Galera Therapeutics, Inc

# Transforming Radiotherapy

*with*

# Dismutase Mimetics

January 2020

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Whenever the Company uses the terms "transform radiotherapy" or "transforming radiotherapy" in this presentation, it is referring to its mission statement.

# Transforming Radiotherapy With Dismutase Mimetics

## Reducing Toxicity

Rapid elimination of Superoxide ($O_2^{\bullet-}$)

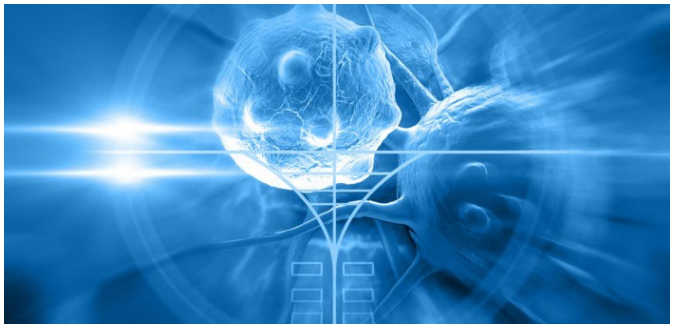
Severe Oral Mucositis in Head & Neck Cancer

Esophagitis in NSC Lung Cancer

IMRT

Other IMRT-related Toxicities

**Normal tissue toxicity limits optimal radiotherapy treatment of tumor**

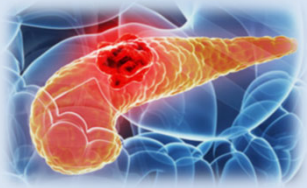


Over half of cancer patients receive radiotherapy as part of their care[1, 2]

## Increasing Anti-Cancer Efficacy

Increase $H_2O_2$ in tumors

Locally-Advanced Pancreatic Cancer



Centrally-Located NSC Lung Cancer

Other SBRT-Treated Tumors

SBRT

**Radiotherapy is standard-of-care for many local tumors but need remains for greater efficacy**

[1] *Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment… Cancer. 2005;104:1129-1137*

[2] *Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer. 2011;11:239-253*

# Investment Highlights

**Lead Product in Phase 3**

Robust Efficacy in Randomized Phase 2b (n=223)

- Breakthrough Therapy designation
- Single Phase 3 sufficient for registration (n=365)


**Substantial Unmet Medical Need**

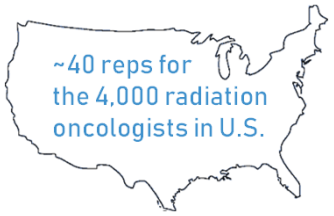
Radiation-Related Severe Oral Mucositis (SOM)

- 65,000 patients/year in US get Head & Neck Cancer
- SOM most burdensome side-effect: 70% of patients

