GC4419, small molecule superoxide (SO) dismutase (SOD) mimetic: Randomized trial to reduce chemoradiotherapy (CRT)-induced mucositis (OM) in oral cavity (OC)/ oropharyngeal (OP) carcinoma (OCC) patients (pts)

Carryn M. Anderson, Christopher M. Lee, Deborah Saunders, Amarinthia Curtis, Neal Dunlap, Chaitali Nangia, Arielle S. Lee, Jon Holmlund, Jeffrey M. Brill, Stephen T. Sonis, Matt Downs, John M. Buatti

2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

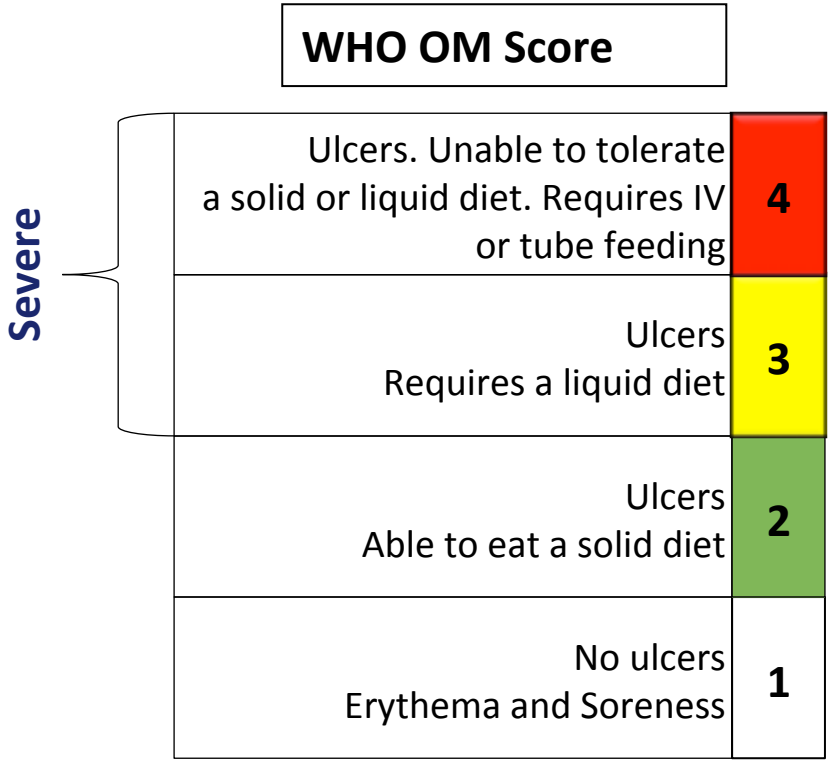
Faculty Disclosure

x	No, nothing financial to disclose
	Yes, please specify:

- Will discuss an investigational use of a drug
- Research funding provided by Galera Therapeutics, Inc
- Safety and efficacy results presented at ASCO Annual Meeting in Chicago, IL, June 3, 2018

Background

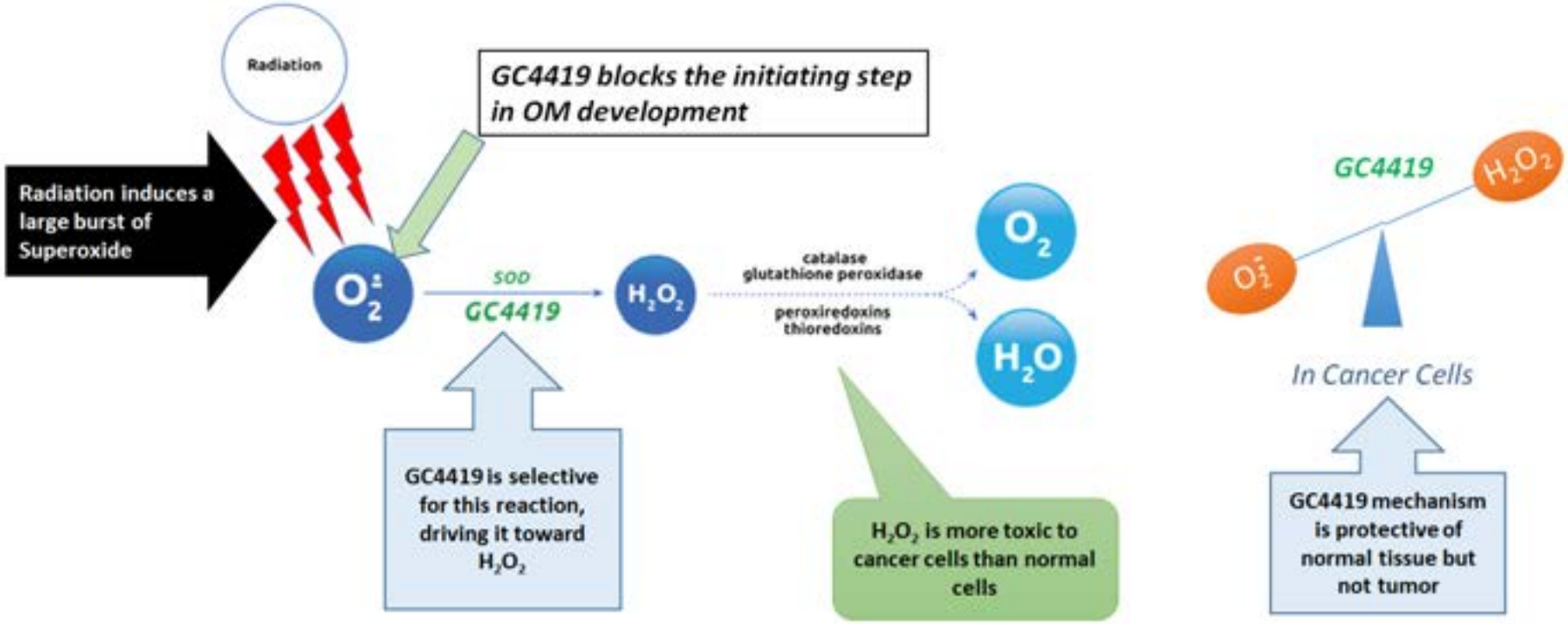
- IMRT + cisplatin is SOC for locally advanced oral cavity/ oropharyngeal cancer
- Approx 70% of patients develop severe OM (SOM), defined as WHO Grade 3 or 4
  - **~20-25% Grade 4**
  - **~40 Gy median onset**
  - **3-4 weeks median duration**



GC4419 Mechanistic Rationale:

Differential effect on cancer & normal cells

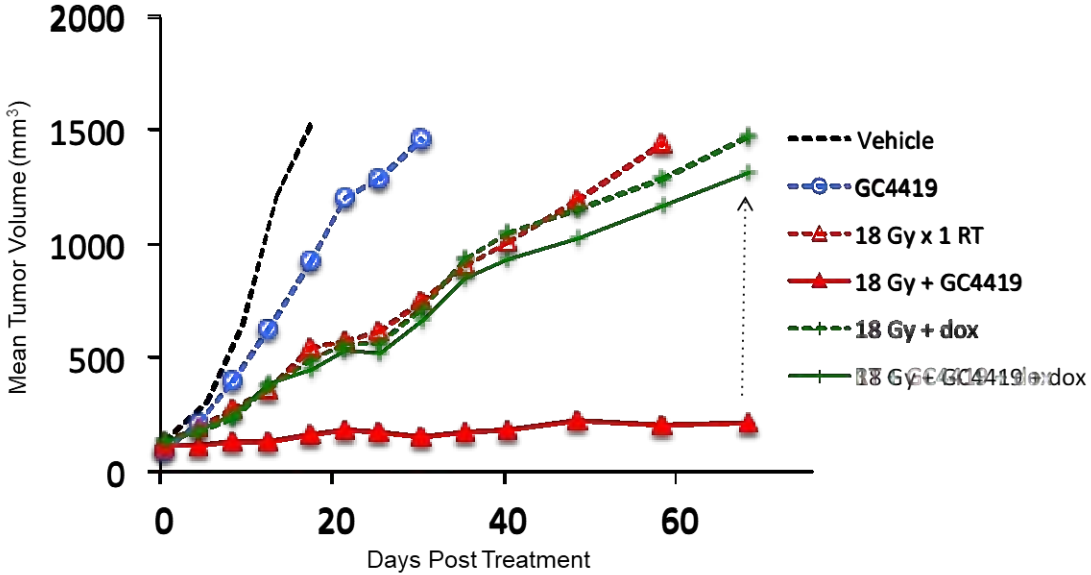
Superoxide is a key initiator of radiation-induced mucosal injury

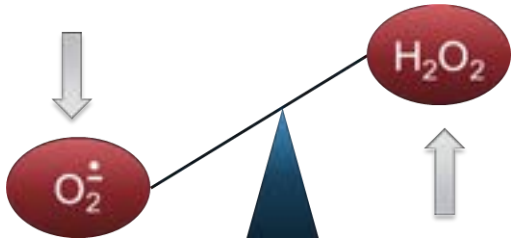


GC4419 Enhances Tumor Response via H_2O_2

Definitive Proof of H_2O_2 MOA in Tumors

- Catalase is a disposal enzyme for Hydrogen Peroxide (H_2O_2)
- $H1299^{CAT}$ – WT engineered for doxycycline-induced Catalase overexpression
- Overexpressing catalase blocks RT synergy by removing GC4419-generated H_2O_2





Sishc et al AACR 2018

GC4419 Phase 1b/2a Clinical Data

Anderson, et al. IJROBP, 2018 Feb 1;100(2):427-435

- Established doses (30, 90 mg) throughout IMRT for further study
  - 2.5 days median SOM duration
  - 29% SOM thru 60 Gy
- Acceptable safety profile
- 1 yr. tumor outcomes not impaired

GC4419 Phase 2b Study Outline

Patient Population	• Locally advanced OC/OP SCCa • Standard-of-care IMRT + cisplatin (weekly or Q3wk) • ≥50 Gy to 2+ oral sites
GC4419 Treatment	• 60-minute IV, Mon-Fri • Ending <60 minutes pre RT
Endpoints	• Grade 3 or 4 OM – duration, incidence, onset • Safety per NCI-CTCAE v4.03

Presented by: Carryn Anderson, MD

GC4419 Phase 2b Study Schema

2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

Randomize (1:1:1)

- Arm A: GC4419 90mg x 7 weeks
- Arm B: GC4419 30mg x 7 weeks
- Arm C: Placebo x 7 weeks

POST-RT FOLLOW UP for OM: up to 8 weeks post RT OR until the OM score is 0 or 1

COMPLETE

2-yr POST-RT TUMOR FOLLOW UP (OS, PFS, LRC, DM-free)

