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Henry B. González Convention Center
San Antonio, Texas
Welcome

Tumor Outcomes for ROMAN: Phase 3 Trial of Avasopasem Manganese (GC4419) for Severe Oral Mucositis (SOM) in Patients Receiving Chemoradiotherapy (CRT) for Locally Advanced Head and Neck Cancer (LAHNC)

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Disclosures

- Employment – University of Iowa Hospitals & Clinics
- Uncompensated Research Advisor for Galera Therapeutics, Inc.
- Will discuss Investigational Use of a drug

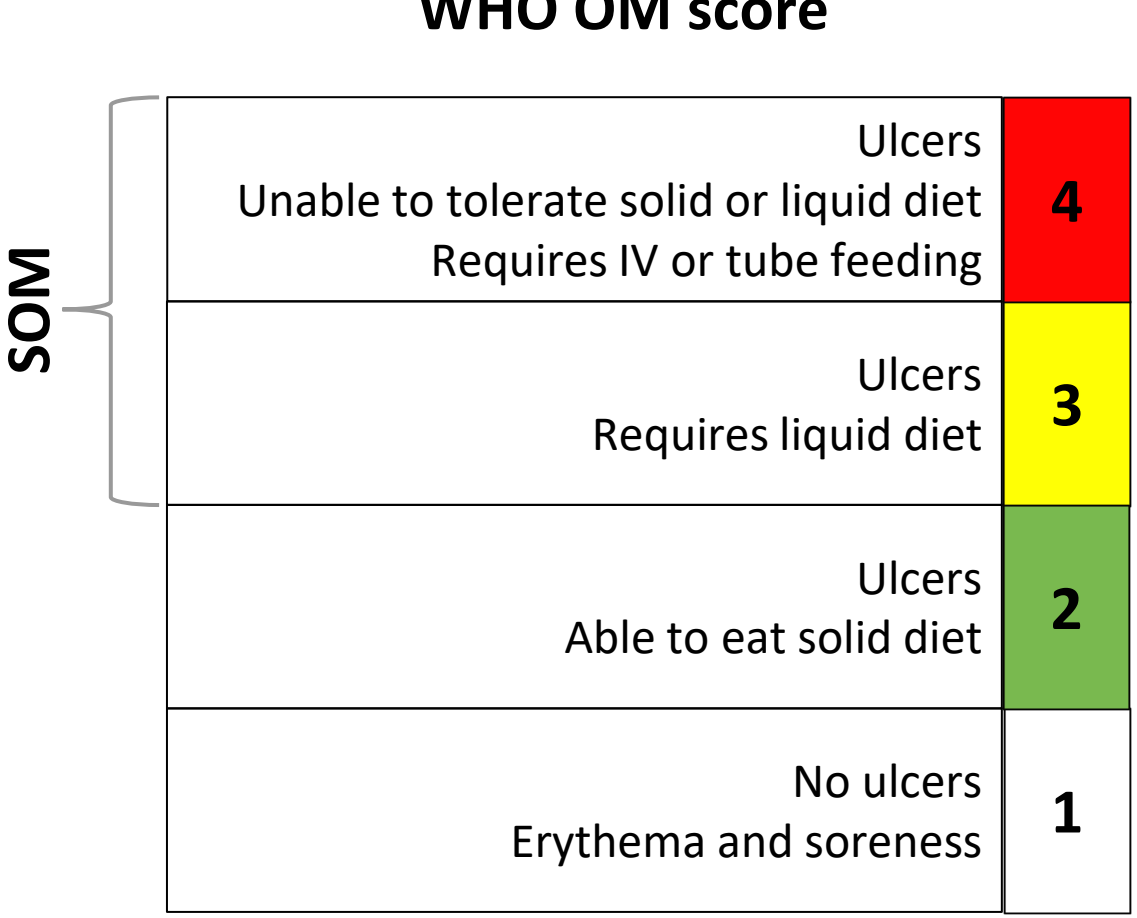
Learning Objectives

To gain an understanding of the phase 3 ROMAN trial including:

- Study design and patient population
- Avasopasem reduction of chemoradiotherapy-related Severe Oral Mucositis in patients with Locally Advanced Head and Neck Cancer
- Long-term outcomes
  - Tumor control
  - Avasopasem reduction of cisplatin-related Chronic Kidney Disease
- Safety and most frequent adverse events

Background

- IMRT + cisplatin SoC for LAHNC
- ~70% of patients develop SOM (WHO grade 3 or 4)
  - Grade 4 OM: ~20–25%
  - Median duration: 3–4 weeks
  - Median onset: ~40 Gy
- WHO score: combines anatomic, symptomatic, functional aspects into one OM severity score
- No FDA-approved HNC SOM drugs



1. Henke M et al. *J Clin Oncol* 2011;29:2815–20; **2.** Le QT et al. *J Clin Oncol* 2011;29:2808–14; **3.** Kudrimoti MA et al. *J Biotechnol* 2016;239:115–25.
FDA, United States Food and Drug Administration; IMRT, intensity-modulated radiation therapy; LAHNC, locally advanced head and neck cancer; OM, oral mucositis; SoC, standard of care; SOM, severe OM; WHO, World Health Organization.

Avasopasem Manganese (AVA, GC4419)

- Investigational new drug product
- Selective small molecule dismutase mimetic
- Converts RT-induced superoxide to hydrogen peroxide
- Protects normal cells, but not cancer cells, from RT
  - Superoxide initiates tissue damage & inflammatory cascade → OM

1. El-Mahdy MA et al. *Free Radic Biol Med* 2020;160:630–42; **2.** Riley DP and Schall OF. *Adv Inorg Chem* 2006;59:233–63.
OM, oral mucositis; RT, radiation therapy.

Promising Phase 2b SOM Data

Anderson, *JCO* 2019

Avasopasem manganese 90 mg appeared to reduce SOM

- SOM duration reduced (*P*=0.024)
- SOM incidence through IMRT reduced (*P*=0.009*)
  - Grade 4 OM incidence reduced (*P*=0.045*)
- Adverse event profile comparable, avasopasem vs placebo arm
- Tumor outcomes maintained at 1 & 2 years, avasopasem vs placebo
  - Anderson, *IJROBP* 2022
- Avasopasem manganese 30 mg appeared to be intermediate in effect between 90 mg and placebo