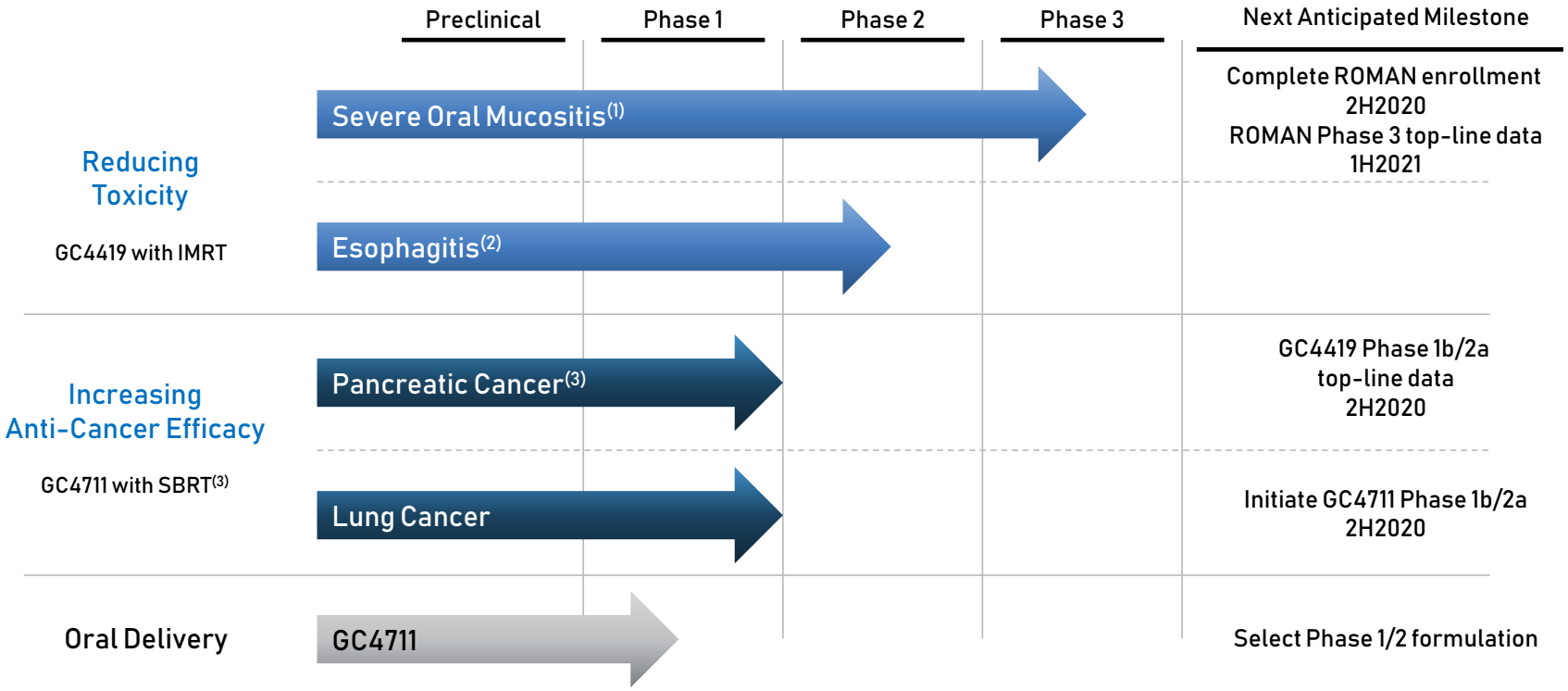
**Focused Commercial Opportunity**

Galera Intends to Commercialize in US

- ~60% treatments in ~500 centers
- Current SOM treatments are marginally effective



# Clinical Stage Pipeline




(1) We also plan to conduct a Phase 2a multi-center trial in Europe assessing the safety of 90 mg GC4419 in up to 70 patients with HNC undergoing standard-of-care radiotherapy. We plan to initiate this trial in the first half of 2020.
(2) Phase 2a trial in patients with lung cancer building on GC4419 safety and tolerability findings in patients with HNC SOM studies.
(3) Observations from our Phase 1b/2a pilot trial of GC4419 in combination with SBRT in patients with LAPC whose tumor cannot be resected will be used to help develop GC4711 to increase the anti-cancer efficacy of SBRT.

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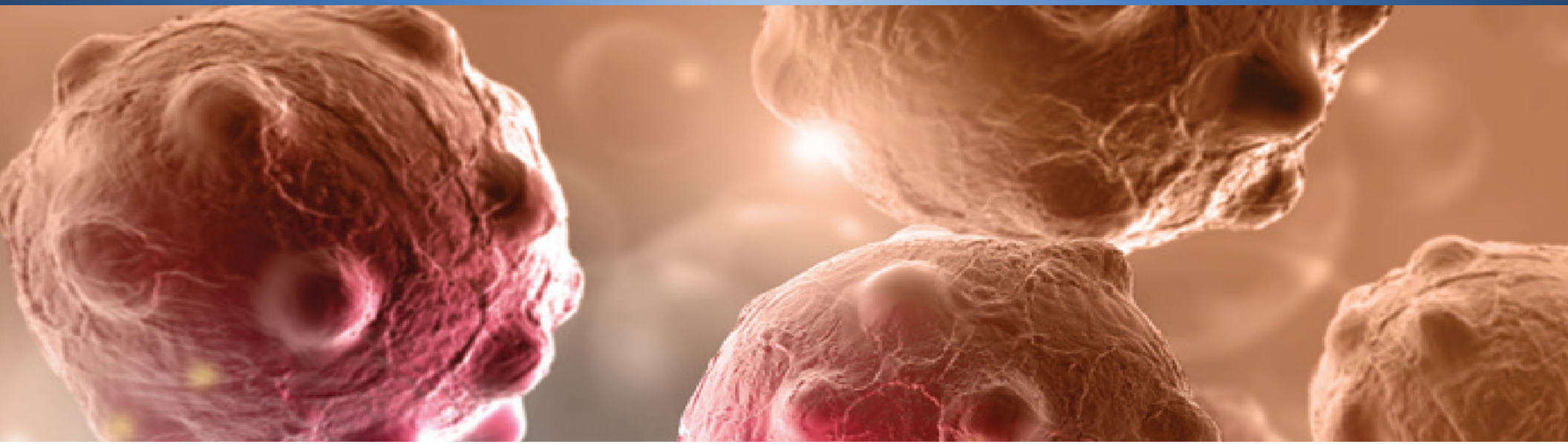
# Dismutase Technology & Portfolio

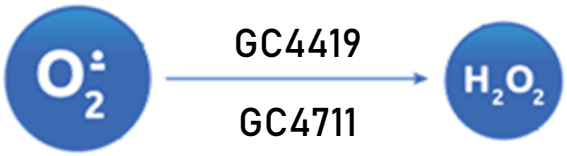


# Unique Technology

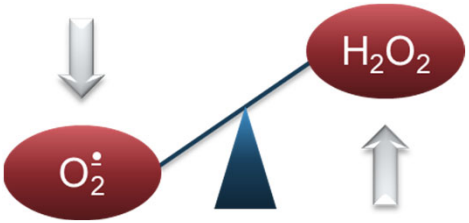
Dismutase Mimetics

Small Molecule Enzyme Mimetics

- Mimic human superoxide dismutase (SOD) enzymes
- Rapidly convert superoxide ($O_2^{\cdot}$) to hydrogen peroxide ($H_2O_2$)




