoma (ELEVATE HNSCC)

TPS6102

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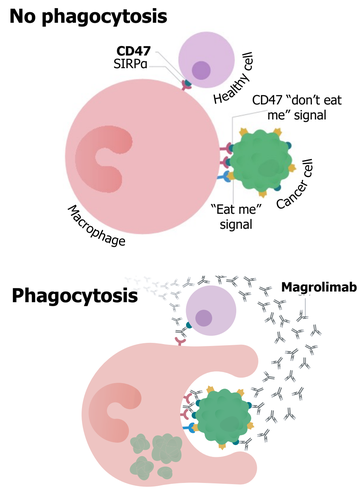
Introduction

- Novel combination therapies are needed to extend the survival of patients with recurrent or metastatic head and neck squamous-cell carcinoma (RM-HNSCC).
- Magrolimab is a humanized monoclonal antibody that blocks the immune checkpoint cluster of differentiation 47 (CD47), a "do not eat me" signal, which is overexpressed on cancer cells.[1,2]
- Magrolimab binding to CD47 leads to phagocytosis of cancer cells and enhances antitumor efficacy through stimulation of both innate and adaptive immune responses.[1]
- This study (NCT04854499) is investigating the safety, tolerability, recommended Phase 2 dose (RP2D), and efficacy of up to four magrolimab-containing regimens in patients with RM-HNSCC:
  - Magrolimab + pembrolizumab (pembro) + platinum + 5-fluorouracil (5-FU)
  - Magrolimab + zimberelimab (zim) + platinum + 5-FU
  - Magrolimab + docetaxel
  - Magrolimab + pembro

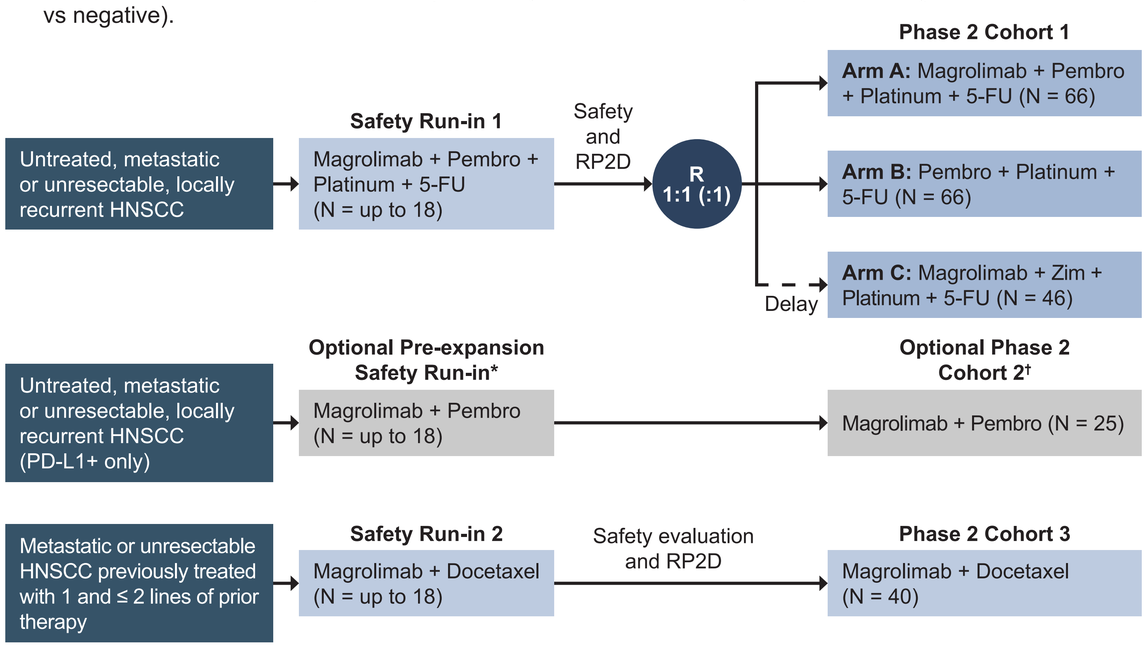
Magrolimab Mechanism of Action[2]



SIRPα, signal-regulatory protein alpha.

Study Design

- This is a Phase 2, open-label, multicenter study consisting of two safety run-in cohorts and two Phase 2 cohorts (with an additional optional Phase 2 cohort).
- Patients in Phase 2 Cohort 1 will be randomized in a 1:1 ratio for Arms A and B. Once 20 patients are enrolled into each arm, a third arm (Arm C) will open, and randomization will continue 1:1:1 across all 3 arms.
  - Zim is a fully human IgG4 mAb-targeting human PD-1.[3,4]
  - Arm C will determine safety and efficacy of zim compared to standard pembro-combination in RM-HNSCC.
- Randomization stratified by: PD-L1 expression (CPS ≥ 1 vs CPS < 1) and p16 status (positive vs negative).