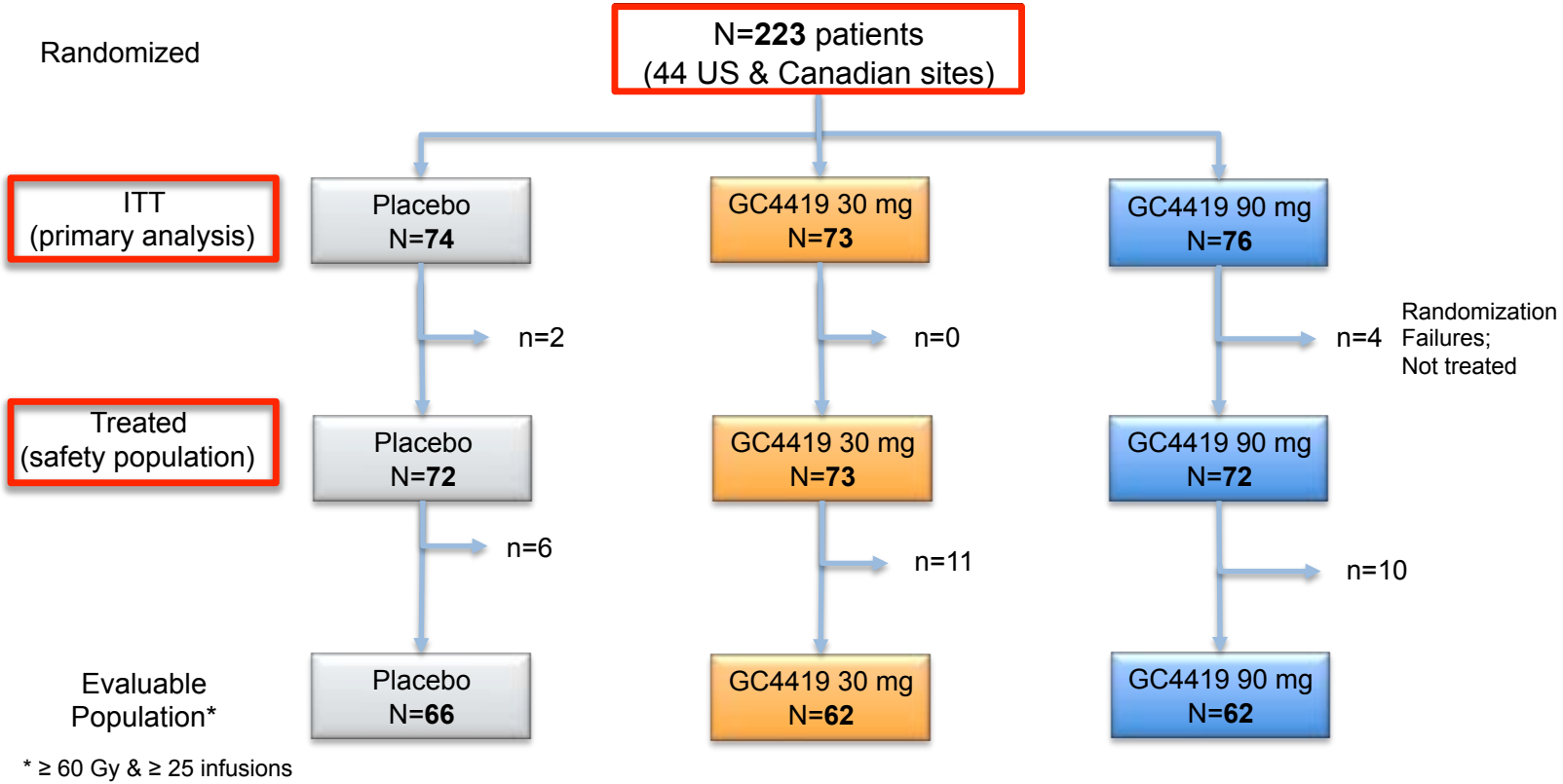
ONGOING

STRATIFICATION
Tumor HPV Status
Cisplatin dosing

Statistical Methods

- Efficacy on ITT population
- Each GC4419 arm compared separately vs placebo
- SOM duration: Van Elteren test on all pts/arm
  - First WHO of 3-4 to last WHO of 3-4 with no subsequent 3-4
  - NO WHO of 3-4: zero days' SOM duration
- Incidence: Cochran-Mantel-Haenszel test
- 2-sided α=0.05
- Duration on subset w/observed SOM explored descriptively

GC4419 Phase 2b Enrollment & Assignment



GC4419 Phase 2b Patient Characteristics (n=223)

Arms well-balanced

		Placebo (N=74)	30 mg GC4419 (N=73)	90 mg GC4419 (N=76)
Oropharyngeal (%)		76	84	71
Oral Cavity (%)		19	12	22
Unknown (%)		5	4	6
HPV positive (%)		72	73	71
negative (%)		28	27	29
Definitive (%)		80	77	75
Post-operative treatment (%)		20	23	25
Cisplatin q3wks (%)		38	37	39
qw (%)		62	63	61
Normal mucosa sites ≥ 50 Gy (%)	2	5	14	9
	3-4	55	48	54
	5+	39	39	37

Presented by: Carryn Anderson, MD

GC4419 Phase 2b Treatment Adherence (n=217)

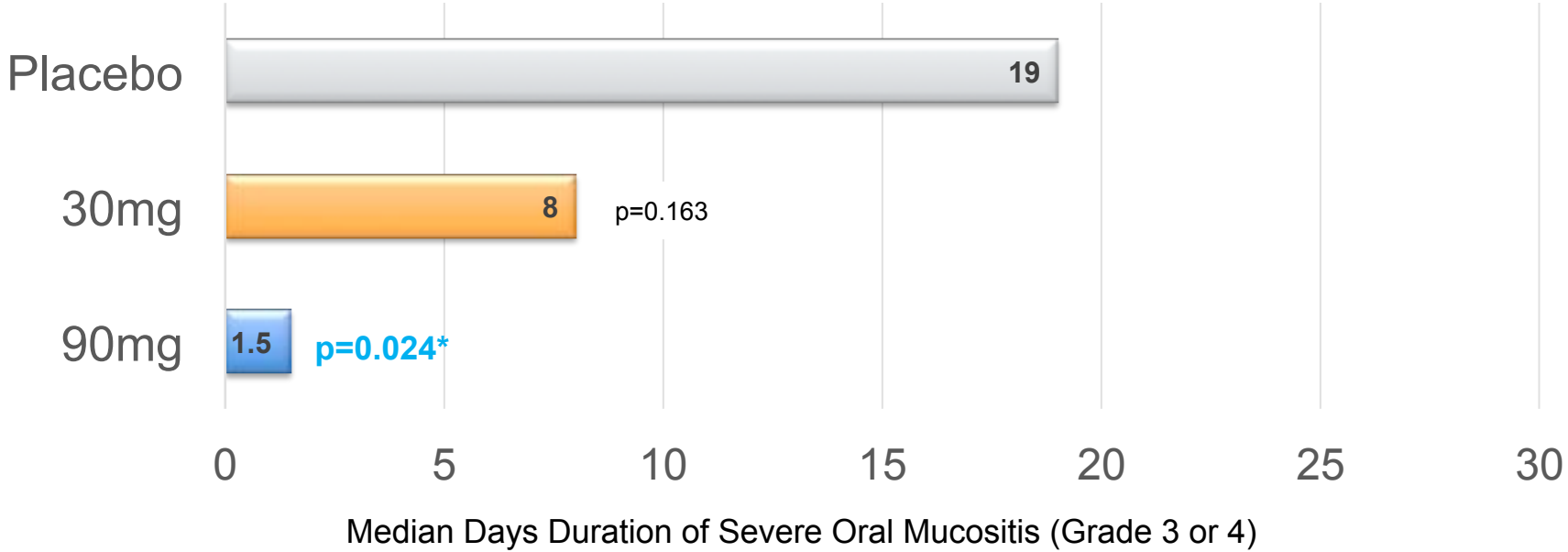
	Placebo (N=72)	30 mg GC4419 (N=73)	90 mg GC4419 (N=72)
IMRT Mean/Median total dose (range)	66.3/70 (11-70)	64.8/70 (4-72)	65.7/70 (11-74)
% receiving ≥ 60 Gy	94	89	92
% of subjects with RT treatment breaks ≥ 5 consecutive fractions	8	1	7
% w/Cisplatin total dose delivered ≥ 200 mg/m^2			
q3week	89	79	87
qw	80	70	78
% of planned GC4419/placebo doses received			
Median	100	97	100
Mean	93	89	90

Efficacy Results

Primary Endpoint – Duration of SOM (Grade 3+4)

92% Reduction in Median Duration of SOM

Duration was defined as number of days from 1st occurrence of grade 3 or 4 OM until the first event of grade 2 or less (there being no subsequent grade 3 or 4 events), and was calculated on the ITT population incl. those who did not develop SOM