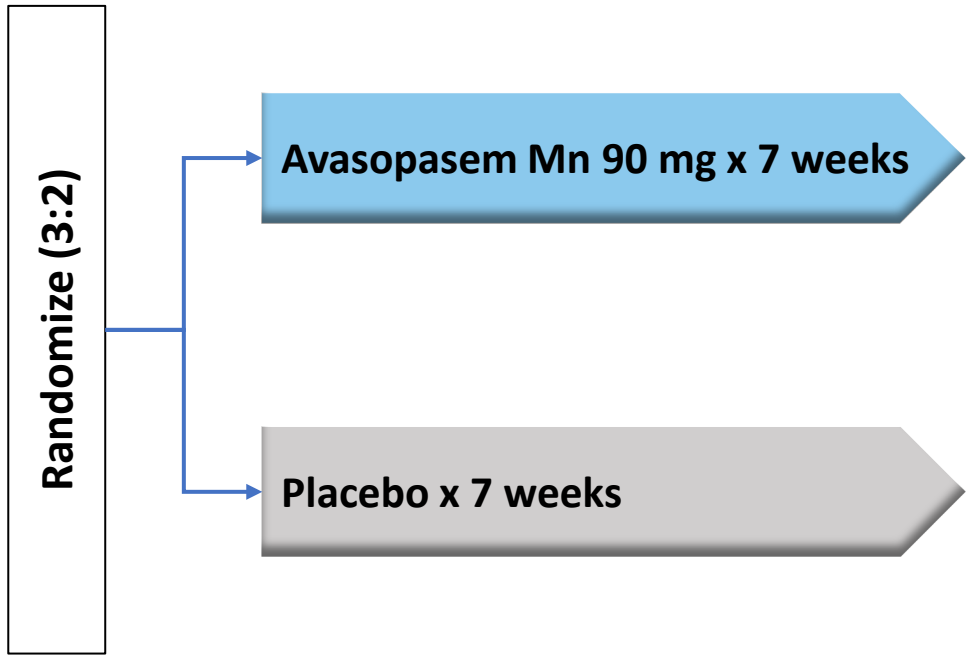
* Nominal *P* value not formally tested.
IMRT, intensity-modulated radiation therapy; OM, oral mucositis; SOM, severe OM.

ROMAN: Phase 3
90 mg Avasopasem Manganese vs Placebo

Reduction in Oral Mucositis with Avasopasem Manganese

GT-301: The ROMAN Trial

Population	• Oral cavity/oropharynx tumor • Locally advanced, squamous cell • Eligible for SoC: 7 weeks IMRT + cisplatin
Treatment	• Avasopasem Mn 90 mg or placebo • 60-minute IV infusion, Mon-Fri • Ending ≤60 mins pre-RT
Stratification factors	• Surgery status: post-op or definitive • Cisplatin schedule: q3wks or weekly



WHO scoring by trained investigator–evaluators, QC'd process BIW during RT then QW x 2

BIW, twice a week; IMRT, intensity-modulated RT; IV, intravenous; QW, once weekly; q3wks, once every three weeks; RT, radiation therapy; SoC, standard of care; WHO, World Health Organization.

ROMAN Endpoints

Primary endpoint

- Incidence of SOM through IMRT
  - Cochrane-Mantel-Haenszel relative risk calculated

Secondary efficacy endpoints

Holm-Bonferroni correction for multiple comparisons

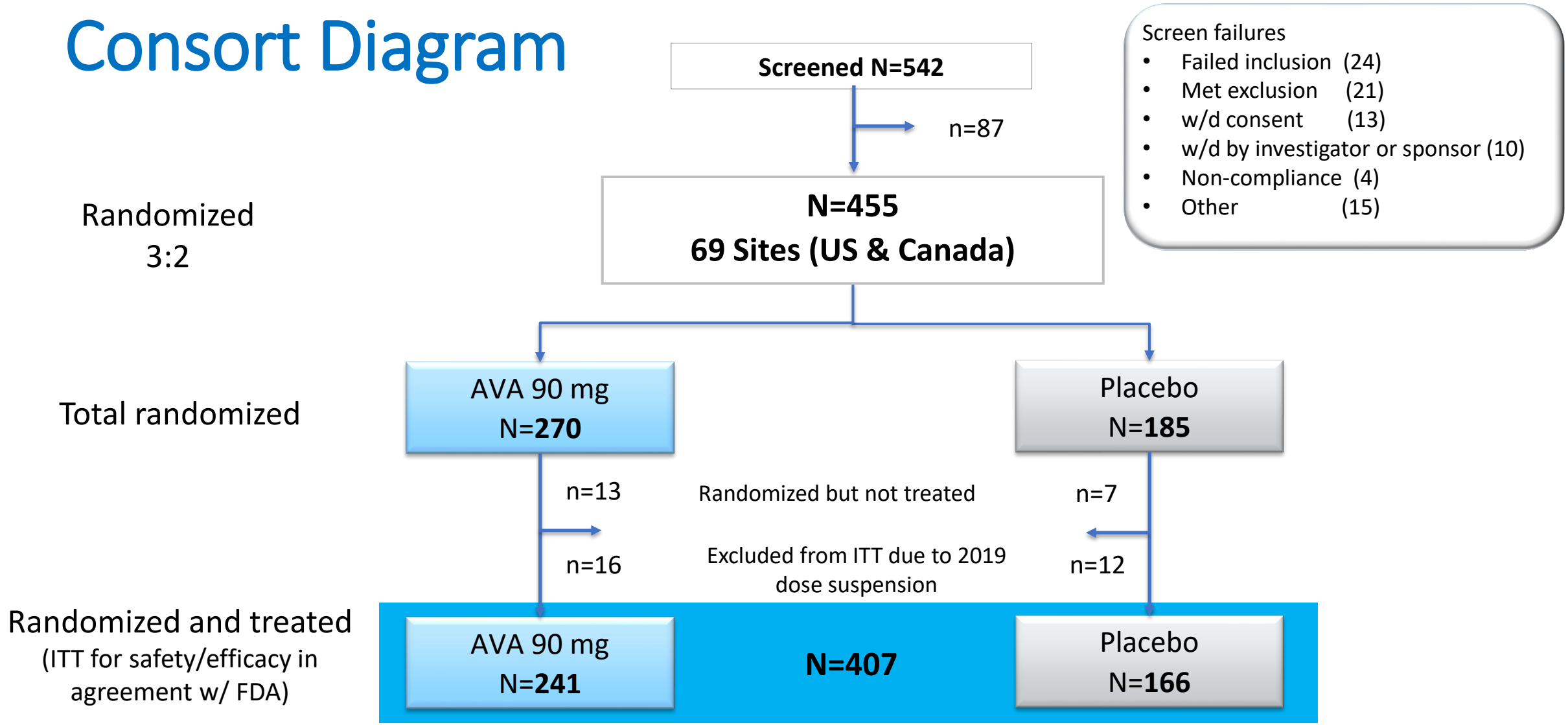
- Total number of days of SOM ("duration" in phase 2b)
  - In all patients
  - 0 days for patients w/o SOM
- Incidence & total number of days of grade 4 SOM

Additional endpoints

- Safety and tolerability
- Tumor outcomes: LRC, DM, PFS - 1 year; OS – 1 & 2 years
- Renal function: 1 year

