Advances in Radiation Oncology (2025) **10**, 101674

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Benefit of Avasopasem Manganese on Severe Oral Mucositis in Head and Neck Cancer in the ROMAN Trial: Unplanned Secondary Analysis

Carryn Anderson, MD,[a,*] Samuel Salvaggio, PhD,[b] Mickaël De Backer, PhD,[b] Jean-Christophe Chiem, PhD,[b] Gary Walker, MD, MPH, MS,[c] Deborah Saunders, DMD, BSc,[d] Christopher M. Lee, MD,[e] Neal Dunlap, MD,[f] Eugene Kennedy, MD,[g] Robert Beardsley, PhD,[g] Benton Schoen, BA,[g] and Marc Buyse, ScD[b]

[a]Department of Radiation Oncology University of Iowa Hospitals & Clinics, Iowa City, Iowa; [b]International Drug Development Institute (IDDI), Louvain-la-Neuve, Belgium; [c]Banner MD Anderson Cancer Center, Gilbert, Arizona; [d]Northeast Cancer Centre of Health Sciences North, Health Sciences North, Northern Ontario School of Medicine, Sudbury, Canada; [e]Cancer Care Northwest, Spokane, Washington; [f]University of Louisville/James Graham Brown Cancer Center, Louisville, Kentucky; and [g]Galera Therapeutics, Inc, Malvern, Pennsylvania

Received 28 March 2024; accepted 25 October 2024

Purpose: Oral mucositis (OM) is a debilitating side effect of cisplatin and intensity-modulated radiation therapy (IMRT) in patients with head and neck cancer. The phase 3 ROMAN trial showed avasopasem manganese (AVA) significantly decreased individual endpoints of incidence and duration of severe oral mucositis (SOM, World Health Organization [WHO] grade 3-4), with nominal decrease in severity (WHO grade 4) and significant increase in the delay in onset of SOM. We sought to determine the Net Treatment Benefit (NTB) of AVA versus placebo (PBO) using the generalized pairwise comparisons (GPC) method.

Methods and Materials: GPC is a statistical method that permits simultaneous analysis of several prioritized outcomes, comparing all possible pairs of a patient in the active (ie, AVA) group and a patient from the control (ie, PBO) group. NTB is the net benefit across all the outcomes for AVA compared to PBO. Key clinically relevant outcomes from ROMAN were prioritized: (1) WHO grade 4 OM incidence; (2) SOM incidence; (3) days of SOM; (4) days to SOM onset, with 7 days difference defined as the clinical relevance threshold for SOM days and SOM onset.

Results: GPC analysis of 407 patients (AVA = 241, placebo = 166) stratified by cisplatin schedule and treatment setting resulted in 13,969 pairwise comparisons. AVA showed statistically significant net benefit on all 4 key outcomes with a 53.9% probability that AVA would benefit patients versus a 35.0% probability that PBO would; the difference between these probabilities was a NTB of 18.9% (P = .0012), translating to an AVA number needed to treat of 5.3 patients. All outcomes contributed to NTB, reflecting improvements in SOM incidence, onset and duration, and in grade 4 OM incidence seen in the original ROMAN analysis.

Presented in part at the European Congress on Head & Neck Oncology, March 8-11, 2023, Lisbon, Portugal.

Sources of support: Funding for this Global Pairwise Comparison of the ROMAN study (NCT03689712 available from www.clinicaltrials.gov) was provided by Galera Therapeutics, Inc (Galera). Medical editorial support (assembling tables and figures, collating author comments, copyediting, fact checking, and referencing) and graphic services were provided by AOIC, LLC, and were funded by Galera.

Data for this study are not available.

*Corresponding author: Carryn M. Anderson, MD; Email: carryn-anderson@uiowa.edu

https://doi.org/10.1016/j.adro.2024.101674

Conclusions: This GPC analysis shows compelling evidence from the ROMAN trial of AVA's clinical benefit across key parameters of SOM burden.