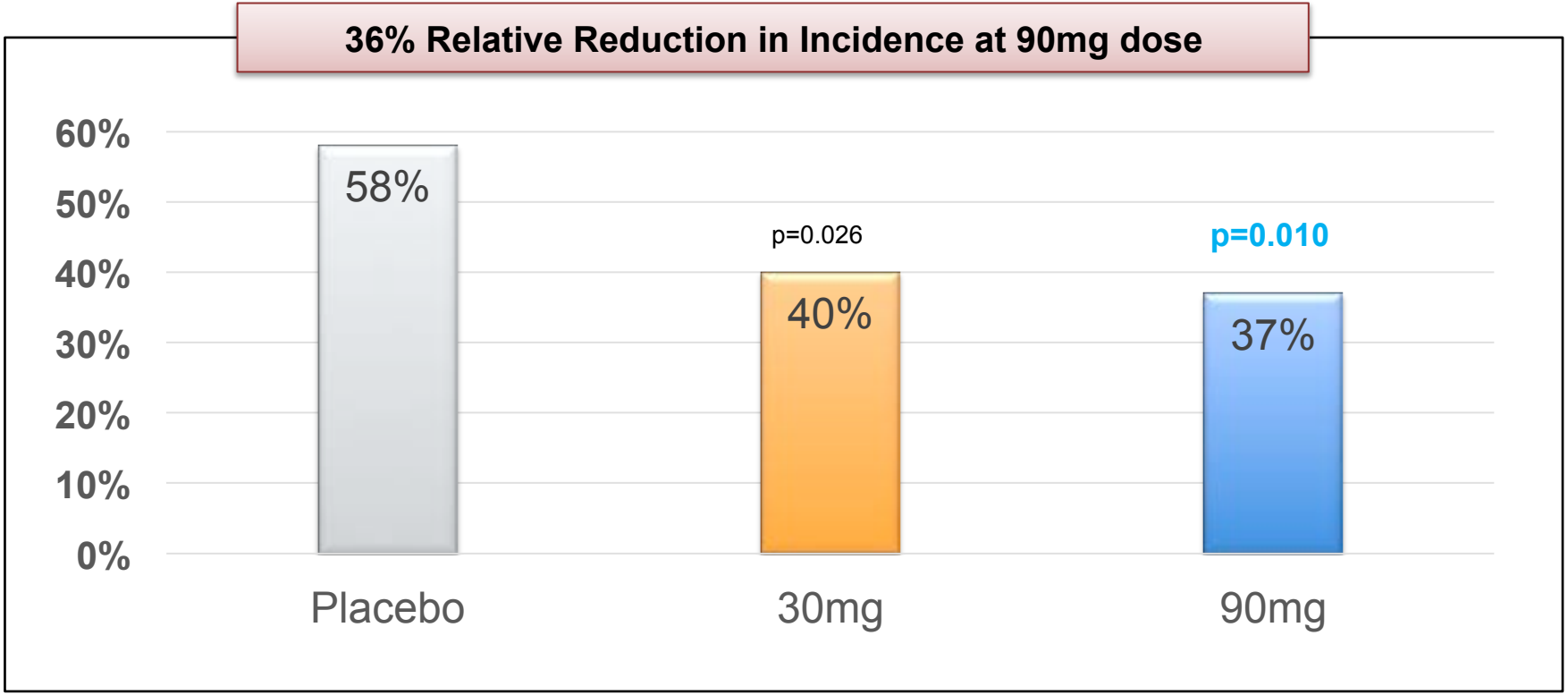


Subjects without SOM had a duration of 0 days

* Statistically significant (Van Elteren test)

Secondary Endpoint – Incidence of SOM (Grade 3+4)

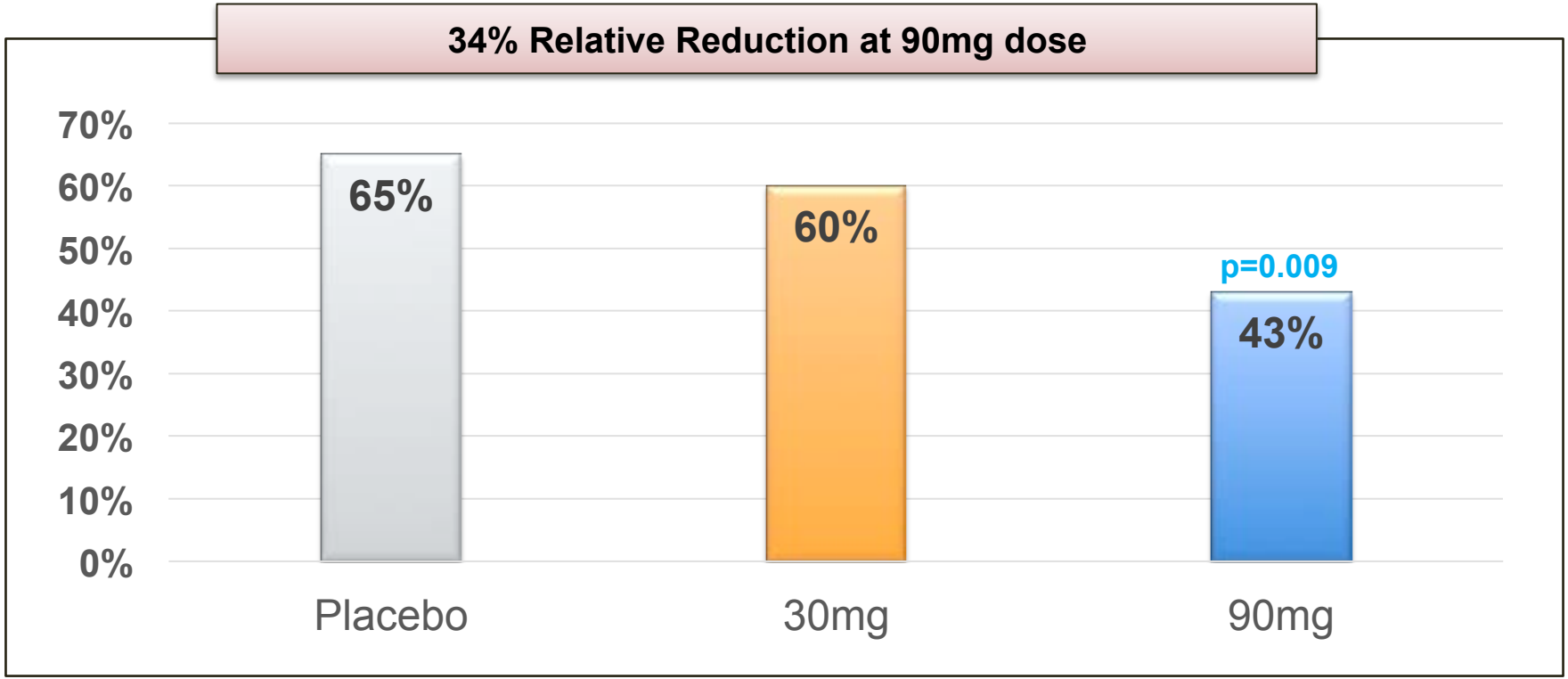
Thru 60 Gy



Nominal p values

Secondary Endpoint – Incidence of SOM (Grade 3+4)