Shifts balance in normal & cancer cells from superoxide to hydrogen peroxide

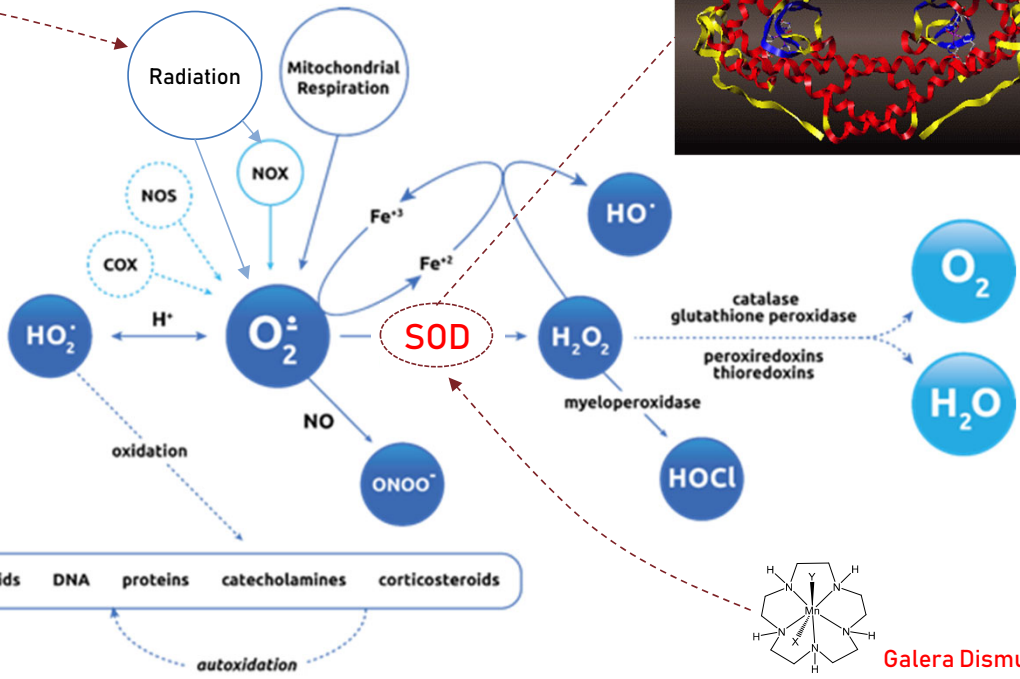


# Radiation & Superoxide

## Radiation

Produces bursts of superoxide, causing
- Radiolysis of water
- Stimulation of NOX, etc.
- Inflammatory response

RT-induced superoxide overwhelms SODs, resulting in normal tissue damage








Galera Dismutase Mimetics

## Superoxide ($O_2^{\cdot-}$)

Produced by every cell as part of cellular respiration & substrate for HOCl.

Highly toxic & leads to cell death.

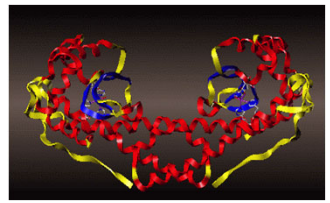
SOD enzymes evolved to rapidly convert $O_2^{\cdot-}$ to $H_2O_2$ ($10^{-7}$ seconds)

# Galera's Dismutase Mimetics

**Natural SOD Enzymes**

Limitations of Natural SOD Enzymes

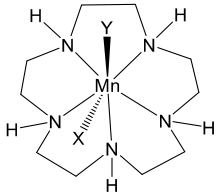
- Large size prevents entry into cells
- Immunogenicity & short half-lives
- Inactivation/inhibition by reactive oxygen species



**Small Molecule Mimetics**

Challenge: suitable small molecule dismutase mimetics

- Fast catalytic rates & high selectivity for superoxide
- Firmly hold manganese in macrocyclic ring
- Stable, safe & suitable for manufacturing