Introduction

Intensity-modulated radiation therapy (IMRT), typically with concurrent cisplatin (CRT) remains the standard of care for locally advanced head and neck squamous cell carcinoma (LAHNC).[1-7] Approximately 70% of CRT patients will experience severe oral mucositis (SOM) during their treatment course, limiting their ability to take solids (World Health Organization [WHO] grade 3) or liquids (WHO grade 4) by mouth, often necessitating feeding tube placement. Typical median duration of SOM is 3 to 4 weeks and median onset is 4 weeks into a 7-week treatment course. Severe oral mucositis is associated with substantial pain, impairment of quality of life, potential for infection and hospitalization, and treatment breaks that can decrease efficacy.[8] Current management focuses mostly on symptoms and supportive care.[9] There are no drugs approved to reduce SOM in LAHNC.

Preclinical work has shown that a radiation-induced burst of superoxide initiates oral mucositis (OM) development.[10] Reduction in Oral Mucositis with Avasopasem Manganese (ROMAN), a phase 3, randomized, placebo-controlled, double-blinded trial of the selective superoxide dismutase inhibitor avasopasem manganese (AVA), showed significantly reduced incidence and duration of SOM, as well as decreased severity and delay of SOM onset in patients receiving CRT for LAHNC,[11] consistent with results from a previous clinical trial in the same population.[12]

Generalized pairwise comparisons (GPC) is a statistical method that allows for simultaneous analysis of several outcomes prioritized by clinical importance.[13,14] This method is useful to determine the Net Treatment Benefit (NTB) of multiple outcomes with 1 intervention compared to another and has recently been used to analyze the efficacy-toxicity trade-off for several oncologic drug regimens.[14-17] In the setting of IMRT for LAHNC, patient SOM burden is reflected by several key independent clinical endpoints assessed in ROMAN, and here we used the GPC method to determine the NTB of AVA over placebo (PBO) across 4 of these key parameters.

Methods and Materials

The ROMAN trial was sponsored and financially supported by Galera Therapeutics. The trial was registered at ClinicalTrials.gov, (NCT03689712), approved by the ethics committee at every participating institution, and conducted according to the recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent to participate in the study. Data were anonymized to protect patients' identities.

Eligible patients had stage III to IVb (according to American Joint Committee on Cancer, seventh Edition) nonmetastatic oral cavity (OC) or oropharyngeal (OP) squamous cell cancer, Eastern Cooperative Oncology Group performance status of 2 or less, and planned treatment with standard fractionation IMRT and concurrent cisplatin (100 mg/m^2 every 3 weeks or 40 mg/m^2 weekly) administered definitively or after surgical resection. Decision on which cisplatin regimen to use was at the discretion of the investigator. IMRT plans had to include at least 2 OM sites within the cumulative 50-Gy isodose line and were centrally reviewed by an independent radiation oncologist to confirm protocol adherence. IMRT was administered in daily 2.0- to 2.2-Gy fractions, Monday through Friday, to a cumulative tumor dose of 60 to 72 Gy. Patients were randomized 3:2 to AVA 90 mg vs PBO, each delivered as a 60-minute IV infusion prior to IMRT. Enrollment was stratified by 2 factors: cisplatin schedule (weekly vs every 3 weeks) and treatment setting (postoperative vs definitive). Oral mucositis was assessed by trained evaluators biweekly during radiation therapy and weekly for 2 weeks thereafter using WHO criteria (grade 0, no mucositis; grade 1, pain and erythema; grade 2, ulceration, able to eat solid food; grade 3, ulceration, able to eat only liquids; and grade 4, ulceration, inability to eat, requiring tube or parenteral feeding) (Table E1). The primary endpoint of the trial was SOM incidence (WHO grade 3 or 4), with other endpoints including days of SOM and grade 4 OM incidence, and days to SOM onset. Multiple imputation was used to address missing SOM data, and for the GPC analyses this was done as described in the Appendix E1. All patients were followed for adverse events. The primary GPC analysis included the ROMAN intent-to-treat (ITT) population stratified as described above.