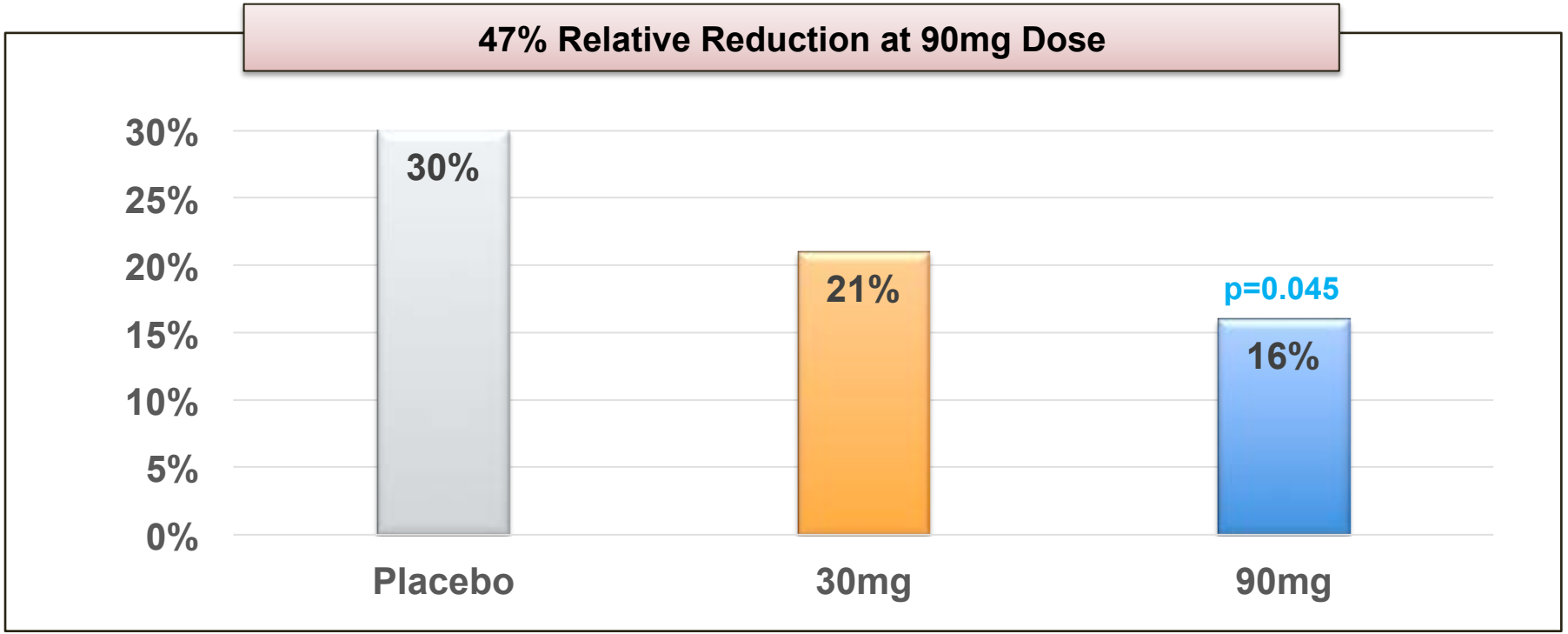
Thru all IMRT



Nominal p value

Secondary Endpoint – Incidence of Grade 4 OM

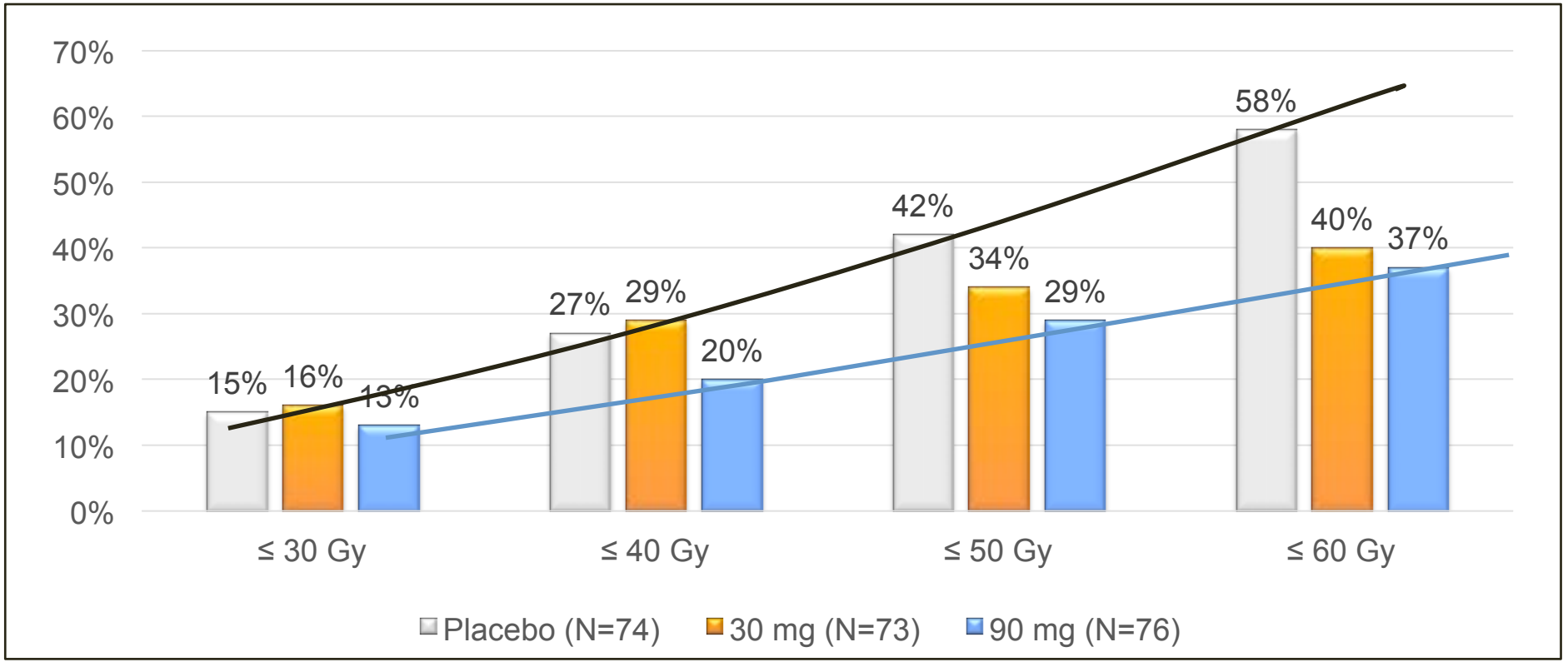
Thru all IMRT



Nominal p value