Dismutase Mimetics Core Structure
Pentaaza Macrocycles

## Small Molecule Dismutase Mimetics with Attractive Drug Characteristics

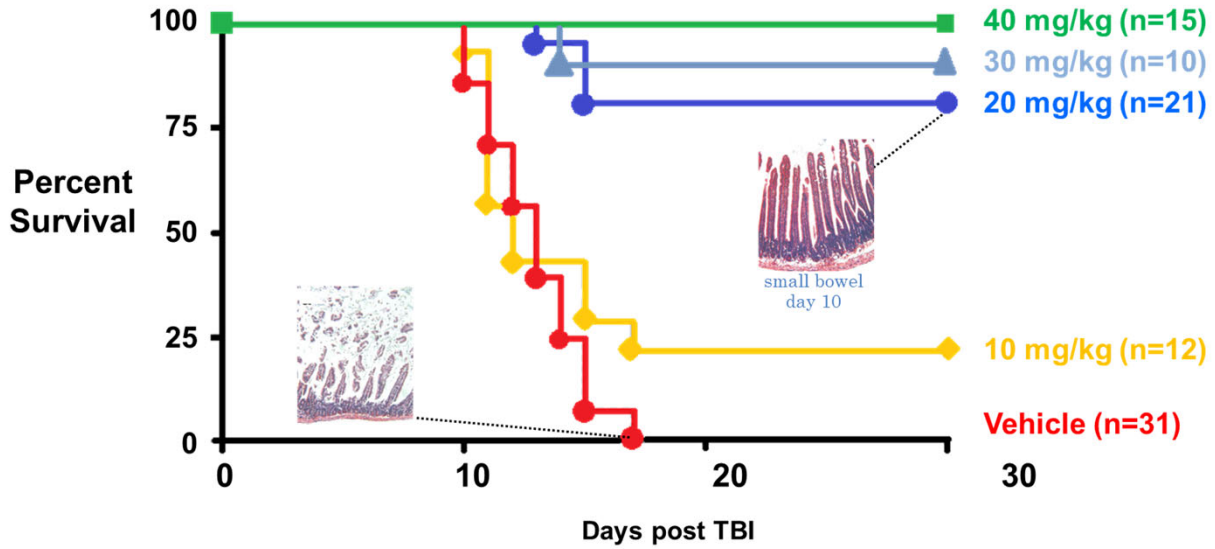
| Speed | Selectivity | Stability | Safety | Synthesis |
|---|---|---|---|---|
| Comparable to native SODs ($2x10^7$ molecules per sec) | Interact with superoxide alone, not other reactive oxygen species | Firmly hold Mn atom in macrocyclic ring | Well-tolerated preclinically and clinically | Efficient & cost-effective manufacturing process |

# Dismutase Mimetics Reduce Radiation Toxicities

**Reduce Radiation Mucositis**

Lethal dose of Total Body Irradiation (8.5 Gy) to mice

- 100% death on control, 100% survival with 40mg/kg
- Main cause of death was intestinal mucositis



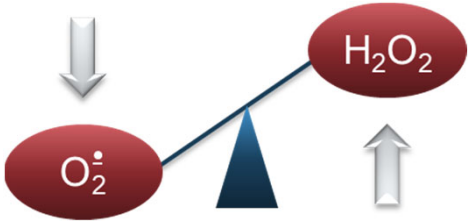

*Thompson, et al., Free Radical Research, 44(5):529-540, 2010*
*Galera internal data*

# Dismutase Mimetics Increase Anti-Cancer Efficacy with High Fraction-Dose RT

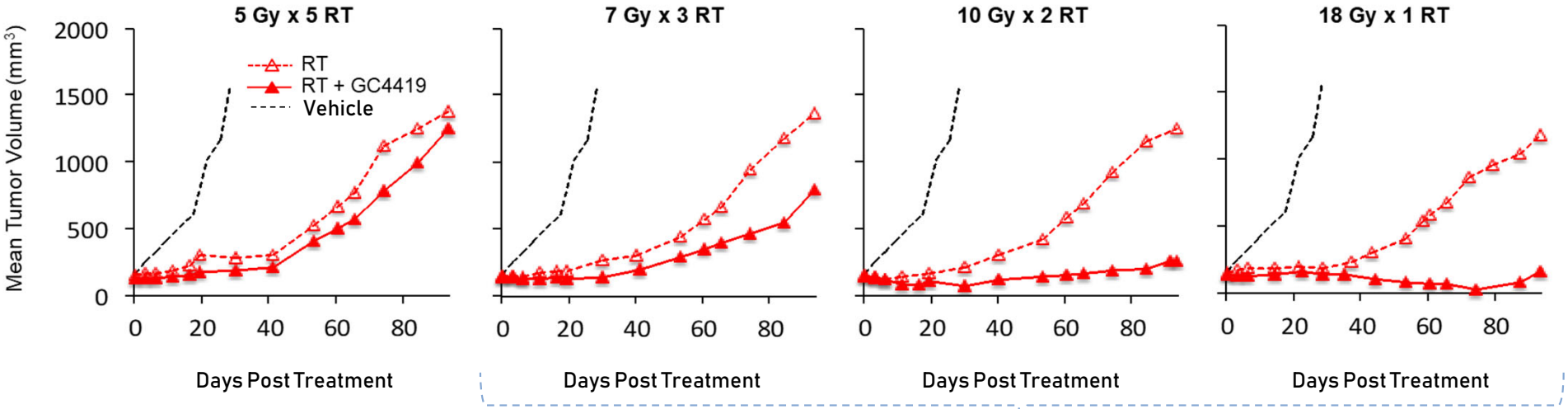
**Increase Radiotherapy Efficacy**

Focal irradiation of human tumor xenografts (H1299 NSCLC) in mice

- RT anti-cancer synergy of GC4419 increases with bigger RT fractions:
- Bigger fraction → More $O_2$ → More $H_2O_2$