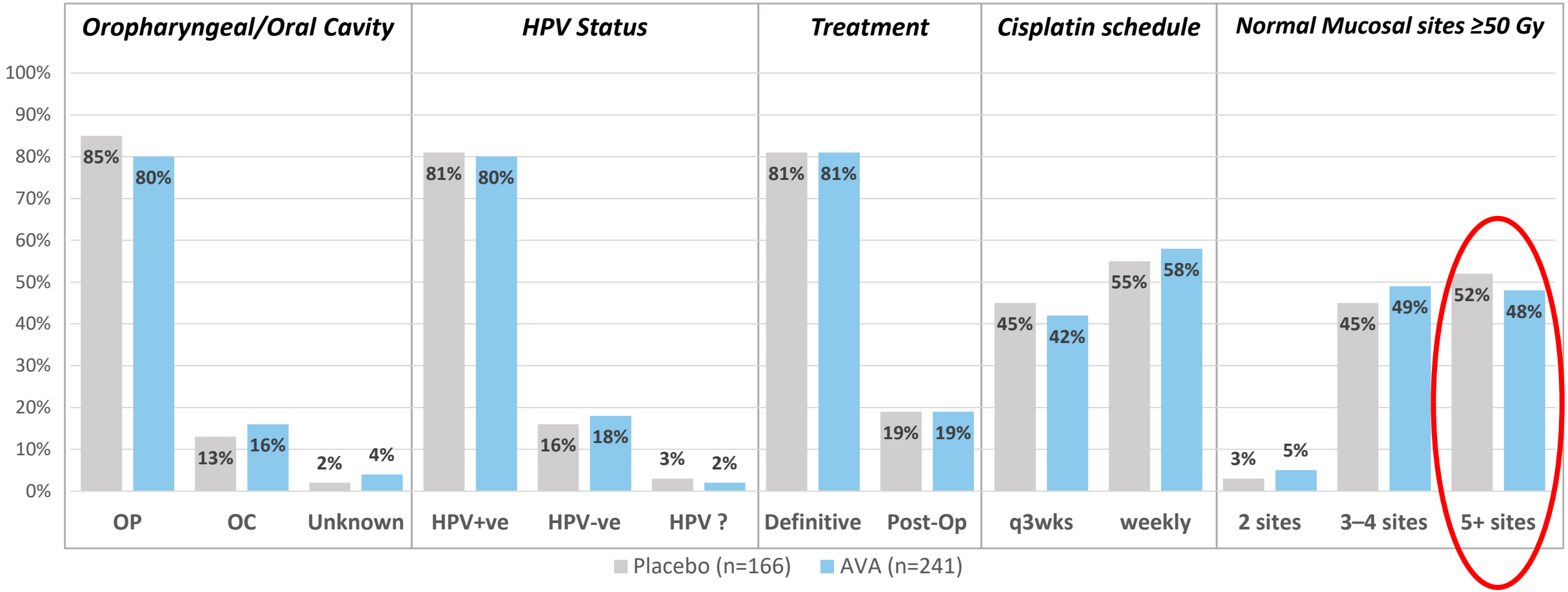
DM, distant metastasis; IMRT, intensity-modulated radiation therapy; LRC, locoregional control; OS, overall survival; PFS, progression-free survival; SOM, severe oral mucositis.

Consort Diagram



AVA, avasopasem Mn; FDA, United States Food and Drug Administration; ITT, intent-to-treat population.

Patient Characteristics



HPV, human papillomavirus; qw, once weekly; q3wks, once every three weeks.

ROMAN: Phase 3 Results

Treatment Adherence

ITT Population

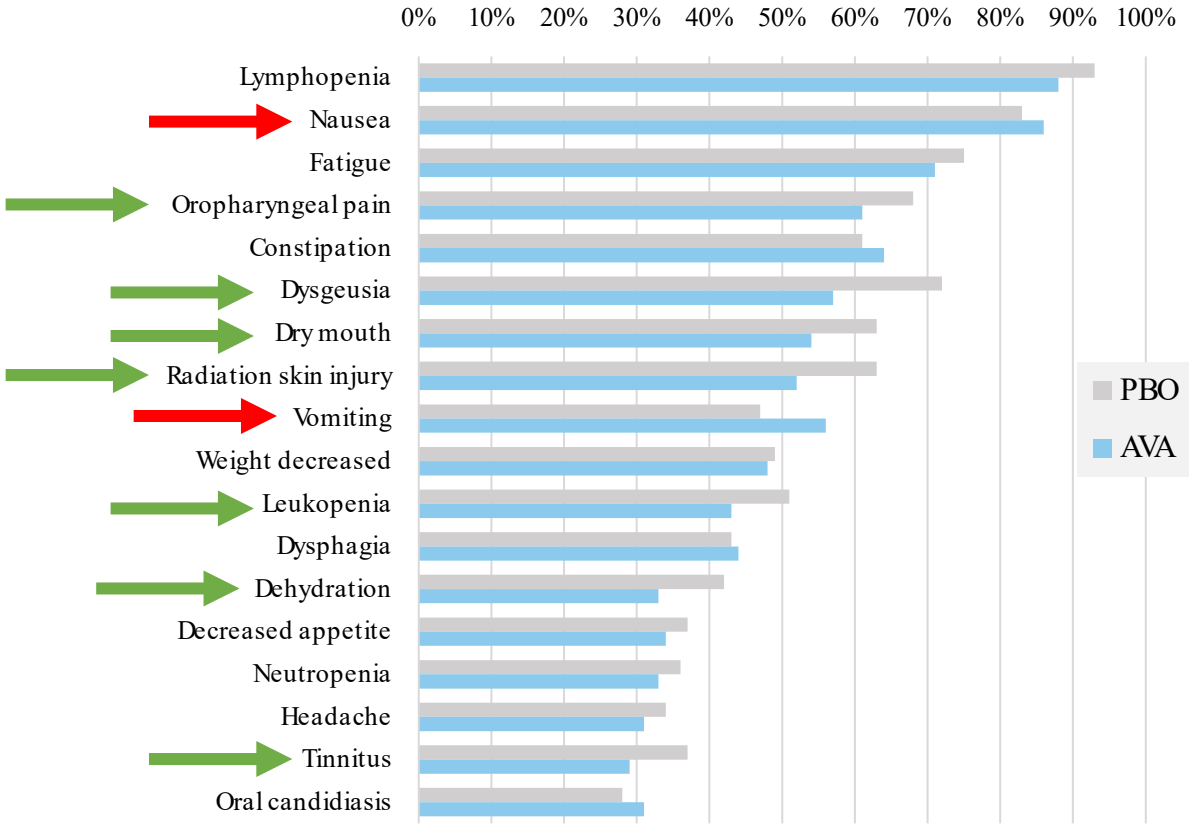
	Avasopasem (N=241)	Placebo (N=166)
IMRT mean/median total dose (range)	64.4/70 (8-70)	68.2/70 (13-71)
% with RT breaks > 5 consecutive fractions	8	10
Cisplatin median relative dose intensity, % • Q3wks • Qw	 90 99	 88 97
Planned avasopasem/placebo doses received • Median/Mean, % • Permanently stopped dosing for adverse event, % • Dose reductions[a], % - One - Two	 100/87 10 10 6	 100/96 7 5 1

[a]Dose reductions were 25% of the starting dose.