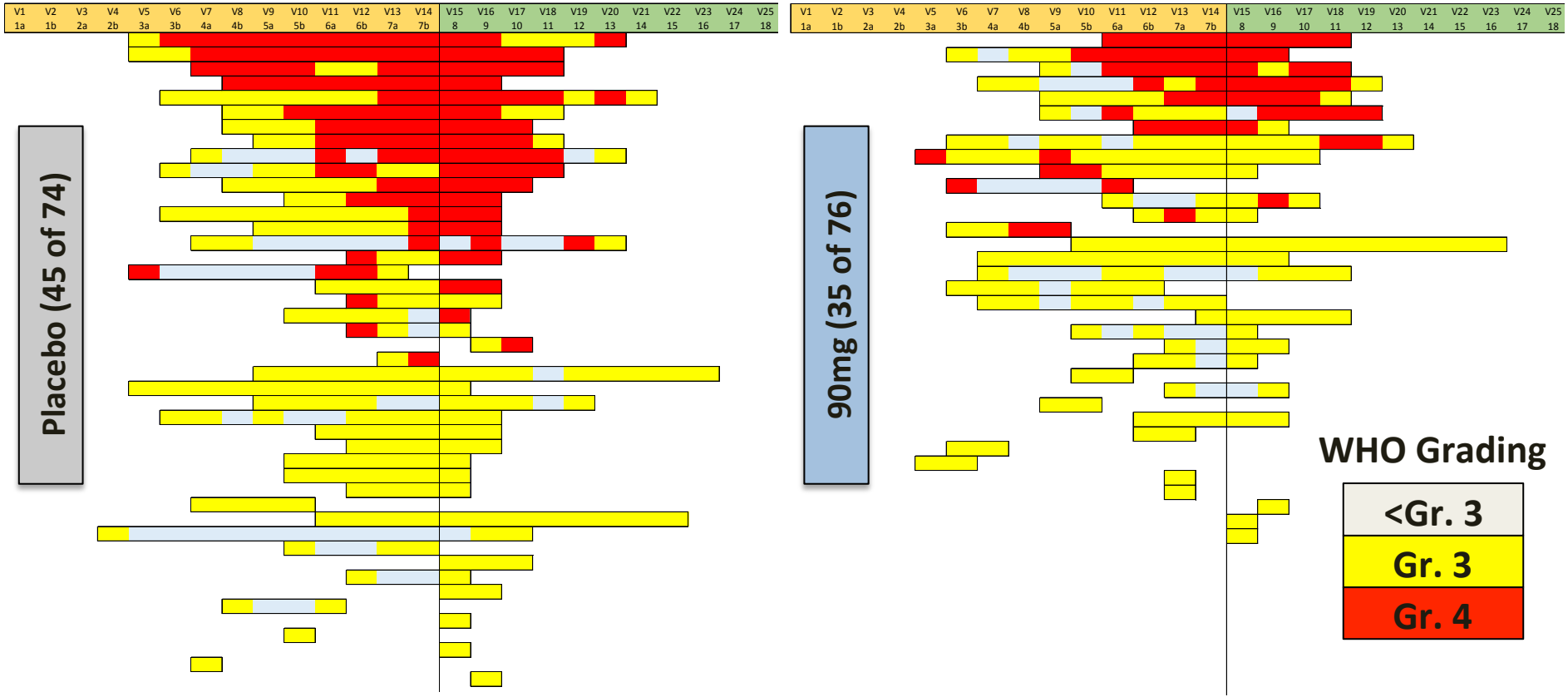
SOM Onset Delayed by GC4419

Cumulative incidence with progressive RT total dose



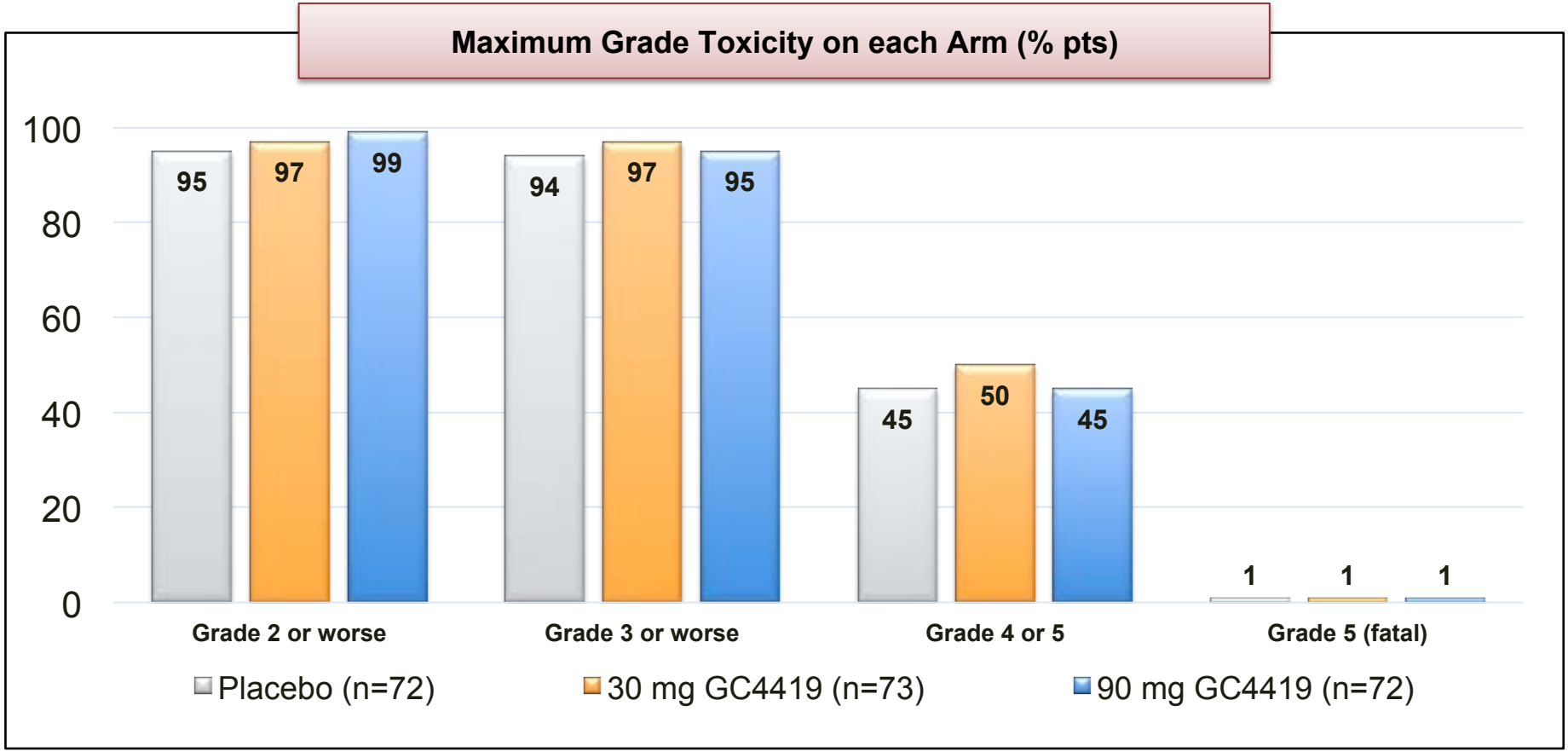
Individual Patient “Swimmers’ Plot”—90 mg v PBO