RT with Biological Equivalent Doses



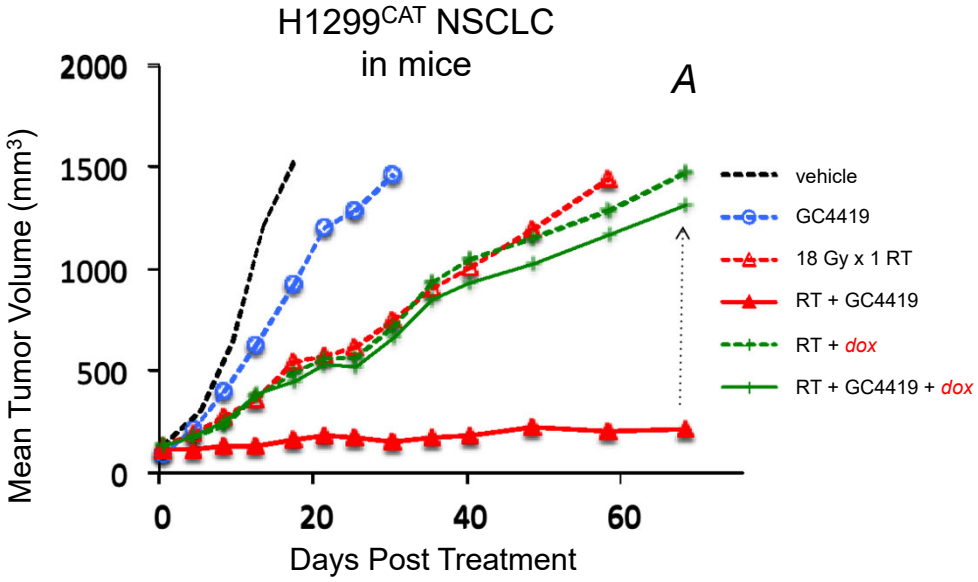

*Courtesy of M Story (UTSW)*

# …Increase Anti-Cancer Efficacy via $H_2O_2$

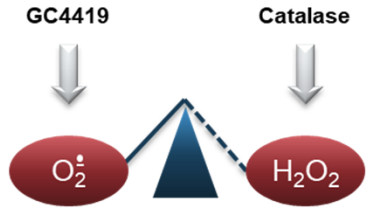
**$H_2O_2$ Drives Increased Efficacy**

SBRT Irradiation of human tumor-derived xenografts ($H1299^{CAT}$) in mice

- Engineered to overexpress catalase (disposes of $H_2O_2$) when induced by doxycycline
- Overexpressing catalase blocks synergy with RT by removing GC4419-generated $H_2O_2$