The GPC analysis compared pairs formed by all combinations of 1 patient each from the AVA and PBO arms within a given stratum (eg, postoperative/weekly cisplatin). For each pair, the prioritized outcomes were sequentially considered to evaluate which patient had a better outcome. Each pair was classified as a win (if AVA patient did better), a loss (if PBO patient did better), or a tie for the top prioritized outcome. If the pair was tied on that outcome, it was evaluated similarly on the next prioritized outcome. The process was repeated until the pair was classified as a win or a loss, or all outcomes had been

used and the pair remained tied. Results of all pair comparisons were aggregated in summary measures for each outcome, by calculating the proportion of pairs classified as wins minus the proportion of pairs classified as losses for that outcome. This difference in proportions estimated the NTB for each outcome, that is the expected advantage on that outcome for an AVA patient compared to a PBO patient. The separate outcome NTB's were added to estimate the NTB for AVA. As NTB is a difference in probabilities, the ratio 1/NTB represents the Number Needed to Treat (NNT) for 1 patient to benefit from AVA. Given the hierarchy of outcomes contributing to the NTB, sequential testing was carried out to address the issue of multiplicity. Testing started from the overall NTB and, conditional on that being significant (α = .05), repeated testing deleting 1 outcome at a time from the least important to the most important outcome was analyzed alone, or until a nonsignificant test was reached. Statistical inference was based on the asymptotic distribution of the NTB statistic.[18] GPC analyses were carried in R (4.1.0) with the package BuyseTest (2.3.10).

For the primary GPC analysis, the key SOM clinical outcomes measures were prioritized based on clinical judgment: (1) WHO grade 4 OM incidence; (2) SOM incidence; (3) days of SOM; (4) days to SOM onset. With this ordering, SOM incidence was essentially the incidence of WHO grade 3 SOM, and days of SOM was effectively considered only in the subset of patients who developed SOM. For days of SOM and days to onset of SOM, based on physician feedback, a difference of at least 7 days was defined as the clinical relevance threshold, meaning that a pair comparison was only classified as a win or loss if the difference between the 2 patients was at least that large.

Unless otherwise indicated, GPC analyses were stratified by cisplatin schedule (weekly vs every 3 weeks) and treatment setting (postoperative vs definitive RT). Stratum results were combined using Cochran−Mantel−Haenszel (CMH) weighting (approximately proportional to the numbers of patients in each stratum).

Several sensitivity analyses were performed after the initial GPC analysis, including: without stratification, without imputation, reprioritizing outcomes, combining WHO grade 4 and grade 3 OM incidence, and varying thresholds of clinical relevance for days of SOM and days to SOM onset. Exploratory GPC analyses were also performed considering only days of SOM and days to SOM onset of SOM in both orders. Finally, alternate analyses using weighting proportional to the number of pairs in each stratum[13] are presented in the Appendix E1.

Results

The ROMAN trial enrolled and randomized 455 patients between October 3, 2018 and August 13, 2021 at 69 of 97 activated US and Canadian sites.[11] Twenty patients were randomized but never received AVA or PBO, and 28 were excluded because of an administrative suspension of drug dosing. Per guidance of the Food and Drug Administration (FDA), these 48 patients were excluded, leaving an ITT population of 407 (241 AVA/166 PBO). Avasopasem 90 mg statistically significantly decreased the incidence and duration (days) of SOM and nominally decreased the incidence of grade 4 SOM as well as delayed onset of SOM. All-grade and serious (grade 3+) adverse events occurred with similar frequencies for AVA and PBO.[11]

Stratified GPC analyses used the 4 strata defined by the ROMAN stratification: cisplatin schedule and treatment setting, resulting in 13,969 pairwise comparisons (Table 1). For the unstratified analysis, there were 241 × 166 = 40,006 pairs.