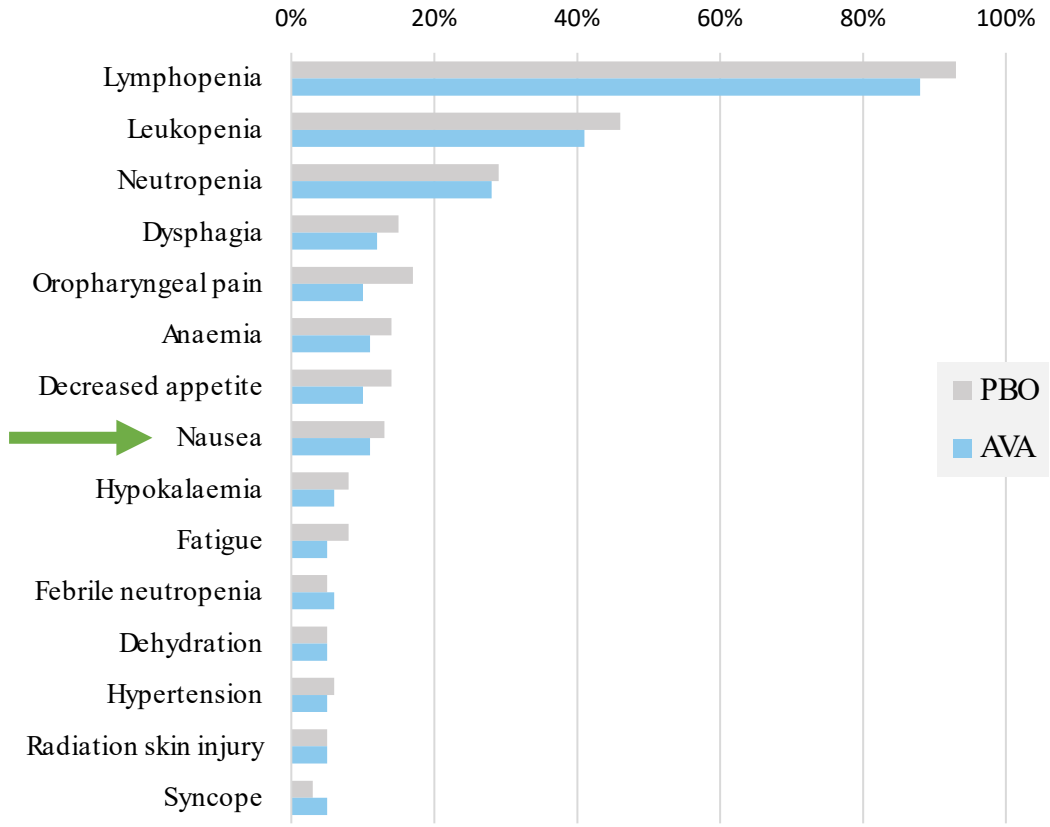
Gy, gray; IMRT, intensity-modulated radiation therapy; ; ITT, intent-to-treat; qw, once weekly; q3wks, once every three weeks RT, radiation therapy.

Most Frequent Adverse Events

Adverse events[a] (all grades, all causes)



Adverse events[a] grades ≥3

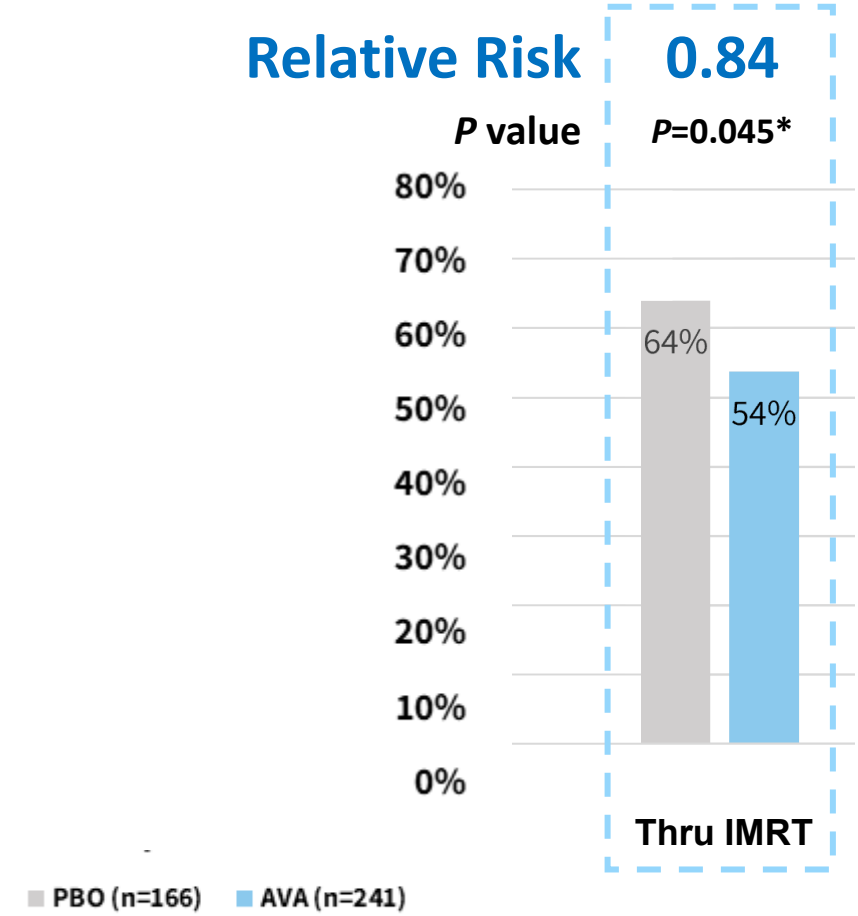


[a]ITT population.
AVA, avasopasem Mn; ; ITT, intent-to-treat; PBO, placebo.

PBO =Placebo n=166 **AVA** =Avasopasem n=241

SOM Incidence Reduced

Primary Endpoint ITT Population



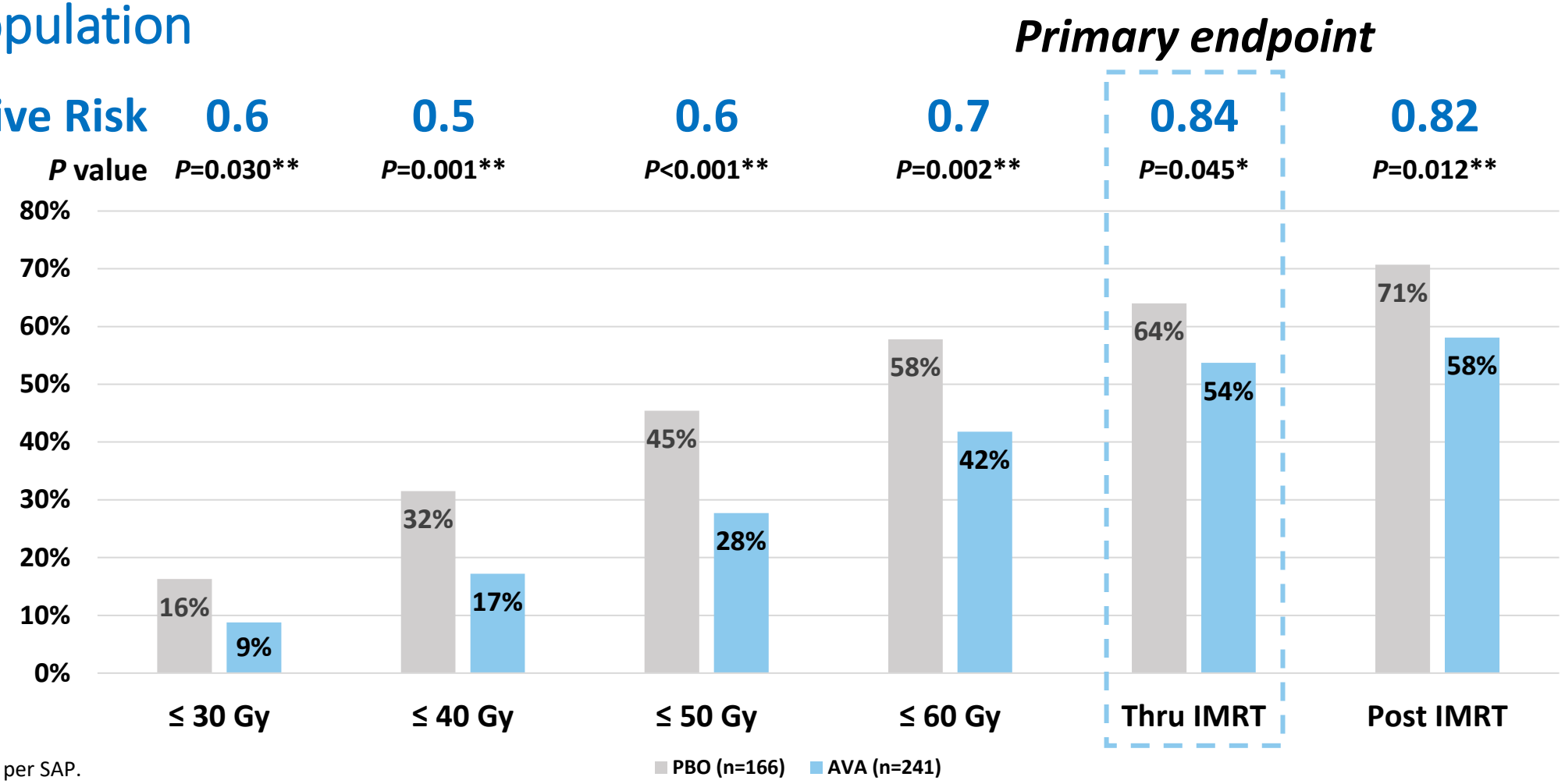
* Statistically significant per SAP.

