Supplementary Online Content

Sio TT, Le-Rademacher JG, Leenstra JL, et al. Effect of doxepin mouthwash or diphenhydramine-lidocaine-antacid mouthwash vs placebo on radiotherapy-related oral mucositis pain: the Alliance A221304 randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.3504

This supplementary material has been provided by the authors to give readers additional information about their work.

eBox. Participating Institutions (30 groups)

The following institutional networks participated in this study: Altru Cancer Center, Grand Forks ND, Grant Seeger; Morton Plant Hospital, Clearwater FL, Peter Blumencranz; Mount Sinai Health System, Miami Beach, FL, Michael Schwartz; MedStar Georgetown University Hospital, Washington, DC, Chaitra Ujjani; Memorial Regional Hospital/Joe DiMaggio Children's Hospital, Hollywood FL, Luis Raez; Avera Cancer Institute, Sioux Falls, SD, Amy Krie; Colorado Cancer Research Program NCORP, Denver, CO Keren Sturtz, UG1CA189805; Mayo Clinic NCTN LAPS, Rochester, MN, Steven Alberts, U10CA180790; Michigan Cancer Research Consortium NCORP, Ann Arbor, MI, Philip Stella, UG1CA189971; Nevada Cancer Research Foundation NCORP, Las Vegas, NV, John Ellerton, UG1CA189829; Northern Indiana Cancer Research Consortium, South Bend, IN; The Ohio State University NCTN LAPS, Columbus, OH, Claire Verschraegen, U10CA180850; Roswell Park Cancer Institute NCTN LAPS, Buffalo, NY, U10CA180866; Southeast Clinical Oncology Research (SCOR) Consortium NCORP, Winston-Salem, NC, James Atkins, UG1CA189858; Washington University NCTN LAPS, Saint Louis, MO, Nancy Bartlett, U10CA180833; Virginia Commonwealth University Massey Cancer Center NCI MBCCOP, Richmond, VA, Steven Grossman, UG1CA189869; Geisinger Cancer Institute NCI Community Oncology Research Program, Danville, PA, Srilatha Hosur, UG1CA189847; Wichita NCI Community Oncology Research, Wichita, KS, Shaker Dakhil, UG1CA189808; Wisconsin NCI Community Oncology Research Program, Marshfield, WI, Anthony Jaslowski, UG1CA189956; Heartland Cancer Research NCORP, Decatur, IL, James Wade, UG1CA189830; Metro Minnesota Community Oncology Research Consortium, Saint Louis Park, MN, Daniel Anderson, UG1CA189863; Sanford NCI Community Oncology Research Program of the North Central Plains, Sioux Falls, SD, Preston Steen, UG1CA189825; NCORP of the Carolinas (Greenville Health System NCORP), Greenville, SC, Jeffrey Giguere, UG1CA189972; Columbia

University Minority Underserved NCORP, New York, NY, Gary Schwartz, UG1CA189960; Iowa-Wide Oncology Research Coalition NCORP, Des Moines, IA, Robert Behrens, UG1CA189816; Montana Cancer Consortium NCORP, Billings, MT, Benjamin Marchello, UG1CA189872; Cancer Research for the Ozarks NCORP, Springfield, MO, Jay Carlson, UG1CA189822; Cancer Research Consortium of West Michigan NCORP, Grand Rapids, MI, Kathleen Yost, UG1CA189860; Northwell Health NCORP, Lake Success, NY, Daniel Budman, UG1CA189850; UC San Diego Moores Cancer Center, La Jolla, CA, Barbara Parker

Abbreviations: NCI, National Cancer Institute; NCI MBCCOP, National Cancer Institute Minority-based Community Clinical Oncology Program; NCORP, National Cancer Institute Community Oncology Research Program; NCTN LAPS, National Clinical Trials Network-lead academic participating site.

eTable 1. Unpleasant Taste and Stinging/Burning Sensations for 105 Patients Who Continued With Cycle 2