Results of the primary GPC analysis are illustrated in Figs 1 and 2. For the 4 key SOM outcomes, there was a 53.9% probability that a random AVA patient had a *better* outcome than a random PBO patient and a 35.0% probability that a random AVA patient had a *worse* outcome than a random PBO patient, resulting in a NTB of 0.539 − 0.350 = 0.189 (P = 0.0012). This translates to a NNT of 1/0.189 = 5.3 patients (95% confidence interval, 3.3-13.3 patients). In addition, each of the 4 outcomes contributed to the overall benefit to patients, though the size of individual contribution depended on the testing hierarchy.

The predefined sensitivity analyses and exploratory analyses also found consistent highly significant benefit for AVA over placebo in a variety of scenarios testing robustness of the results, with NTB varying in a narrow range from 0.189 to 0.219 (Table 2). Varying clinical relevance thresholds over wide ranges for SOM days and days to onset in the primary analysis also showed modest impact on the estimated NTB of 0.149 − 0.232 (Table 3).

Discussion

Mitigation of OM in head and neck cancer patients is an unmet medical need.[9,12] In the large ROMAN phase 3 trial in patients with OC and OP squamous cell cancer

Table 1 Pairs by stratum

Stratum	Number of pairs
Weekly cisplatin / Postoperative treatment	693
Weekly cisplatin / Definitive treatment	7526
Every 3 weeks cisplatin / Postoperative treatment	143
Every 3 weeks cisplatin / Definitive treatment	5607
All patients	**13969**

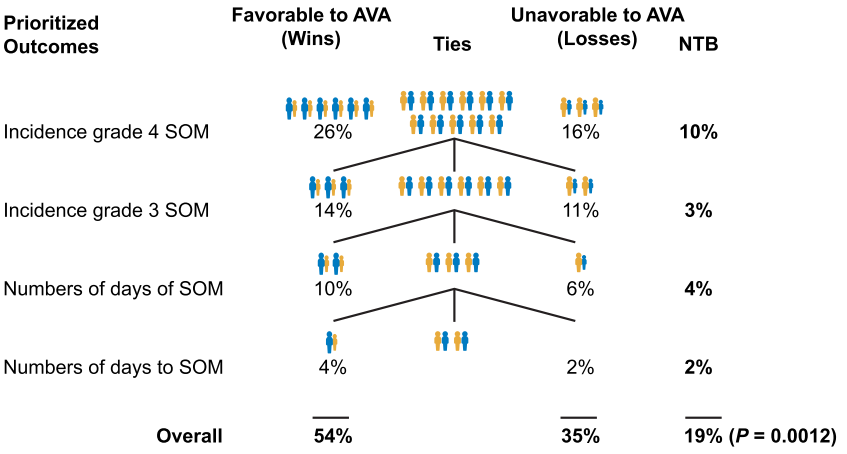

Figure 1 Calculation of avasopasem net treatment benefit based on prioritized outcomes.
Abbreviations: AVA = avasopasem manganese; NTB = net treatment benefit; SOM = severe oral mucositis.

receiving IMRT with concurrent cisplatin, AVA showed statistically significant reductions in SOM on the primary and other endpoints.

We know that for patients, the SOM experience is much more than just a single endpoint of incidence; duration, severity and time of onset are also key factors. To accurately assess patient SOM burden, it is critical to consider multiple SOM parameters in a "holistic" approach, rather than a single endpoint in isolation. For example, simply whether a patient has SOM says nothing about how long they have it, if it worsens into grade 4, or whether it starts problematically early in the IMRT course, or toward the end of the regimen. GPC offers a statistical methodology that captures the full patient experience in 1 analysis and allows a quantitative assessment of the AVA benefit across key SOM parameters. This metric, the NTB, can also be directly translated into the NNT.

