ROMAN: Reduction in Oral Mucositis with Avasopasem Manganese (GC4419) – Phase III Trial in Patients Receiving Chemoradiotherapy for Locally Advanced, Nonmetastatic Head and Neck Cancer

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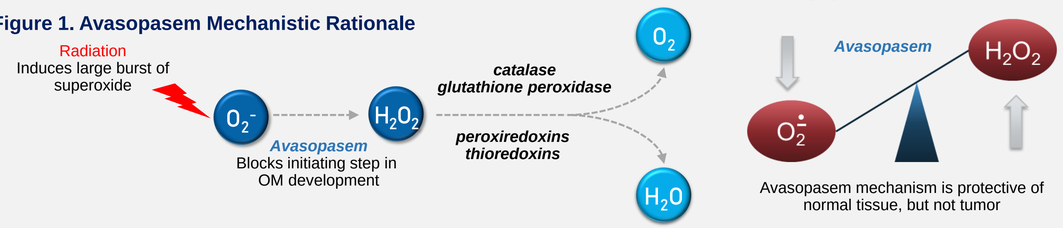
Background

- ~70% of patients receiving concurrent intensity-modulated radiotherapy (IMRT)/cisplatin for head and neck cancer (HNC) develop severe oral mucositis (SOM)[1-3]
- Radiotherapy (RT)-induced burst of superoxide initiates oral mucositis (OM)[4]
- Avasopasem, a superoxide dismutase mimetic, interrupts this process by converting superoxide to H_2O_2[5–6] **(Figure 1)**

Figure 1. Avasopasem Mechanistic Rationale



- Avasopasem showed promising reduction of SOM in an open-label Phase Ib/IIa trial[5]
  - Doses of 30 mg and 90 mg selected for future trials
- SOM duration and incidence reduced in a randomized, double-blind, placebo-controlled trial (**Figures 2** and **3**)[6]
- Tumor outcomes were maintained for 2 years (**Figure 4**)[7]
- Safety results were acceptable and consistent with the known toxicities of IMRT/cisplatin[6]

Breakthrough Therapy Designation – Granted February 2018

Figure 2. 223-Patient Randomized Phase IIb OM Trial Design[6]

Treatment	• Avasopasem 90 mg, 30 mg, or placebo • 60-minute IV infusion, Mon–Fri • Ending <60 mins pre-RT
Population	• Locally advanced HNC • Eligible for SoC – 7 weeks IMRT + cisplatin (definitive or postoperative)
Stratification Factors	• Cisplatin schedule: q3wks or weekly • Tumor HPV status: positive or negative

Randomize (1:1:1)

- Avasopasem 90 mg x 7 weeks
- Avasopasem 30 mg x 7 weeks
- Placebo x 7 weeks

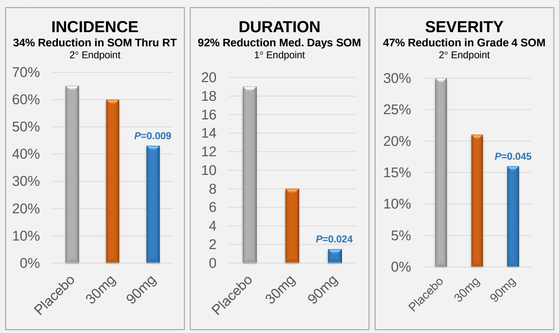
WHO Grading Scale

No ulcers Erythema and soreness	1
Ulcers Able to eat a solid diet	2
Ulcers Requires a liquid diet	3
Ulcers Unable to eat or drink	4

SEVERE

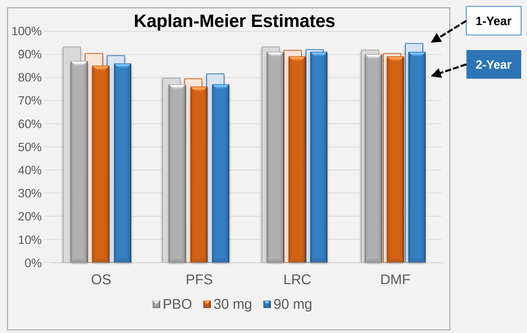
HNC, head and neck cancer; IMRT, intensity-modulated radiotherapy; mins, minutes; OM, oral mucositis; RT, radiotherapy; SoC, standard of care.

Figure 3. Consistent Efficacy Across SOM Parameters[6]



Duration primary: nonparametric test 90 mg vs placebo significant. Duration of SOM defined as number of days from OM score of 3 or 4 to the first score of 2 or less with no subsequent score of 3 or 4. Nominal *P* values compared to placebo for the prespecified severity and incidence secondary endpoints. Efficacy assessed on intent-to-treat population (N=223). OM, oral mucositis; RT, radiotherapy; SOM, severe oral mucositis.