Grade, timing & duration limited to subjects with observed SOM

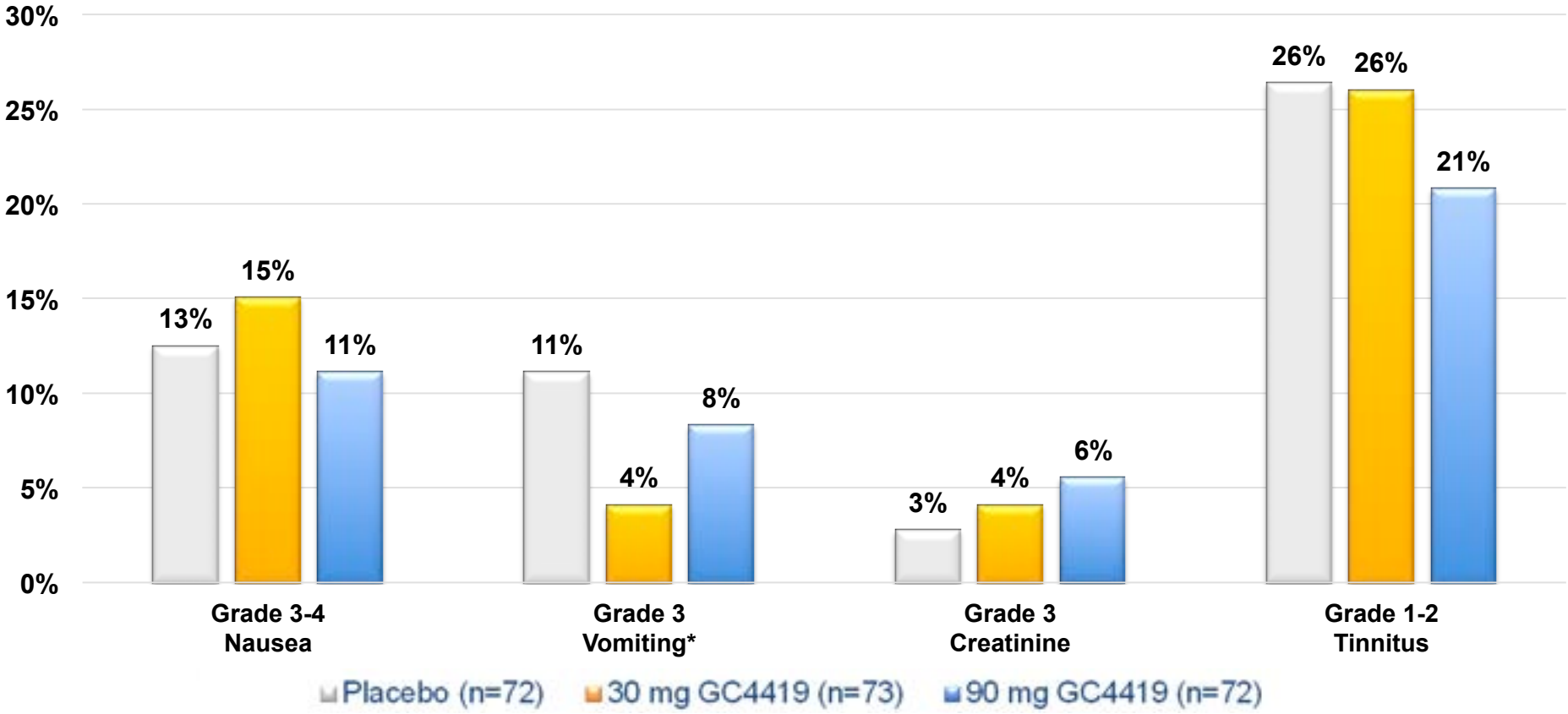


Safety Results

Comparable Safety Across All 3 Arms

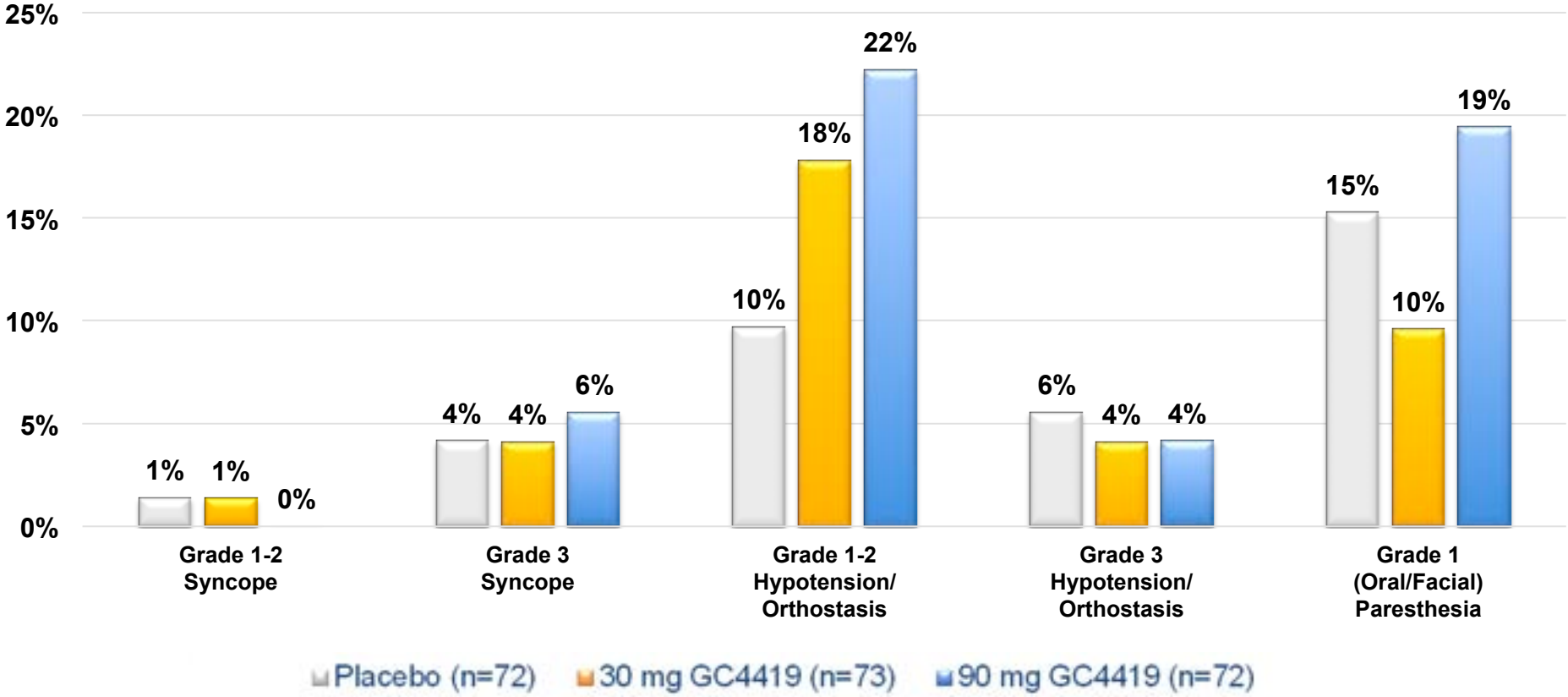


Similar Rates of Cisplatin Toxicity



GC4419 “expected” events were mild and transient

Mechanism-related potentiation of nitric oxide



Exploratory results

SOM and Patient Subgroups

- SOM duration and incidence not affected by:
  - Cisplatin schedule (weekly vs Q3wk)
  - Tumor HPV status
  - Definitive vs post-op IMRT
  - Patient-reported smoking status