Generalized pairwise comparisons has previously been used successfully to assess the clinical benefit-risk tradeoffs with erlotinib, FOLFIRINOX and gemcitabine /+ nab-paclitaxel versus gemcitabine alone in metastatic pancreatic cancer.[15-17] These 3 analyses simultaneously evaluated overall survival and drug toxicity, demonstrating erlotinib inferiority (NTB = −0.036), and superiority for FOLFIRINOX (NTB = 0.270) and gemcitabine /+ nab-paclitaxel (NTB = 0.210) over gemcitabine monotherapy. In this unplanned secondary analysis of the ROMAN study, we demonstrated the utility of GPC for assessing NTB on multiple, at least partially independent, efficacy endpoints.

The primary GPC analysis of AVA versus PBO for the combined mitigation of grade 4 OM incidence, and of overall SOM incidence, duration, and time of onset showed a robust and compelling total benefit for patients who received AVA, when compared with PBO. This analysis also showed that each of these key parameters independently contributed to clinical benefit. Sensitivity analyses confirmed that these conclusions held over a wide range of method assumptions (stratification, imputation, outcome ordering, clinical relevance thresholds).

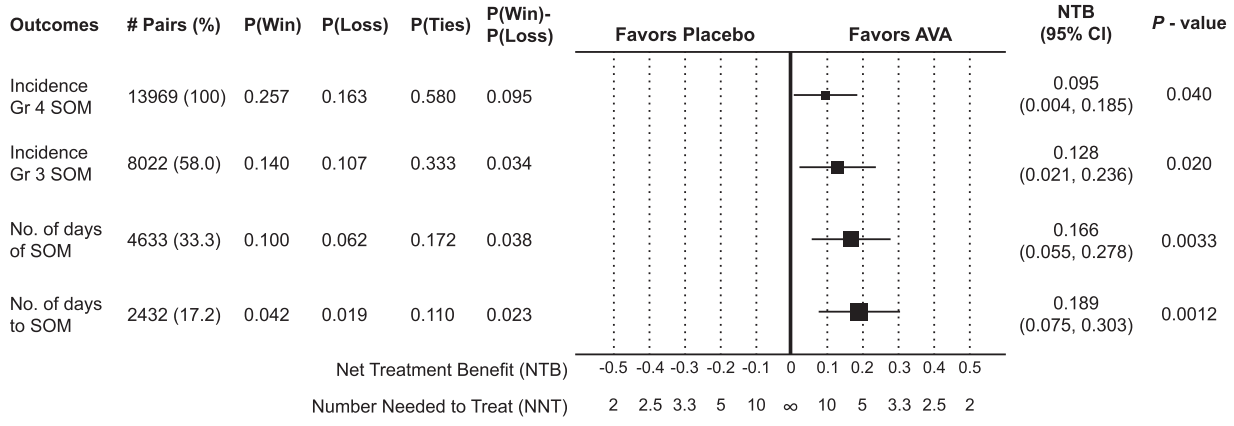

Figure 2 Forest plot of cumulative contributions of individual outcomes to the net treatment benefit.
Abbreviations: CI = confidence interval; Prob = probability; NTB = net treatment benefit; NNH = number needed to harm; NNT = number needed to treat; SOM = severe oral mucositis; WHO = World Health Organization.

Table 2 Secondary analyses

Outcome order	Primary analysis	Secondary analyses					
		Unstratified	Nonimputed	Reordered			
1	Grade 4	Grade 4	Grade 4	Grade 4	SOM	Days	Onset
2	SOM	SOM	SOM	SOM	Days	Onset	Days
3	Days	Days	Days	Onset	Onset		
4	Onset	Onset	Onset	Days			
Combined NTB	**0.189**	**0.191**	**0.196**	**0.197**	**0.200**	**0.205**	**0.219**
***P* value**	**.0012**	**.0020**	**.00061**	**.00067**	**.00056**	**.0004**	**.00015**

Abbreviations: Days = severe oral mucositis days; Grade 4 = grade 4 oral mucositis incidence; NTB = net treatment benefit; Onset = days to severe oral mucositis onset; SOM = severe oral mucositis incidence.
Primary: primary generalized pairwise comparison analysis.
Unstratified: reproduced primary generalized pairwise comparison analysis without accounting for GTI-4419-301 stratification.
Nonimputed: reproduced primary generalized pairwise comparison analysis with raw data without GTI-4419-301 imputation.