Tumor tissue $H_2O_2$ reduced when doxycycline added to RT + GC4419



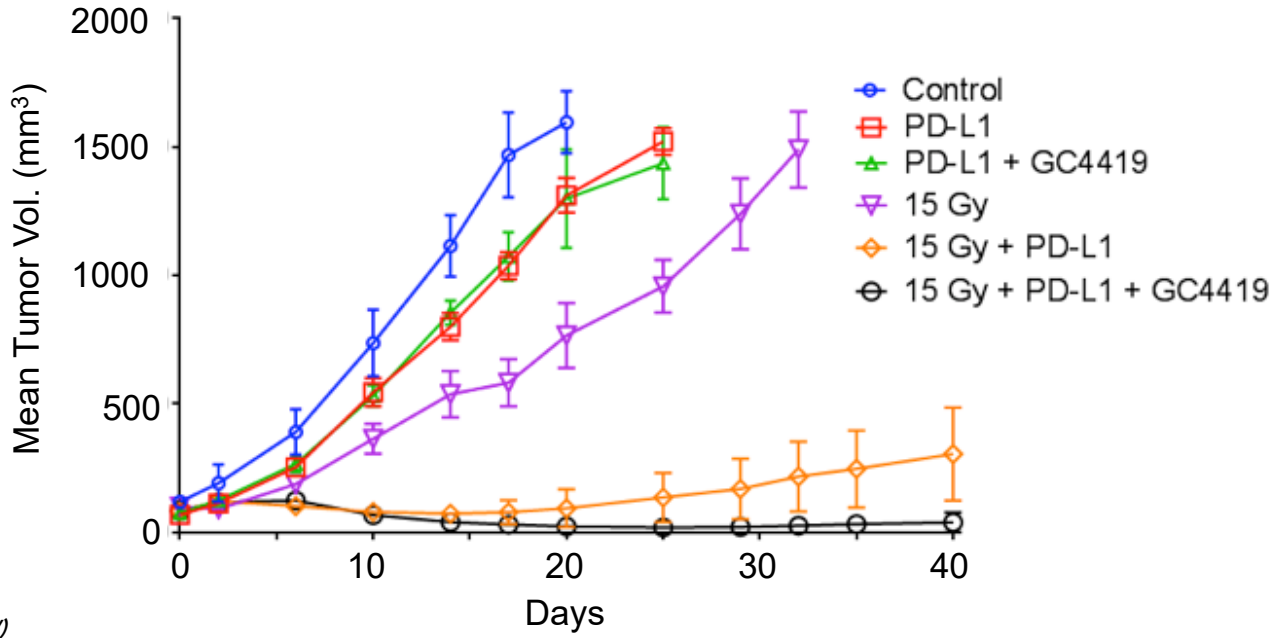

*Sishc et al, AACR 2018*

# …Also Enhance Immuno-Radiotherapy

Increase IO + SBRT Efficacy

SBRT + Checkpoint Inhibitor therapy of syngeneic tumors (LLC) in mice

- GC4419 enhances tumor response to SBRT + anti-PD-L1, PD-1 or CTLA-4
- Also appeared to reduce metastasis & increase response in unirradiated secondary tumors




*Courtesy of M Story (UTSW)*

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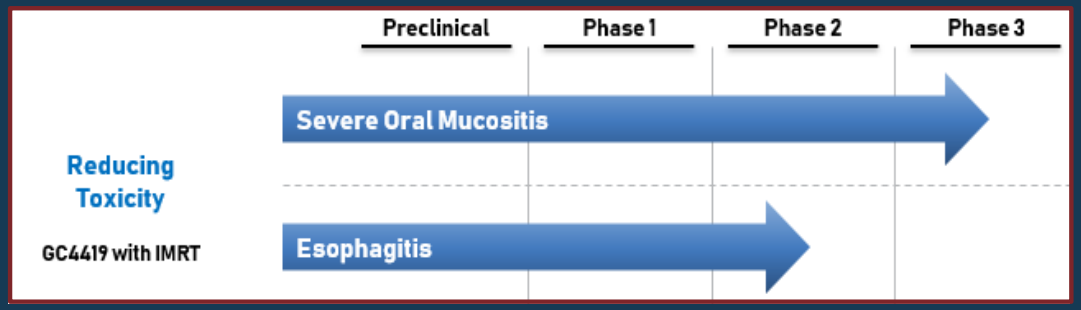
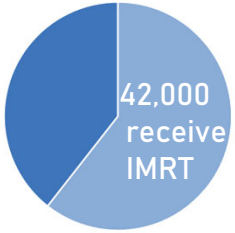



# Clinical Trials: Reducing Toxicity of IMRT

# Oral Mucositis in HNC – Large Unmet Medical Need

## SOM and Head & Neck Cancer

- ~65,000 new HNC patients in US/Year
- ~65% get IMRT & cisplatin as standard-of-care
- ~70% of patients get SOM (can't eat)
- ~20-30% get Grade 4 (can't eat or drink)
- No approved drug available




## Can Have Devastating Complications

- **Dehydration & Malnutrition**
  Often requiring PEG tube feeding
- **Pain**
  Often severe pain requiring opioids
- **Treatment interruption**
  Each week of treatment delay decreases tumor control by >10%
- **Increased economic burden**
  OM Dx → ~$32,000 in additional medical expenses in first 6 months from RT start

WHO Grading Scale

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

SEVERE

## Current Treatments are Marginally Effective

MASCC / ISOO Guidelines for HNC OM

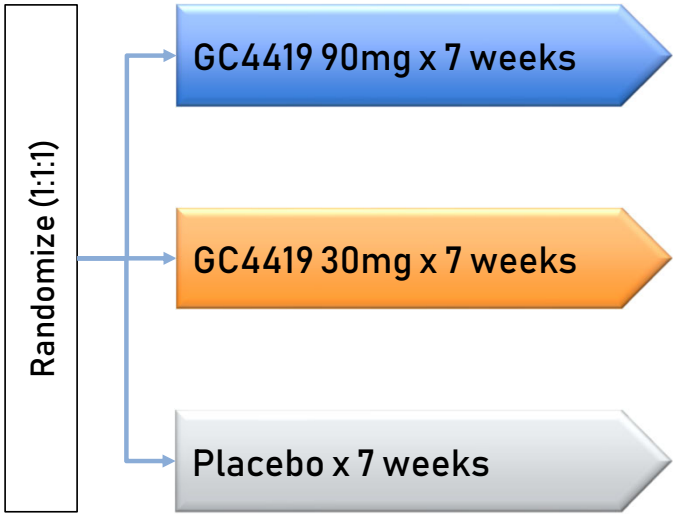
| Treatment Approach | Recommended for HNC OM due to RT? |
|---|---|
| Basic oral care | ✓ |
| Anti-microbials, coating agents, anesthetics, & analgesics (0.2% morphine mouthwash) | ✓ |
| Anti-inflammatories, benzydamine | ? |
| Low level laser & other light therapy | ? |
| Cryotherapy for 5-FU chemotherapy | ✗ |
| Natural & other agents | ✗ |