Figure 4. Tumor Outcomes Maintained 1 and 2 years[7]



Final analysis (ITT population).
DMF, free of distant metastases; ITT, intent-to-treat; LRC, locoregional control; OS, overall survival; PBO, placebo; PFS, progression-free survival.

ROMAN Phase III Trial: Reduction in OM with Avasopasem in Patients Receiving Chemoradiotherapy for HNC (NCT03689712)

Trial Design (N=450)

Treatment	• Avasopasem 90 mg or placebo • 60-minute IV infusion, Mon–Fri • Ending <60 mins pre-RT
Population	• Locally advanced HNC • Eligible for SoC – 7 weeks IMRT + cisplatin (definitive or postoperative)
Stratification Factors	• Cisplatin schedule: q3wks or weekly • Surgery status: definitive or postoperative

Randomize (3:2)

- Avasopasem 90 mg x 7 weeks
- Placebo x 7 weeks

WHO Grading Scale

No ulcers Erythema and soreness	1
Ulcers Able to eat a solid diet	2
Ulcers Requires a liquid diet	3
Ulcers Unable to eat or drink	4

SEVERE

HNC, head and neck cancer; IMRT, intensity-modulated radiotherapy; mins, minutes; OM, oral mucositis; RT, radiotherapy; SoC, standard of care; SOM, severe OM.

Primary Endpoint

- Cumulative incidence of SOM defined as any occurrence of WHO Grade 3/4 OM, from the first IMRT fraction until the end of the study treatment period (last IMRT fraction)

Secondary Efficacy Endpoints

- Cumulative incidence of Grade 4 OM from first dose of IMRT through end of treatment period
- Total number of days of SOM during the observation period for all patients
- Total number of days of Grade 4 OM

Additional Endpoints

- Safety of avasopasem
- Effect of treatment assignment on tumor outcomes

Key Inclusion Criteria

- ✓ Locally advanced squamous cell carcinoma of oral cavity or oropharynx
- ✓ Treatment plan calls for standard IMRT/cisplatin
- ✓ ≥2 oral mucosal sites within 50 Gy isodose line of initial RT plan
- ✓ Definitively or postoperatively treated patients eligible
- ✓ Age 18+
- ✓ ECOG PS 0–2
- ✓ Acceptable renal, hepatic, hematologic function

Key Exclusion Criteria

- ✗ Tumor of the lips, larynx, hypopharynx, nasopharynx, sinuses, or salivary glands
- ✗ Distant metastasis
- ✗ Presence of OM at baseline
- ✗ Inability to eat soft solid food for reasons other than mouth soreness after surgery or dental procedures
- ✗ Complete reliance on parenteral or gastrointestinal tube-delivered nutrition at baseline[a]
- ✗ Prior induction chemotherapy
- ✗ Prior RT to cancer region or adjacent anatomical sites or >25% of total body marrow-bearing area
- ✗ Concurrent approved or investigational anticancer agent
- ✗ Female patients who are pregnant or breastfeeding
- ✗ Requirement for concurrent treatment with nitrates or other drugs that may create a risk for a precipitous decrease in blood pressure

[a]Patients who have gastrostomy tubes prophylactically placed are eligible. Patients receiving supplemental nutrition through a gastrostomy tube at baseline may be eligible depending on diet.
ECOG PS, Eastern Cooperative Oncology Group performance status; IMRT, intensity-modulated radiotherapy; OM, oral mucositis; RT, radiotherapy.

Treatment Plan

- **Standard IMRT/cisplatin**
  - IMRT: 2 Gy/fraction, M–F, total 60–72 Gy
  - Cisplatin: investigator choice
    - Q3weeks x 3 doses at 100 mg/m^2
    - Q weekly x 6–7 doses at 40 mg/m^2
- **Avasopasem/Placebo**
  - 60-minute IV infusion M–F before each IMRT fraction

Major Study Evaluations

- **OM evaluation**
  - WHO scoring 2x/week during RT, weekly x 2 weeks post-RT
  - Trained investigator-evaluators
- **Sparse pharmacokinetic sampling**
- **Post-RT follow up for tumor outcomes**

Sample Size/Statistics

- N=450
- 3:2 randomization favoring avasopasem arm
- Stratification at randomization
  - Assigned cisplatin schedule (q3weeks vs weekly)
  - Treatment setting (definitive vs postoperative)
- Primary endpoint: Cochran-Mantel-Haenszel test, 2-sided alpha 0.05

Status

- Enrolling: first patient enrolled October 2018
- Recruiting: US and Canada
- NCT03689712

Conclusions

- SOM is a critical problem in patients with HNC treated with IMRT
- In a Phase IIb trial, avasopasem (90 mg) demonstrated significant reduction in the duration and meaningful reduction in the incidence and severity of SOM
- Confirmatory Phase III trial (“ROMAN”) is in progress

REFERENCES

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