With a NTB of 0.189 (or a NNT of 5.3 patients to prevent episodes of SOM, reduce their severity or duration, or delay their onset) in the primary GPC analysis, this drug has promise to be practice changing. As a comparison, the NNT of only 5.3 patients is better than a pivotal phase 3 randomized trial that contributed to United States FDA approval of netupitant/palonosetron (Akynzeo) for prevention of chemotherapy-induced nausea and vomiting (NNT = 13.5 to prevent emesis).[19,20]

A first limitation of this analysis that it uses a novel statistical methodology that produces an unfamiliar (but patient-relevant) estimate of the NTB, taking multiple dimensions of the treatment effect simultaneously into account. A second limitation is that this unplanned secondary analysis of the data took place with knowledge of the results of the primary analyses. Hence the outcomes selected for the GPC analysis, as well as their priorities, were not prespecified and were chosen to reflect patient benefit in the most meaningful way as possible. From an inferential point of view, the *P* values reported in our paper must be considered exploratory rather than confirmatory. The technical overview of GPC, sensitivity analysis, and alternative analyses included in the Appendix E1 are available to be as transparent and reproducible as possible.

In August 2023, the FDA concluded its review of avasopasem and ultimately requested a confirmatory phase 3 trial to better estimate the benefit of avasopasem in this population. There were a couple of contributing factors, including that the *P* value for primary endpoint of incidence was not as robust as typical for approval with a single phase 3, and that missing follow-up data increased uncertainty with the duration secondary endpoint analysis. This latter issue was raised by FDA despite a prespecified missing data imputation strategy approved by them. With respect to missing data, it should be noted ROMAN was in the middle of enrollment when the COVID pandemic began, impacting ability to complete OM assessments and follow-up appointments. The FDA also raised the issue of the numerical, yet statistically nonsignificant

Table 3 NTB with varying clinical relevance thresholds

NTB (*P* value)		Threshold for SOM days						
		0	**3**	**7**	**10**	**14**	**17**	**21**
Threshold for days to SOM onset	0	0.185 (0.0016)	0.186 (0.0014)	0.191 (0.001)	0.187 (0.0014)	0.191 (0.0011)	0.195 (0.0008)	0.197 (0.00069)
	3	0.185 (0.0016)	0.186 (0.0014)	0.19 (0.0011)	0.185 (0.0015)	0.19 (0.0011)	0.195 (0.00081)	0.197 (0.00069)
	7	0.184 (0.0016)	0.186 (0.0015)	**0.189 (0.0012)**	0.184 (0.0016)	0.188 (0.0012)	0.193 (0.00089)	0.195 (0.00076)
	10	0.158 (0.0057)	0.159 (0.0053)	0.162 (0.0045)	0.155 (0.0067)	0.159 (0.0053)	0.163 (0.0041)	0.166 (0.0034)
	14	0.158 (0.0058)	0.159 (0.0054)	0.162 (0.0044)	0.153 (0.0073)	0.155 (0.0061)	0.16 (0.0046)	0.162 (0.0042)
	17	0.159 (0.0056)	0.16 (0.0052)	0.162 (0.0044)	0.149 (0.0086)	0.153 (0.007)	0.157 (0.0053)	0.158 (0.0048)
	21	0.159 (0.0055)	0.16 (0.005)	0.162 (0.0045)	0.149 (0.0086)	0.149 (0.008)	0.153 (0.0063)	0.153 (0.0061)

Abbreviations: NTB = net treatment benefit; SOM = severe oral mucositis.
Highlighted cell depicts thresholds chosen for the primary analysis.

difference in overall survival between the 2 arms. Precedent data show that avasopasem does not interfere with chemoradiation efficacy.[12,21-23] In addition, both ROMAN arms out-performed historical tumor outcome expectations for an unselected OC and oropharynx population.[3] A comprehensive analysis of the ROMAN trial, including primary and secondary endpoints with 2-year tumor outcome data are under revision. Meanwhile, this GPC analysis may inform future trial design for OM agents.