Adverse Effect	Doxepin (n=35)	DLA (n=38)	Placebo (n=32)	Doxepin vs Placebo		DLA vs Placebo	
				Difference (95% CI)[a]	*P* Value[b]	Difference (95% CI)[c]	*P* Value[b]
Unpleasant taste[a]							
Day 1	2.0 (0-4.0)	1.0 (0-2.0)	1.0 (0-3.0)	0 (0 to 1.0)	.18	0 (−1.0 to 0)	.73
Day 2	2.0 (0-3.0)	1.0 (0-3.0)	1.0 (0-2.0)	1.0 (0 to 2.0)	.08	0 (0 to 1.0)	.27
Day 3	2.0 (0-4.0)	1.0 (0-3.5)	0 (0-2.0)	1 (0 to 2.0)	.007	1 (0 to 2.0)	.06
Day 4	1.0 (0-3.0)	1.0 (0-3.0)	0.5 (0-2.0)	0 (0 to 1.0)	.20	0 (0 to 2.0)	.42
Day 5	2.0 (0-3.0)	1.0 (0-2.5)	0 (0-2.0)	1 (0 to 2.0)	.11	0 (0 to 1.0)	.40
Day 6	1.0 (0-3.0)	1.0 (0-2.0)	0 (0-2.0)	0 (0 to 2.0)	.26	0 (0 to 1.0)	.78
Day 7	1.0 (0-2.0)	1.0 (0-5.0)	0 (0-2.0)	0 (0 to 1.0)	.37	0 (0 to 1.0)	.14
Stinging/burning[a]							
Day 1	3.0 (2.0-4.0)	1.0 (3.0)	1.0 (0-3.0)	1 (0 to 2.0)	.02	0 (0 to 1.0)	.88
Day 2	3.0 (2.0-4.0)	1.0 (3.0)	1.0 (0-3.0)	1 (0 to 2.0)	.02	0 (−1.0 to 1.0)	.81
Day 3	3.0 (2.0-5.0)	1.0 (0-3.0)	0.5 (0-2.0)	2 (1.0 to 3.0)	<.001	0 (0 to 1.0)	.27
Day 4	3.0 (2.0-5.0)	1.0 (0-2.0)	1.0 (0-0-2.0)	2 (1.0 to 3.0)	.002	0 (−1.0 to 1.0)	.97
Day 5	3.0 (2.0-5.0)	1.0 (0-2.0)	1.0 (0-2.0)	2 (1.0 to 3.0)	<.001	0 (−1.0 to 1.0)	.74
Day 6	3.0 (2.0-5.0)	1.0 (0-2.0)	1.0 (0-3.0)	2 (0 to 3.0)	.02	0 (−1.0 to 1.0)	.93

Adverse Effect	Doxepin (n=35)	DLA (n=38)	Placebo (n=32)	Doxepin vs Placebo		DLA vs Placebo	
				Difference (95% CI)[a]	*P* Value[b]	Difference (95% CI)[c]	*P* Value[b]
Day 7	3.0 (1.0-5.0)	1.0 (0-2.0)	0 (0-2.0)	2 (1.0 to 3.0)	.004	0 (0 to 1.0)	.24

Abbreviation: DLA, diphenhydramine-lidocaine-antacid.

[a] Median (IQR).

[b] All *P* values are reported by the Wilcoxon rank-sum test.

[c] Hodges-Lehmann estimate.