*A pre-expansion safety run-in evaluation of magrolimab + pembro may be conducted at the sponsor's discretion if additional dose finding for magrolimab + pembro is needed. †Optional cohort to be opened at the discretion of the sponsor. CPS, combined positive score; IgG4, immunoglobulin G4; mAb, monoclonal antibody; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; RP2D, recommended phase 2 dose; zim, zimberelimab.

Key Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
All Patients — Adults ≥ 18 years, ECOG performance status ≤ 1, measurable disease by RECIST 1.1, and adequate marrow and organ function **Safety Run-in 1 and Phase 2 Cohorts 1 and 2** — Untreated metastatic or locally recurrent HNSCC incurable by local therapies ▪ Phase 2 Cohort 1: regardless of PD-L1 status ▪ Phase 2 Cohort 2: PD-L1 CPS ≥ 1 **Safety Run-in 2 and Phase 2 Cohort 3** — Locally advanced/metastatic HNSCC regardless of PD-L1 status with 1-2 lines of prior systemic therapy	**All Patients** — History of hemolytic anemia, autoimmune thrombocytopenia, or Evans syndrome — Prior CD47 or SIRPα-targeting agents — Diagnosis of immunodeficiency; active autoimmune disease that has required systemic treatment **Safety Run-in 1 and Phase 2 Cohorts 1 and 2** — Progressive disease within 6 months of CD47, cluster of differentiation 47; curatively intended systemic treatment for locoregionally advanced HNSCC — Prior treatment with anti–PD-1, anti–PD-L1, or anti-CTLA4 checkpoint inhibitors **Safety Run-in 2 and Phase 2 Cohort 3** — Progressive disease within 6 months of curatively intended systemic treatment for locally advanced/metastatic HNSCC — Prior taxane

CTLA4, cytotoxic T-lymphocyte–associated protein 4; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; SIRPα, signal regulatory protein alpha.

Objectives

Primary
- Determine safety, tolerability, RP2D of up to four magrolimab-containing combinations
- Determine efficacy of magrolimab combinations: PFS by ICR (Phase 2 Cohort 1, Arm A vs B) and investigator-assessed ORR (Phase 2 Cohorts 2 and 3)

Secondary
- PK and immunogenicity (Safety Run-in and Phase 2 Cohorts)
- PFS (investigator-assessed and by ICR)
- ORR by ICR
- DoR, OS
- PROs

Exploratory
- Evaluate pharmacodynamic, MOA, and/or therapeutic response biomarkers
- Explore biomarkers that may predict response to therapy

DoR, duration of response; ICR, independent central review; MOA, mechanism of action; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PROs, patient-reported outcomes; RP2D, recommended phase 2 dose.

Endpoints

Primary Endpoints

Safety Run-in Cohorts
- Incidence of AEs and laboratory abnormalities

Phase 2 Cohorts
- PFS by ICR (Cohort 1, Arm A vs Arm B)
- ORR by RECIST 1.1, investigator assessed (Cohorts 2 and 3)

Secondary Endpoints

Safety Run-in Cohorts
- Magrolimab concentration vs time; ADAs

Phase 2 Cohorts
- PFS (Cohort 1, Arm C vs Arm B)
- ORR by ICR, DOR, OS
- PFS by investigator assessment
- Magrolimab concentration vs time; ADAs
- PRO assessments*

Exploratory Endpoints
- Zim concentration vs time and ADAs to zim
- Change in biomarkers in blood and tumor biopsy samples
- Correlation of clinical response with biomarkers at baseline and/or on treatment

*EORTC-QLQ, EQ-5D-5L.
ADA, antidrug antibody; AE, adverse event; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol Group 5-Dimension, 5-Level Instrument.

Statistical Considerations

Sample Size Calculation:

Phase 2 Cohort 1: 66 patients per group (Arm A vs Arm B; 93 PFS events) provides 75% power; 46 patients per group (Arm C vs concurrent Arm B; 61 PFS events) provides 64% power at 1-sided alpha of 0.15 to detect a hazard ratio of 0.7 using unstratified log-rank test.

Phase 2 Cohort 3: 40 patients provides 83% power at 1-sided alpha of 0.15 to detect an ORR of 18% compared with a null ORR of 7.9% using a chi-squared test.