Conclusions

As previously reported, significant improvements in SOM incidence and duration were observed in the phase 3 ROMAN trial. Generalized pairwise comparisons analysis further showed compelling, quantitative evidence of even greater overall clinical benefit of AVA over placebo from the combination of reducing incidence and duration, as well as grade 4 OM incidence, and delaying SOM onset in locally advanced head and neck cancer patients receiving IMRT. The impact of treatment with AVA on each key SOM outcome contributed meaningfully to the overall clinical benefit. A New Drug Application was submitted based on the ROMAN phase 3 results; however, the FDA has indicated an additional confirmatory phase 3 will be needed.

Disclosures

Carryn Anderson, MD reports financial support, administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, travel, and writing assistance were provided by Galera Therapeutics Inc Samuel Salvaggio, PhD reports financial support was provided by Galera Therapeutics Inc Mickaël De Backer, PhD reports financial support was provided by Galera Therapeutics Inc Jean-Christophe Chiem, PhD reports financial support was provided by Galera Therapeutics Inc Gary Walker, MD, MPH, MS reports financial support, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Galera Therapeutics Inc Deborah Saunders, DMD, BSc reports financial support, administrative support, article publishing charges, equipment, drugs, or supplies, statistical analysis, travel, and writing assistance were provided by Galera Therapeutics Inc Christopher M. Lee, MD reports financial support and equipment, drugs, or supplies were provided by Galera Therapeutics Inc Neal Dunlap, MD reports financial support, equipment, drugs, or supplies, statistical analysis, and writing assistance were provided by Galera Therapeutics Inc Eugene Kennedy, MD reports financial support was provided by Galera Therapeutics Inc Robert Beardsley, PhD reports financial support was provided by Galera Therapeutics Inc Benton Schoen, BA reports financial support was provided by Galera Therapeutics Inc Marc Buyse, ScD reports financial support was provided by Galera Therapeutics Inc Carryn Anderson, MD reports a relationship with Galera Therapeutics Inc that includes: consulting or advisory. Deborah Saunders, DMD, BSc reports a relationship with Galera Therapeutics Inc that includes: equity or stocks. Gary Walker, MD, MPH, MS reports a relationship with Galera Therapeutics Inc that includes: consulting or advisory. Benton Schoen, BA reports a relationship with Galera Therapeutics Inc that includes: employment and equity or stocks. Robert A. Beardsley reports a relationship with Galera Therapeutics Inc that includes: employment and equity or stocks. Eugene P. Kennedy reports a relationship with Galera Therapeutics Inc that includes: employment and equity or stocks. Carryn Anderson, MD's institution received research funding from Soligenix to evaluate a drug to mitigate oral mucositis. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank Gareth Smith for assistance with manuscript preparation. Samuel Salvaggio, Mickaël De Backer, Jean-Christophe Chiem, and Marc Buyse were responsible for statistical analysis.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101674.

References

1. Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with n2 or n3 locally advanced head and neck cancer. *J Clin Oncol*. 2014;32:2735-2743.
2. Gebre-Medhin M, Brun E, Engstrom P, et al. Artscan III: A randomized phase iii study comparing chemoradiotherapy with cisplatin versus cetuximab in patients with locoregionally advanced head and neck squamous cell cancer. *J Clin Oncol*. 2021;39:38-47.
3. Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (nrg oncology rtog 1016): A randomised, multicentre, non-inferiority trial. *Lancet*. 2019;393:40-50.
4. Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (paradigm): A randomised phase 3 trial. *Lancet Oncol*. 2013;14:257-264.