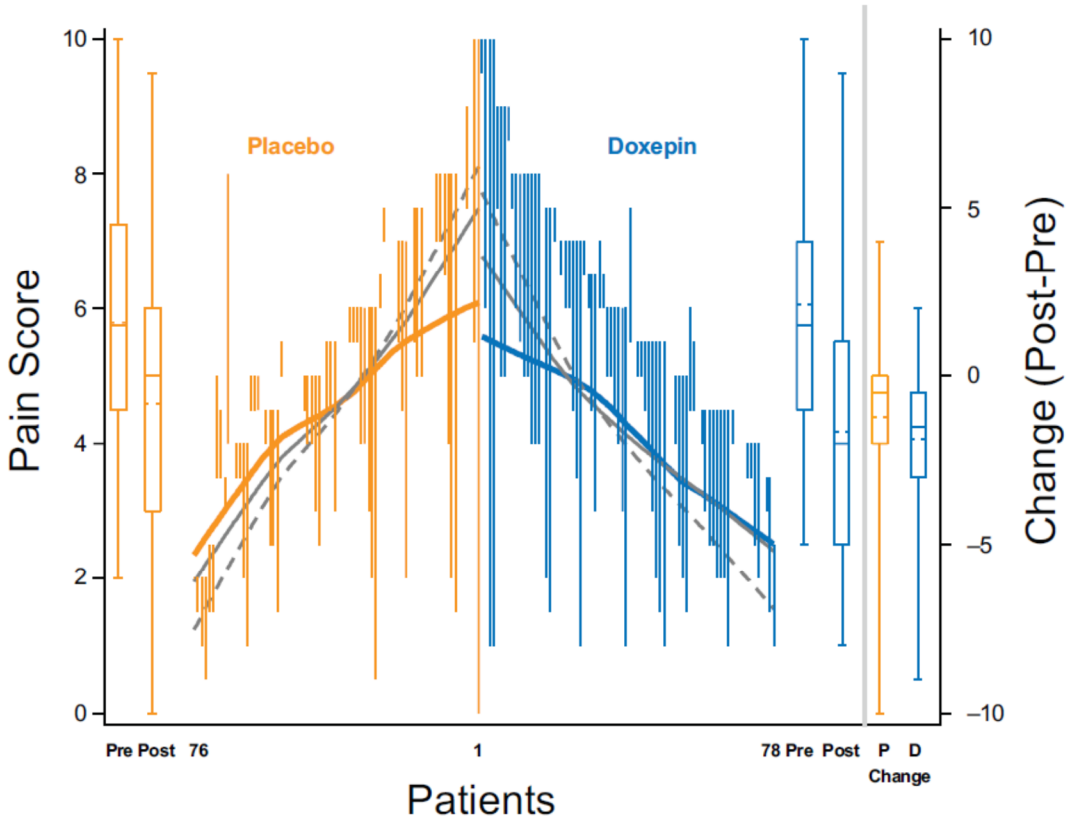
eTable 2. Baseline Analgesic Use During Cycle 1 and Cycle 2 (Continuation Phase)

	No. (%)			
Analgesic Agent	**DLA (n=76)**	**Doxepin (n=78)**	**Placebo (n=76)**	***P* Value**
NSAID (cycle 1)	5 (7)	6 (8)	5 (7)	.95
Non-NSAID (cycle 1)	6 (8)	3 (4)	2 (3)	.28
Short-acting opioid (cycle 1)	41 (54)	43 (55)	44 (58)	.88
Long-acting opioid (cycle 1)	11 (15)	11 (14)	10 (13)	.97
Other[a] (cycle 1)	5 (7)	8 (10)	4 (5)	.47
NSAID (cycle 2 [continuation])	1 (1)	3 (4)	4 (5)	.40
Non-NSAID (cycle 2 [continuation])	0 (0)	2 (3)	2 (3)	.37
Short-acting opioid (cycle 2 [continuation])	26 (34)	21 (27)	21 (28)	.55
Long-acting opioid (cycle 2 [continuation])	9 (12)	6 (8)	4 (5)	.33
Other[a] (cycle 2 [continuation])	3 (4)	1 (1)	3 (4)	.54

Abbreviation: DLA, diphenhydramine-lidocaine-antacid; NSAID, nonsteroidal anti-inflammatory drug.

[a] The "other" category included medications such as anxiolytics and medications for neuropathic pain that did not fit into other categories above.