AVA, avasopasem; IMRT, intensity-modulated radiation therapy; ITT, intent-to-treat; PBO, placebo; SAP, statistical analysis plan; SOM, severe oral mucositis.

ITT population

SOM Incidence Reduced at All IMRT Landmarks

ITT Population



* Statistically significant per SAP.

** Exploratory endpoints, not formally tested as part of SAP.

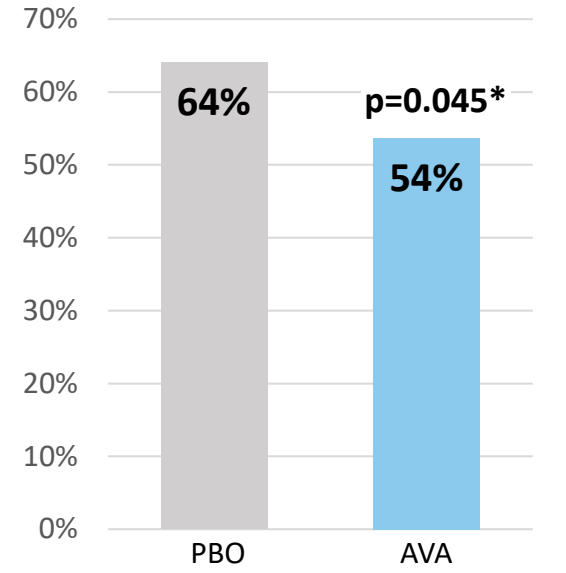
AVA, avasopasem Mn; Gy, gray; IMRT, intensity-modulated radiation therapy; ITT, intent-to-treat; PBO, placebo; SAP, statistical analysis plan; SOM, severe oral mucositis.

ITT population

ROMAN Results across key endpoints (n=407)

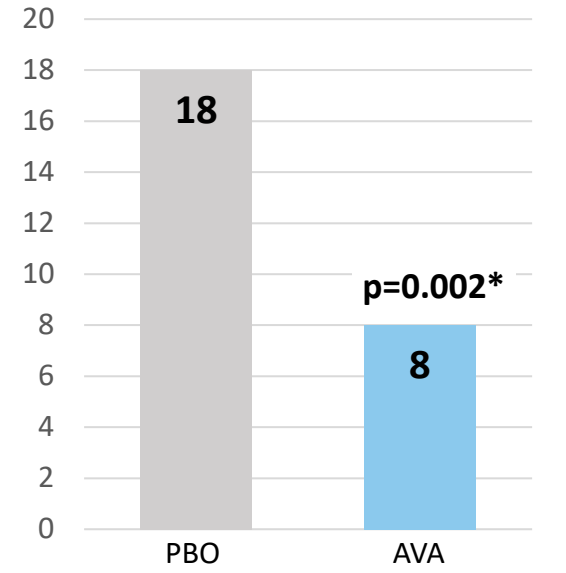
SOM incidence

16% **Reduction** in SOM Incidence



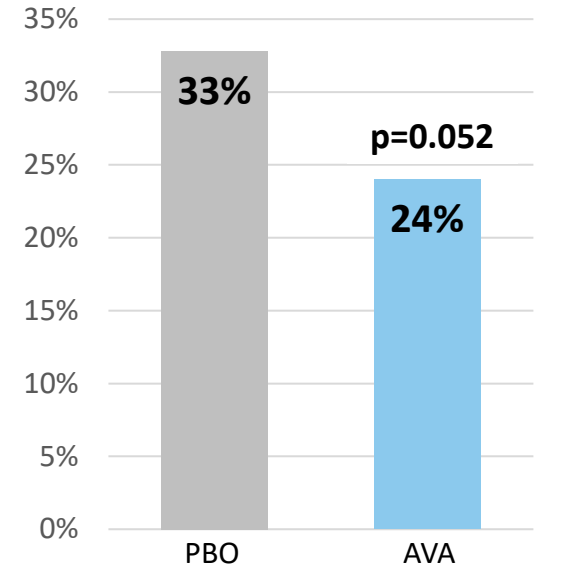
SOM days

56% **Reduction** in Median SOM Days



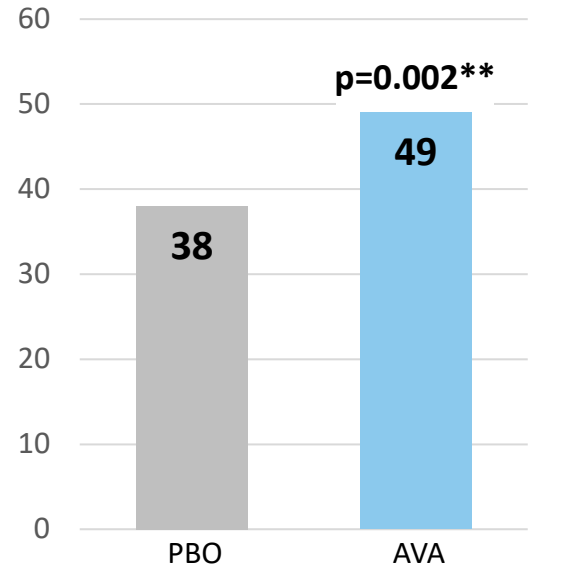
Grade 4 incidence

27% **Reduction** in Gr. 4 OM Incidence



SOM onset

29% **Delay** in median days to 1st SOM



*Statistical significance per statistical analysis plan for this Phase 3 trial
**Time to Onset was an exploratory endpoint. OM = oral mucositis; SOM = severe OM.