2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

Other Exploratory Assessments

- Grade 2+ (ulcerative) OM comparable across arms
- G-tube use appeared to:
  - Track WHO score
  - Depend on institutional policy (not regulated per protocol)
- Narcotics were used commonly, early, ad lib
  - Likely for multiple reasons, including non-OM
  - Trend toward decreased median total dose on GC4419

Conclusions

- GC4419 (90 mg) provides clinically meaningful reduction in SOM
  - Duration
  - Incidence
  - Severity
- Intermediate results for 30 mg
- Safety profile comparable to placebo
- Future analyses include
  - Tumor control
  - Exploratory cytokine correlates
- FDA Breakthrough Designation & Fast Track Status
- Phase 3
  - 90mg vs Placebo

Acknowledgements – Enrolling Sites

Principal Investigator	Institution
Sharon Gordon, DDS, MPH, PhD	School of Dental Medicine at East Carolina University
Philip Kovoor, MD/ Mark Engleman, MD	Texas Oncology, Plano West
Roberto Arevalo-Araujo, MD	Pasco Pinellas Cancer Center
Abhinand Peddada, MD	Renown Regional Medical Center
James Wheeler, MD	Goshen Center for Cancer Care
Voichita Bar Ad, MD	Thomas-Jefferson University Hospital
Kyle Colvett, MD	Mountain States Health Alliance Research Department
Douglas Miller, MD	Meridian Health Research Services
Anshu Jain, MD	Ashland-Bellefonte Cancer Center
Madhavi Venigalla, MD	Lakeland Regional Cancer Center
Sanjiv Agarwala, MD	St. Luke's Hospital Cancer Center
Mercedes Porosnicu, MD/ Marcelo Bonomi, MD	Wake Forest Baptist Health
Madhu Garg, MD	Montefiore Medical Center
Francis Worden, MD	University of Michigan
Dukagjin Blakaj, MD, PhD	Ohio State University
Elizabeth Feldman, MS, DMD	UF Health Cancer Center at Orlando Health
Ariel Birnbaum, MD	Rhode Island Hospital
Michael Trendle, MD/ Clint Daniel Kingsley, MD	Ellis Fischel Cancer Center - University of Missouri
Ronald Maggiore, MD/ Daniel Clayburgh, MD, PhD	VA Portland Health Care System
Kevin Collins, MD, JD	Fowler Family Center for Cancer Care

Principal Investigator	Institution
Waqas Rehman, MD	Hunterdon Hematology Oncology, LLC
Leander Cannick III, MD	Anmed Health Cancer Center
William Wisbeck, MD	Providence Regional Medical Center
Steve P. Lee, MD, PhD	Long Beach Veteran Affairs Healthcare System
Vernon King, MD	St. Mary's Regional Cancer Center
Maria Matsangou, MD	Northwestern University
Ganesh Kudva, MD/ Bianca de Souza, MD	Henry Ford Allegiance Health
Charles Holladay, MD	Charleston Cancer Center
Francois Vincent, MD	Centre Intégré Universitaire de Santé et de Services Sociaux de la Mauricie et du Centre du Québec
Joseph Kelley, MD, PhD	University of Tennessee Medical Center
Jorge Nieva, MD	USC Norris Cancer Center
Rex Mowat, MD	Toledo Clinic Cancer Center
Maura Barry, MD	The University of Vermont Cancer Center
Celine Ord, MD/ Shymal Patel, MD	University of Arizona Cancer Center at Dignity Health St. Joseph's
Patrick Cobb, MD, FACP	St. Vincent Frontier Cancer Center
Alan Gowan, DO	Scott & White Memorial Hospital and Clinic
Khalil Sultanem, MD	Jewish General Hospital

Acknowledgements

- Participating Patients & their Families
- Alira Health
  - Chelsea Eckman
  - Chris Rao
  - Beth Rayworth
  - Jen Petrillo
- Galera Therapeutics, Inc.
  - Dennis Riley, Ph.D.
- Statistics Collaborative
  - Janet Wittes, Ph.D.
- Novella Clinical
  - Mariana Hildesheim

Questions?
Interested in Phase 3?

carryn-anderson@uiowa.edu

2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

SOM duration and incidence similar across other subgroups

GC4419 effects descriptively similar across subgroups (data not shown)

	Tumor HPV Status		Treatment setting		Reported smoking status	
	(+)	(-)	Post-op	Definitive	Never	Past/Current
n	160	63	51	172	65	158
Duration (days)						
Median	8.5	8.0	16.0	8.0	19.0	8.0
Mean	22.7	19.6	24.1	21.1	24.9	20.6
Incidence (%)						
Gr 3-4 through 60 Gy	47	40	49	44	57	40
Gr 3-4 through IMRT	56	57	61	65	63	53

Source: SAS tables 5.5 and 6.5

SOM duration and incidence: similar for weekly or Q3wk platinum

GC4419 improved SOM for both subgroups

	Overall (N=223)		90 mg GC4419 (N=76)		30 mg GC4419 (N=73)		Placebo (N=74)	
	wkly	Q3wk	wkly	Q3wk	wkly	Q3wk	wkly	Q3wk
n	138	85	46	30	46	27	46	28
Duration (days)								
Median	11.5	8.0	2.3	0.8	8.0	8.0	23.5	15.0
Mean	20.2	20.2	17.9	17.2	19.2	20.9	31.4	22.8
Incidence (%)								
Gr 3-4 through 60 Gy	49	39	43	27	37	44	65	46
Gr 3-4 through IMRT	57	54	48	37	57	67	67	61

Source: SAS tables 5.5 and 6.5

Narcotic use—lower median @ 90 mg vs Placebo

> 50% of patients had no OM (WHO=0) at first narcotic use

	Placebo (N=72)	30 mg (n=73)	90 mg (N=72)
% of patients who took any narcotics	86%	86%	88%
Median total morphine equivalents			
• All OM grades (0-4)	847	818	752
• Max OM Gr 1-4	950	890	713
• Gr 2-4	1000	1024	752
• Gr 3-4	1410	1053	752
• Gr 4	1287	1308	1202
Median days to first narcotic	5	9	5
% of patients with WHO=0 at first narcotic use	51%	58%	51%

2018
28-30 JUNE
VIENNA, AUSTRIA
SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

G-tube placement and use

	Placebo	90 mg	Difference
G-tubes placed (overall)	50	41	18%
G-tubes placed (“emergent,” post day 1)	16	13	19%
Patients with any G-tube feedings	42	36	14%

			Number with G-tube use		
	Dose	N	total	emergent	prophylactic
Max WHO of 4	PBO	22	19 (86%)	8	11
	90 mg	12	10 (83%)	3	7
Max WHO of 3	PBO	26	14 (54%)	4	10
	90 mg	21	12 (57%)	6	6
Max WHO of <3	PBO	26	9 (35%)	3	6
	90 mg	43	14 (33%)	4	10