eFigure 1



Parallel line plot for doxepin vs placebo

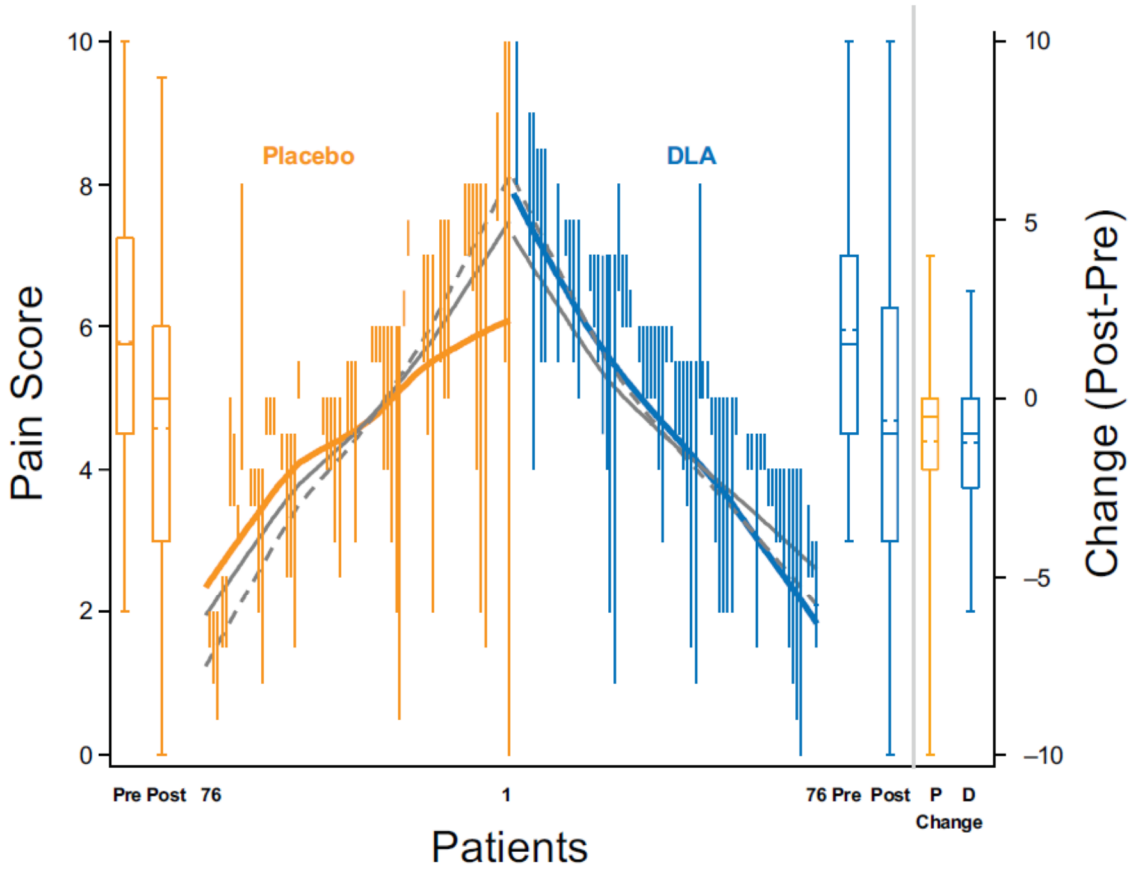
Each vertical line represents an individual patient's change in pain score from baseline to last reported value. The solid-color lines show lowess curves fit to the last pain score in each group. The dashed gray lines show the lowess curves, assuming the association between before (pre) and after (post) scores are additive (post minus pre is equal to a constant). The solid gray lines show the lowess curves, assuming a multiplicative relationship between the pre and post scores (post divided by pre equals a constant).

The 2 boxplots on the left summarize the distributions of pain scores at pre and post times for patients in the placebo group. The second pair of boxplots summarizes the distributions of pain scores at pre and post times for patients in the doxepin group. The final 2 boxplots on the right summarize the distribution of changes in pain score from pre to post for placebo (labeled as

”P”) and doxepin. In the boxplots, the solid lines in the middle of the box are the median values; the dashed lines in the middle of the box are the mean values; the top of the box is the 75th percentile; the bottom of the box is the 25th percentile; and the lines extending from the boxes extend out to the maximum and minimum values.

D indicates doxepin; P, placebo.

eFigure 2



Parallel line plot for DLA vs placebo

Each vertical line represents an individual patient's change in pain score from baseline to their last reported value. The solid-color lines show lowess curves fit to the last pain score in each group. The dashed gray lines show the lowess curves, assuming the association between before (pre) and after (post) scores are additive (post minus pre is equal to a constant), and the solid gray lines show the lowess curves assuming a multiplicative relationship between the pre and post scores (post divided by pre equals a constant).

The 2 boxplots on the left of the figure summarize the distributions of pain scores at pre and post times for patients on placebo. The second pair of boxplots summarizes the distributions of pain scores at pre and post times for patients on DLA. The final 2 boxplots on the right of the figure summarize the distribution of changes in pain score from pre to post for placebo (labeled

as “P”) and DLA. In the boxplots, the solid lines in the middle of the box are the median values, the dashed lines in the middle of the box are the mean values, the top of the box is the 75th percentile, the bottom of the box is the 25th percentile, the lines extending from the boxes extend out to the maximum and minimum values.

D indicates diphenhydramine-lidocaine-antacid; DLA, diphenhydramine-lidocaine-antacid; P, placebo.