PBO =Placebo n=166 **AVA** =Avasopasem n=241

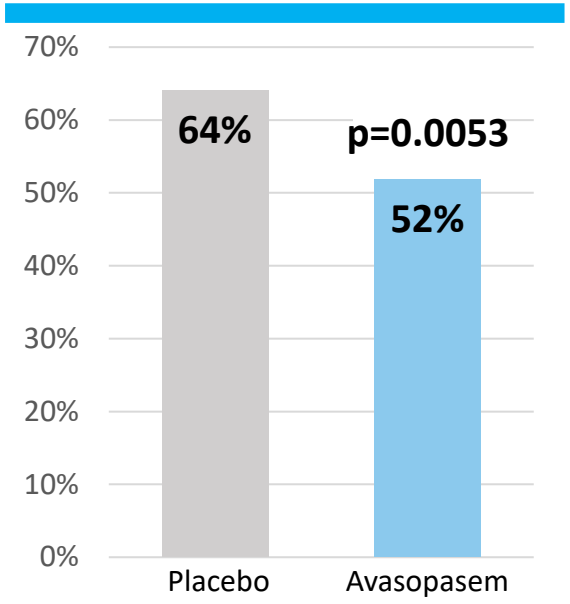
ITT population

Meta-analysis of the Two Randomized Trials (n=551)

Avasopasem SOM improvement consistent across trials and key parameters

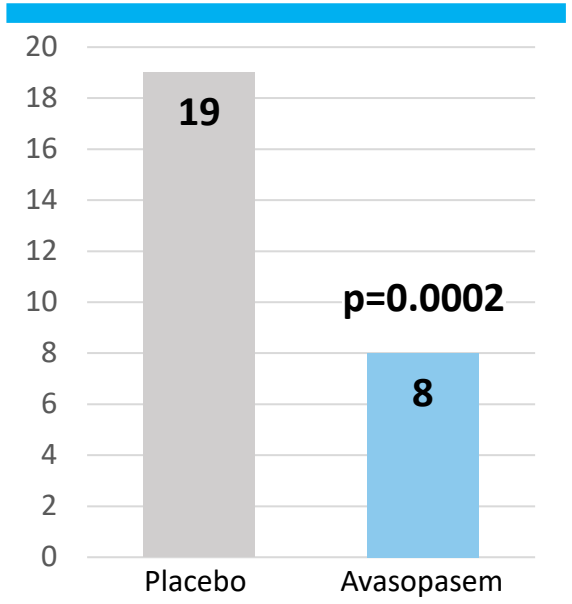
SOM incidence

19% **Reduction** in SOM Incidence



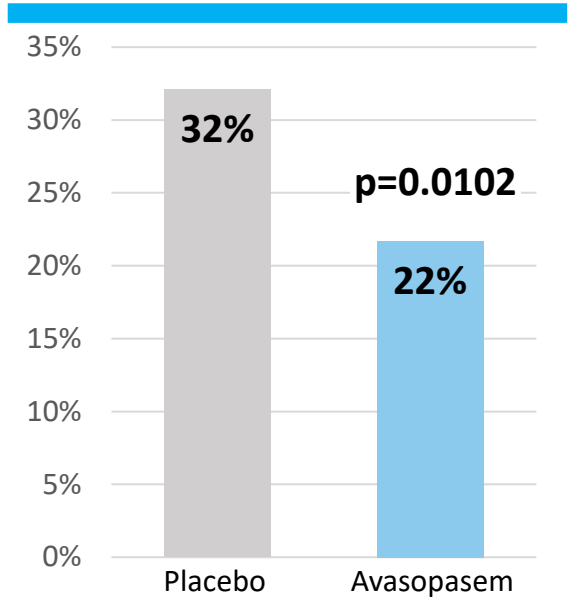
SOM days

58% **Reduction** in Median SOM Days



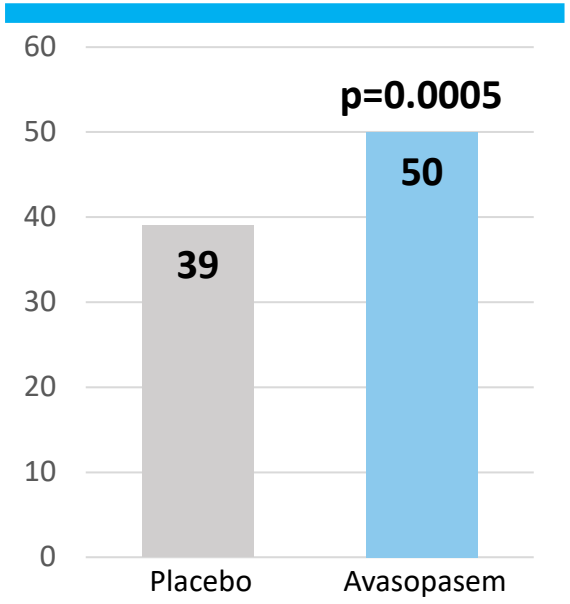
Grade 4 incidence

32% **Reduction** in Gr. 4 OM Incidence



SOM onset

28% **Delay** in median days to 1st SOM



*Nominal p values for all endpoints, calculated according to prespecified statistical analysis plan (SAP) for the meta-analysis
OM = oral mucositis; SOM = severe OM.

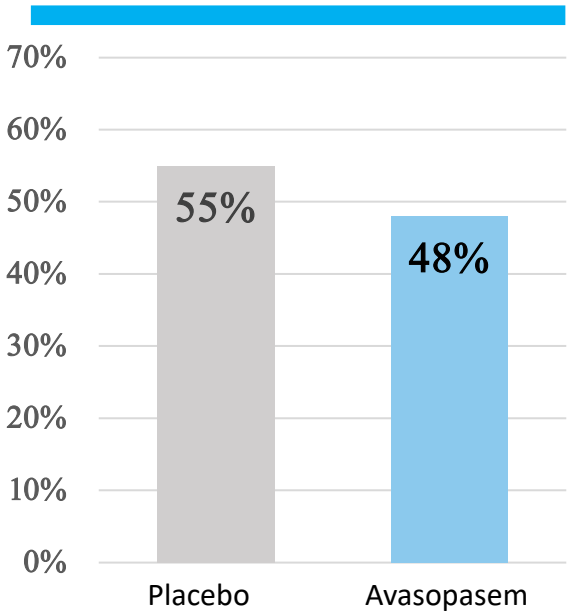
PBO =Placebo n=238 **AVA** =Avasopasem n=313

Reduced Narcotic and Feeding Tube Usage

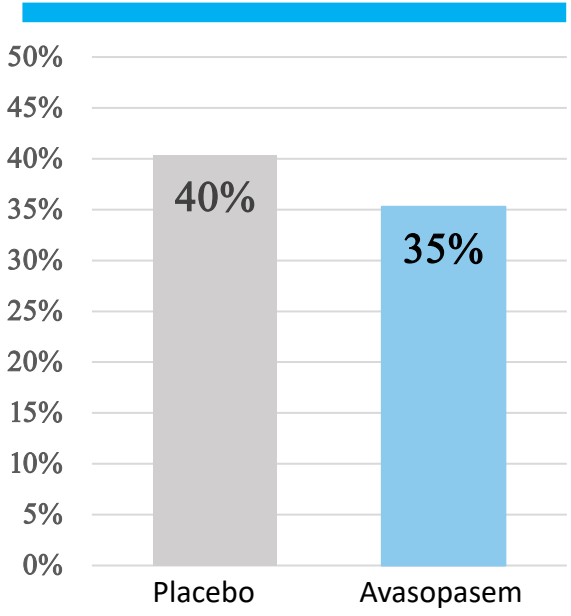
Avasopasem reductions in SOM appeared to decrease utilization