5. Kiyota N, Tahara M, Mizusawa J, et al. Weekly cisplatin plus radiation for postoperative head and neck cancer (jcog1008): A multicenter, noninferiority, phase II/III randomized controlled trial. *J Clin Oncol*. 2022;40:1980-1990.
6. Mehanna H, Robinson M, Hartley A, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (de-escalate hpv): An open-label randomised controlled phase 3 trial. *Lancet*. 2019;393:51-60.
7. Sharma A, Chaudhary MK, Thakar A, et al. Concurrent chemotherapy and external radiation therapy: An open label non-inferiority phase III randomized controlled trial of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma: Concert trial. *Ann Oncol*. 2019;30. v473-v474.
8. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: Pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004;100:1995-2025.
9. Elad S, Cheng KKF, Lalla RV, et al. Mascc/isoo clinical practice guidelines for the management of mucositis secondary to cancer therapy. *Cancer*. 2020;126:4423-4431.
10. Sonis ST. The pathobiology of mucositis. *Nat Rev Cancer*. 2004;4:277-284.
11. Anderson CM, Lee CM, Kelley JR, et al. Roman: Phase 3 trial of avasopasem manganese (gc4419) for severe oral mucositis (som) in patients receiving chemoradiotherapy (crt) for locally advanced, nonmetastatic head and neck cancer (lahnc). *J Clin Oncol*. 2022;40. 6005-6005.
12. Anderson CM, Lee CM, Saunders DP, et al. Phase iib, randomized, double-blind trial of gc4419 versus placebo to reduce severe oral mucositis due to concurrent radiotherapy and cisplatin for head and neck cancer. *J Clin Oncol*. 2019;37:3256-3265.
13. Buyse M. Generalized pairwise comparisons of prioritized outcomes in the two-sample problem. *Stat Med*. 2010;29:3245-3257.
14. Buyse M, Saad ED, Peron J, et al. The net benefit of a treatment should take the correlation between benefits and harms into account. *J Clin Epidemiol*. 2021;137:148-158.
15. Peron J, Giai J, Maucort-Boulch D, Buyse M. The benefit-risk balance of nab-paclitaxel in metastatic pancreatic adenocarcinoma. *Pancreas*. 2019;48:275-280.
16. Peron J, Roy P, Conroy T, et al. An assessment of the benefit-risk balance of folfirinox in metastatic pancreatic adenocarcinoma. *Oncotarget*. 2016;7:82953-82960.
17. Peron J, Roy P, Ding K, et al. Assessing the benefit-risk of new treatments using generalised pairwise comparisons: The case of erlotinib in pancreatic cancer. *Br J Cancer*. 2015;112:971-976.
18. Bebu I, Lachin JM. Large sample inference for a win ratio analysis of a composite outcome based on prioritized components. *Biostatistics*. 2016;17:178-187.
19. Aapro M, Rugo H, Rossi G, et al. A randomized phase III study evaluating the efficacy and safety of nepa, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol*. 2014;25:1328-1333.
20. Cada DJ, Leonard J, Baker DE. Netupitant/palonosetron. *Hosp Pharm*. 2015;50:310-325.
21. Sishc BJ, Ding L, Nam TK, et al. Avasopasem manganese synergizes with hypofractionated radiation to ablate tumors through the generation of hydrogen peroxide. *Sci Transl Med*. 2021;13:eabb3768.
22. Taniguchi CM, Frakes JM, Aguilera TA, et al. Stereotactic body radiation therapy with or without selective dismutase mimetic in pancreatic adenocarcinoma: An adaptive randomised placebo-controlled phase 1b/2 trial. *Lancet Oncol*. 2023;24:1387-1398.
23. Mohanty AJ, Sishc BJ, Falls KC, Heer CD, Spitz DR, Story MD. GC4419 enhances the response of non-small cell lung carcinoma cell lines to cisplatin and cisplatin plus radiation through a ROS-mediated pathway. *Cancer Res*. 2018;78(13_suppl):2929.