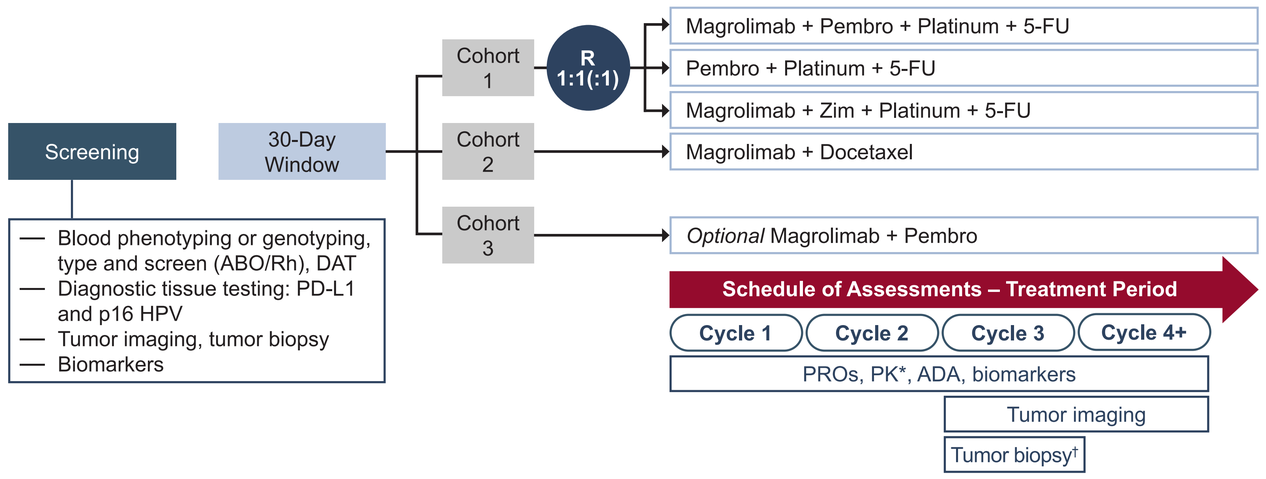
Primary Efficacy Endpoint Analyses: PFS will be analyzed using the Kaplan–Meier method; ORR with 95% confidence interval will be estimated based on the Clopper–Pearson method.

Treatment: Dosing and Schedule

Safety Run-in and Phase 2 Cohorts				
Drug/Dose/Route		**Magrolimab Administration**		
Magrolimab*	1 mg/kg IV	Day 1		
	30 mg/kg IV	QW × 5 weekly doses		
	60 mg/kg IV†	Q3W beginning 1 week after the 5 weekly 30 mg/kg doses		
		Cycle 1§	**Cycle 2**	**Cycle 3+**
Pembro	200 mg IV	Day 1	Day 1	Day 1
5-FU	1000 mg/m²/day continuous IV	Days 1-4	Days 1-4	Days 1-4 (Cycles 3-6)
Cisplatin or carboplatin	100 mg/m² IV AUC 5 IV	Day 1	Day 1	Day 1 (Cycles 3-6)
Zim‡	360 mg IV	Day 1	Day 1	Day 1
Docetaxel	75 mg/m² IV	Day 1	Day 1	Day 1

*Maintenance dose in Phase 2 cohorts will be the RP2D determined in safety run-in cohorts. †Patients enrolled under the initial protocol received a maintenance dose of 45 mg/kg, which was increased to 60 mg/kg in the latest amendment. ‡Zim for Phase 2 Cohort 1, Arm C only. §Days based on 21-day cycle.
AUC, area under curve; IV, intravenous; QW, every week; Q3W, every 3 weeks.

Key Assessments and Timing



*PK for magrolimab on C1D8, C2D1, and for magrolimab and zim on Day 1 of Cycles 3+. †The Cycle 3 tumor biopsy can be collected any time between Cycle 3 Day 1 and Cycle 4 Day 1.
ABO, any of the 4 blood groups (A, B, AB, and O); DAT, direct antiglobulin test; HPV, human papillomavirus; Rh, Rhesus factor.

Enrollment: The study opened to accrual in September 2021 and is currently recruiting participants. Planned enrollment is approximately 230 patients, up to 297. NCT04854499.

References: **1.** Liu J, et al. *PLoS One*. 2015;10(9):e0137345. doi:10.1371/journal.pone.0137345. **2.** Chao MP, et al. *Front Oncol*. 2020;9:1380. doi:10.3389/fonc.2019.01380. **3.** Wu X, et al. *Int J Gynecol Cancer*. 2020;30(suppl 3):A147. Abstract 357. doi:10.1136/ijgc-2020-IGCS.307. **4.** Lin N, et al. *Eur J Cancer*. 2021; https://doi.org/10.1016/j.ejca.2021.07.021.

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