Narcotics

13% **Reduction** in usage after RT start

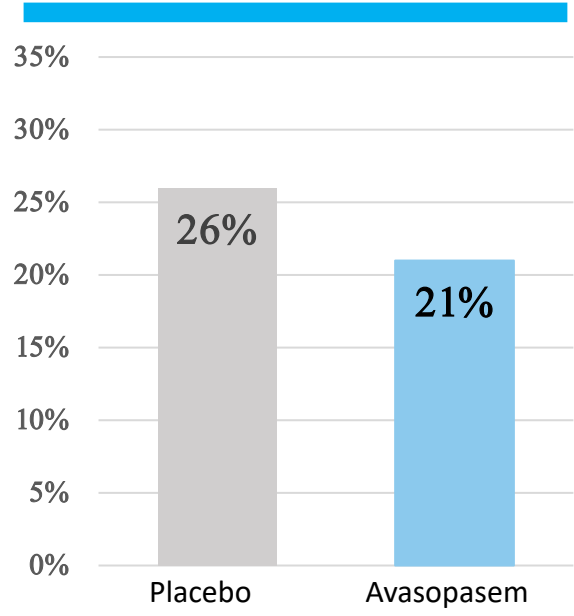


13% **Reduction** in usage for OMpain

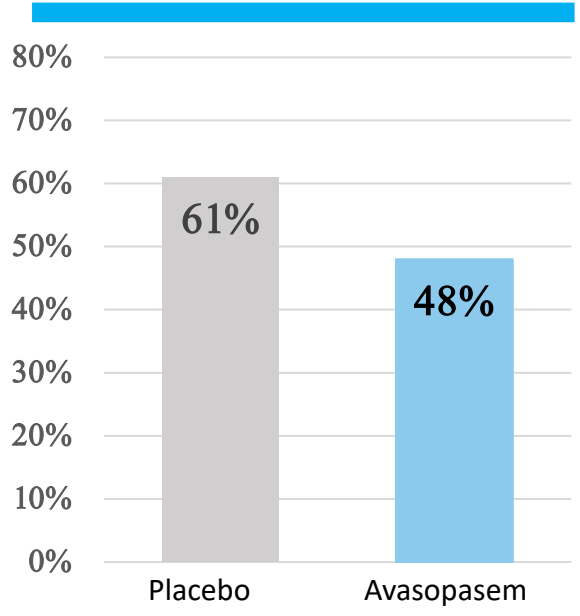


Gastrostomy (Feeding) Tubes

19% **Reduction** in placements after RT start



21% **Reduction** in overall utilization



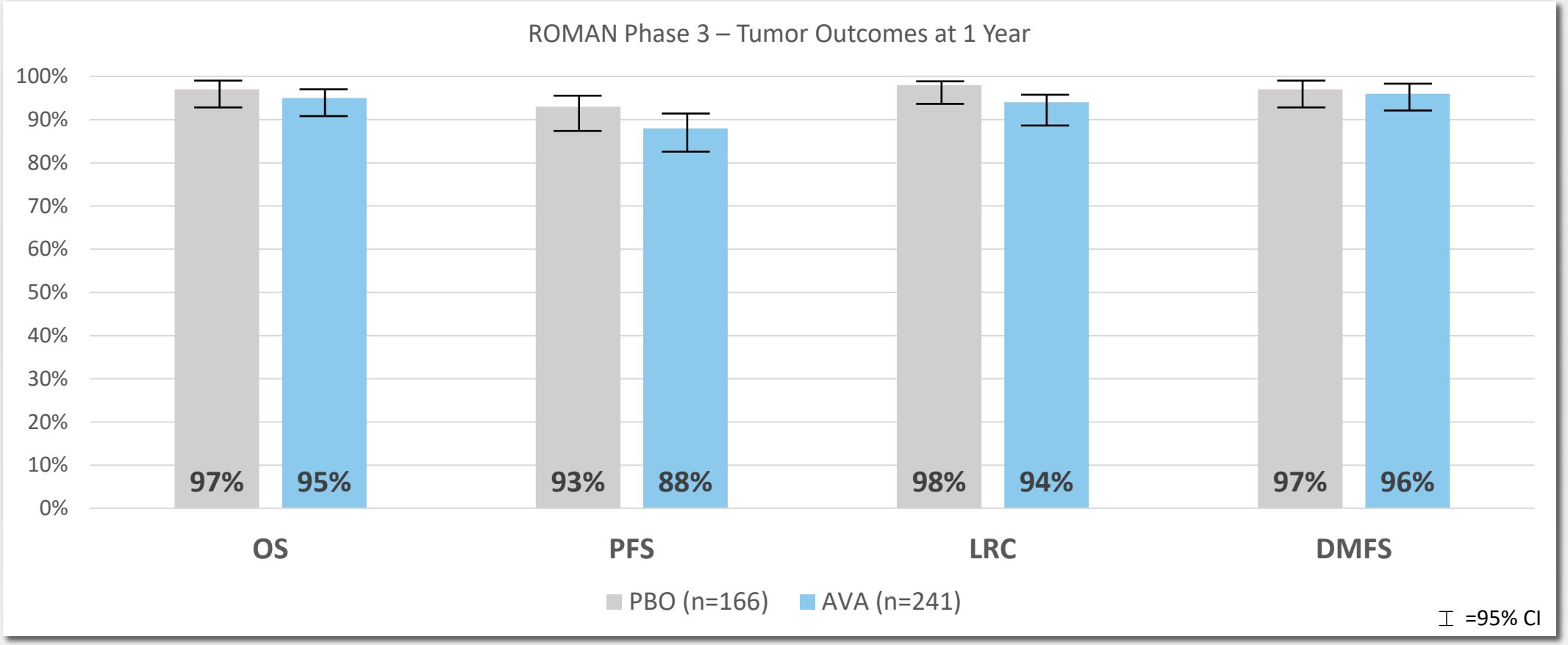
OM, oral mucositis; RT, radiation therapy; SOM, severe OM.

PBO =Placebo n=166 **AVA** =Avasopasem n=241

ITT population

Tumor Outcomes 1 Year after Chemoradiotherapy

Overlapping 95% Confidence Intervals – consistent with Phase 2b tumor outcomes at 1 year*



AVA, avasopasem Mn; CRT, chemoradiotherapy; DMC, distant metastasis control; LRC, locoregional control; OS, overall survival; PFS, progression-free survival; PBO, placebo.

* Two-Year Tumor Outcomes of Phase 2B... Anderson CM et al. Int J Radiat Oncol Biol Phys. 2018 Feb 1;100(2):427-435

ITT population

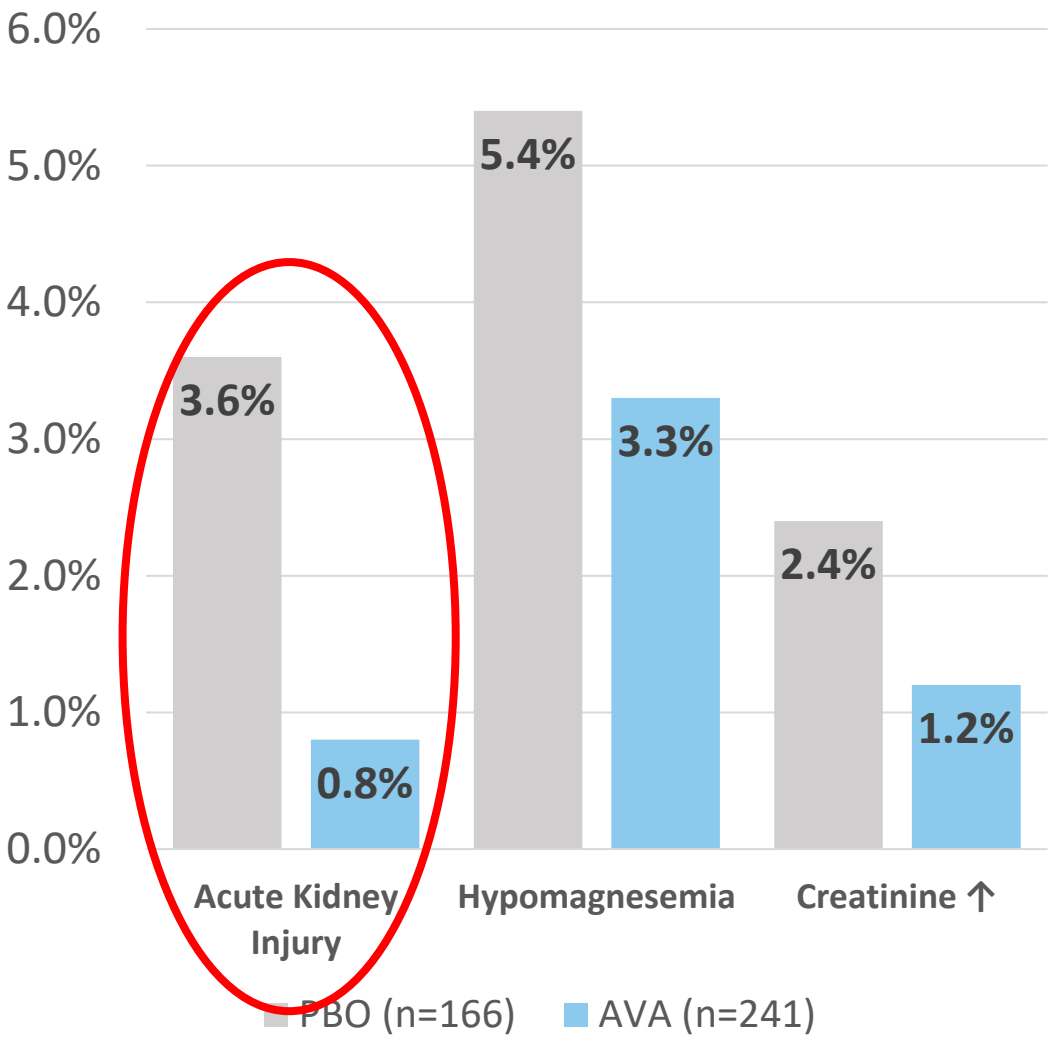
Cisplatin-related Kidney Injury

Avasopasem Mitigates Kidney Injury

- Superoxide drives cisplatin nephrotoxicity
  - Mapuskar, *Antioxid* 2021
- Avasopasem preclinically prevented cisplatin acute kidney injury
  - Mapuskar, *Antioxid* 2018
- Retrospective analysis of Phase 2b subset suggested chronic kidney disease prevention
  - Steinbach, *ASCO* 2020

AVA, avasopasem Mn; Cis, Cisplatin; PBO, placebo.
CKD defined by Nat. Kidney Foundation as eGFR (estimated Glomerular Filtration Rate) < 60 mL/min/1.73 m^2 (approx. the % of normal kidney function that is working)

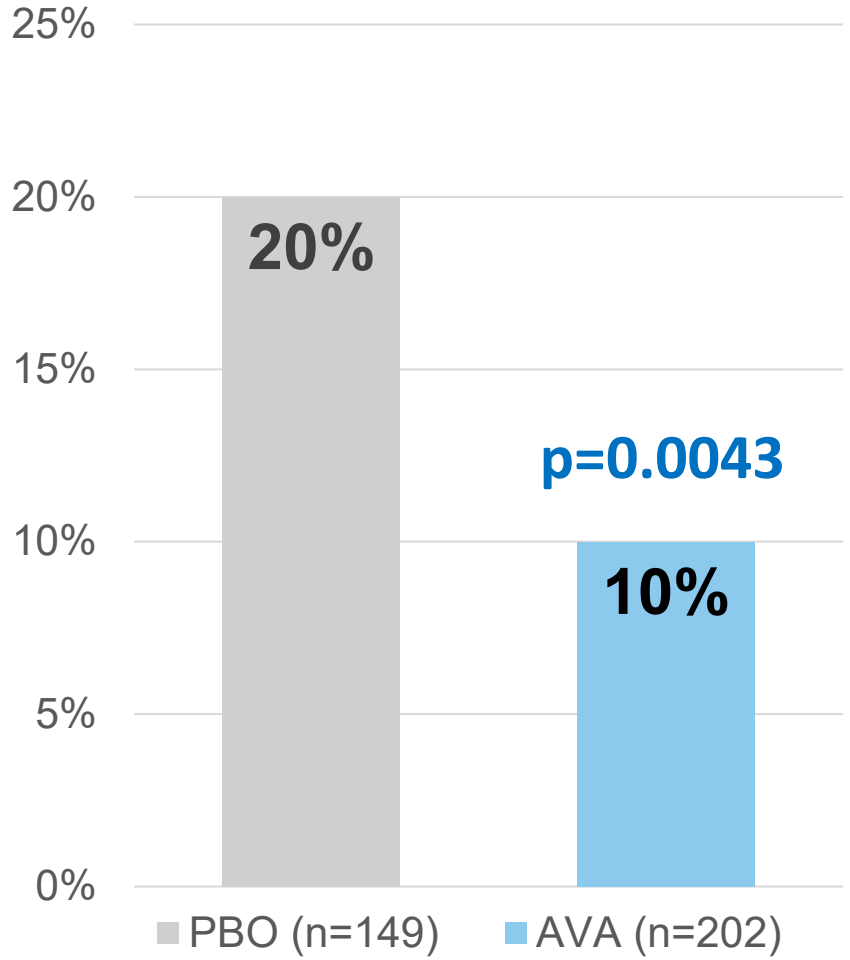
ROMAN: Renal Grade 3+ AEs



ITT population

1 Year Chronic Kidney Disease (CKD) Outcomes

Avasopasem halved predefined endpoint: CKD (<60 mL/min/1.73m^2)



ITT population

Conclusions

- Avasopasem demonstrated statistically significant and clinically meaningful reductions in SOM across key parameters of patient burden
- ROMAN results confirm SOM benefits in prior phase 2b trial
- Meta-analysis of both reinforces the consistency of benefit
- Comparable safety across arms
- Tumor control and overall survival comparable after one-year follow-up
- Cisplatin-induced CKD halved by avasopasem at 1 Year follow-up
- Galera plans to submit NDA to FDA by end 2022

FDA, United States Food and Drug Administration; HNC, head and neck cancer; NDA, new drug application; OM, oral mucositis; SOM, severe OM.

Thank you

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