# GT-201: 223-Patient Randomized Phase 2b OM Trial

*Supportive trial to the ROMAN Phase 3 for the NDA*

## Trial Design

| | |
|---|---|
| **Treatment** | • GC4419 90mg, 30mg, or placebo<br>• 60 minute IV infusion, Mon-Fri.<br>• Ending <60 mins pre-RT |
| **Population** | • Patients with HNC<br>• Locally-advanced, squamous cell<br>• Eligible for SoC – 7 weeks IMRT + cisplatin |
| **Stratification Factors** | • Tumor HPV Status: positive or negative<br>• Cisplatin Schedule: q3wks or weekly |
| **Endpoints** | • Primary – Reduction in median duration of SOM – WHO Grades 3 & 4 |
| | • Secondary – Reduction in incidence and severity of SOM at pre-specified timepoints<br>• Exploratory – Time to SOM onset |
| | • Tumor outcomes (2 year follow-up)<br>• Locoregional control, distant mets, PFS, OS |




**WHO Grading Scale**

1 — No ulcers, Erythema and soreness

2 — Ulcers, Able to eat a solid diet

SEVERE

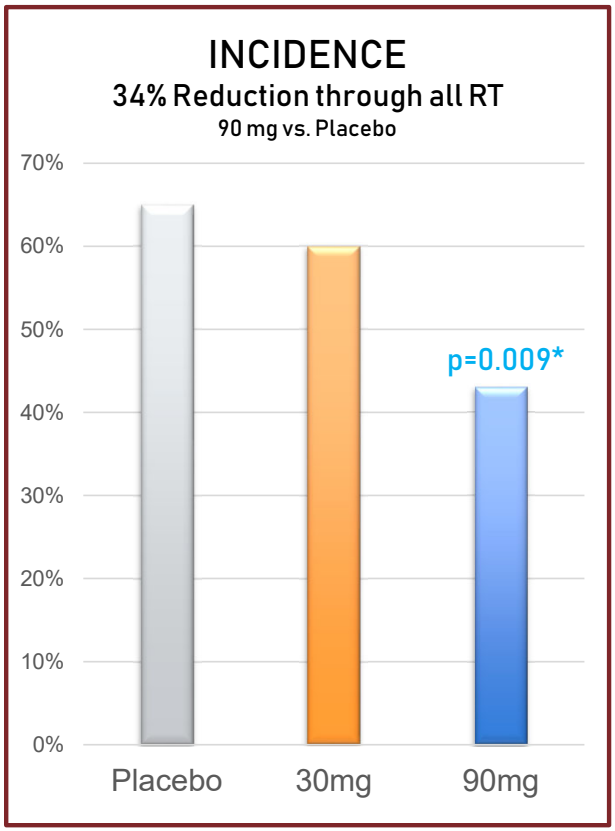
3 — Ulcers, Requires a liquid diet

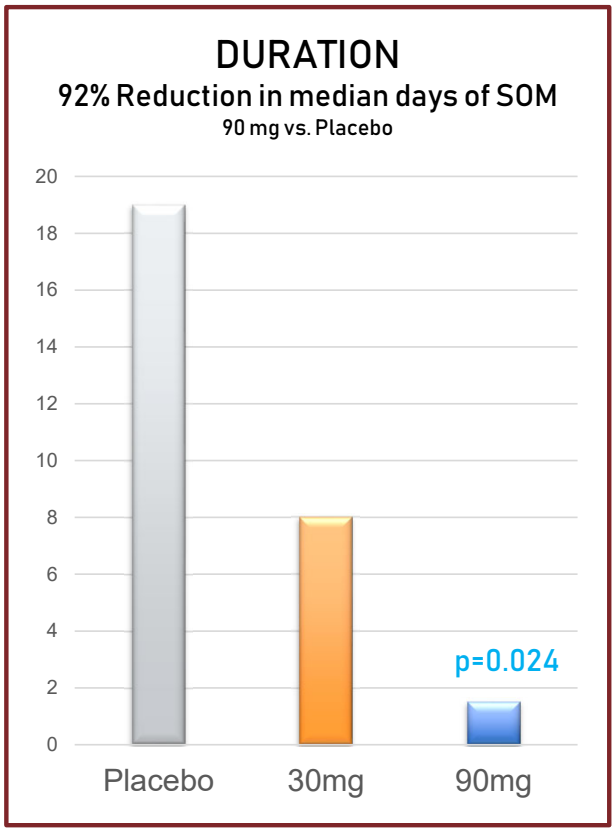
4 — Ulcers, Unable to eat or drink

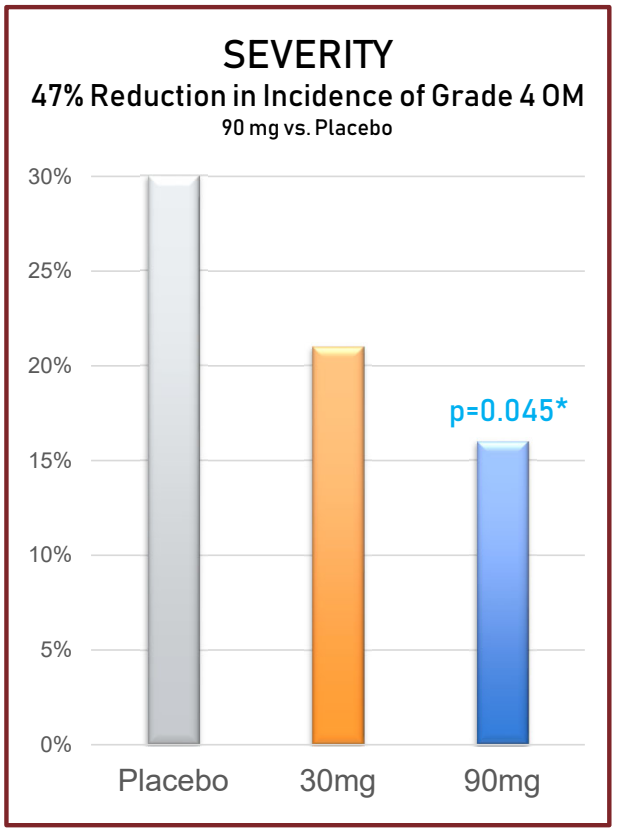
*Anderson et al, JCO, 2019*

# Consistent Efficacy Across All SOM Parameters

*And consistent dose response: 90mg > 30mg*



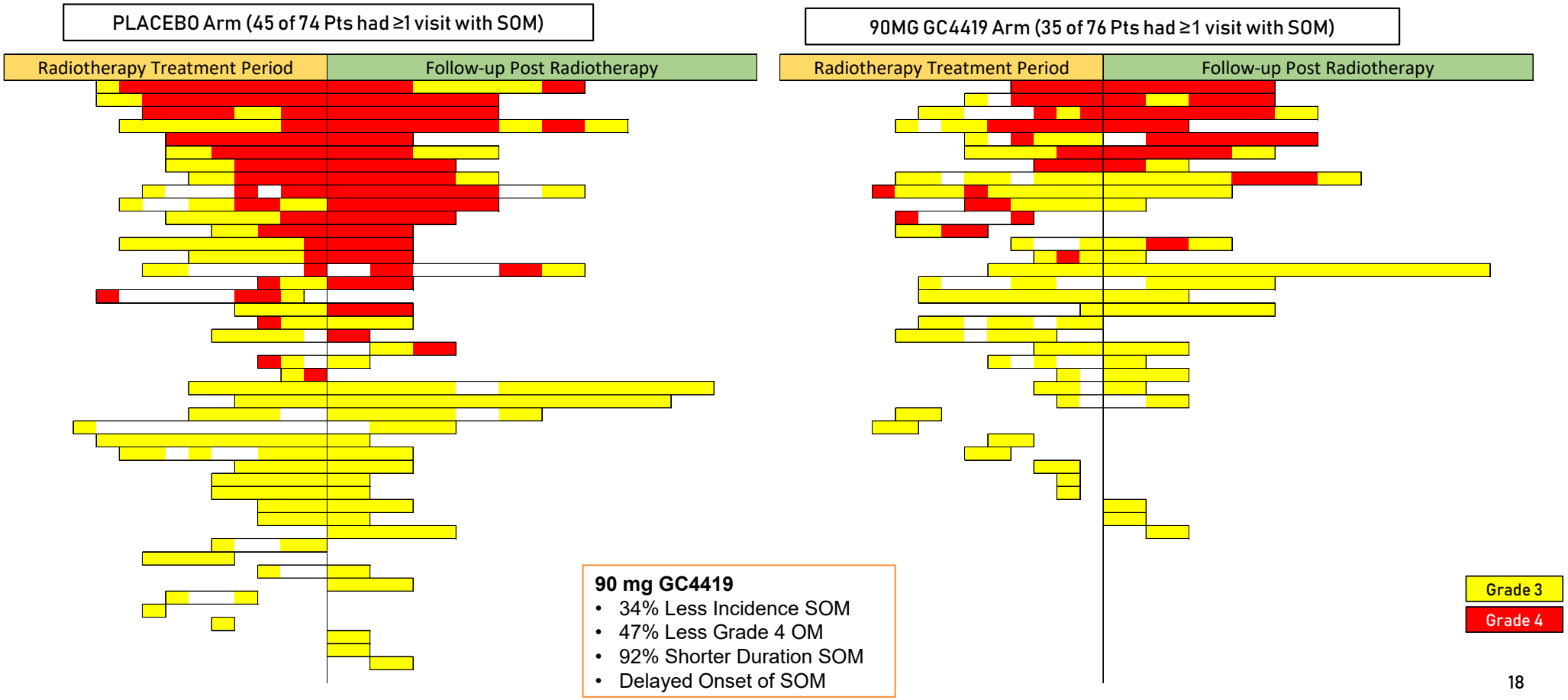

*Primary endpoint was duration - defined as # days from 1st occurrence of grade 3 or 4 SOM until the 1st event of grade 2 or less (there being no subsequent grade 3 or 4 events.)*

**Secondary endpoints (incidence and severity) have nominal p values compared to placebo*

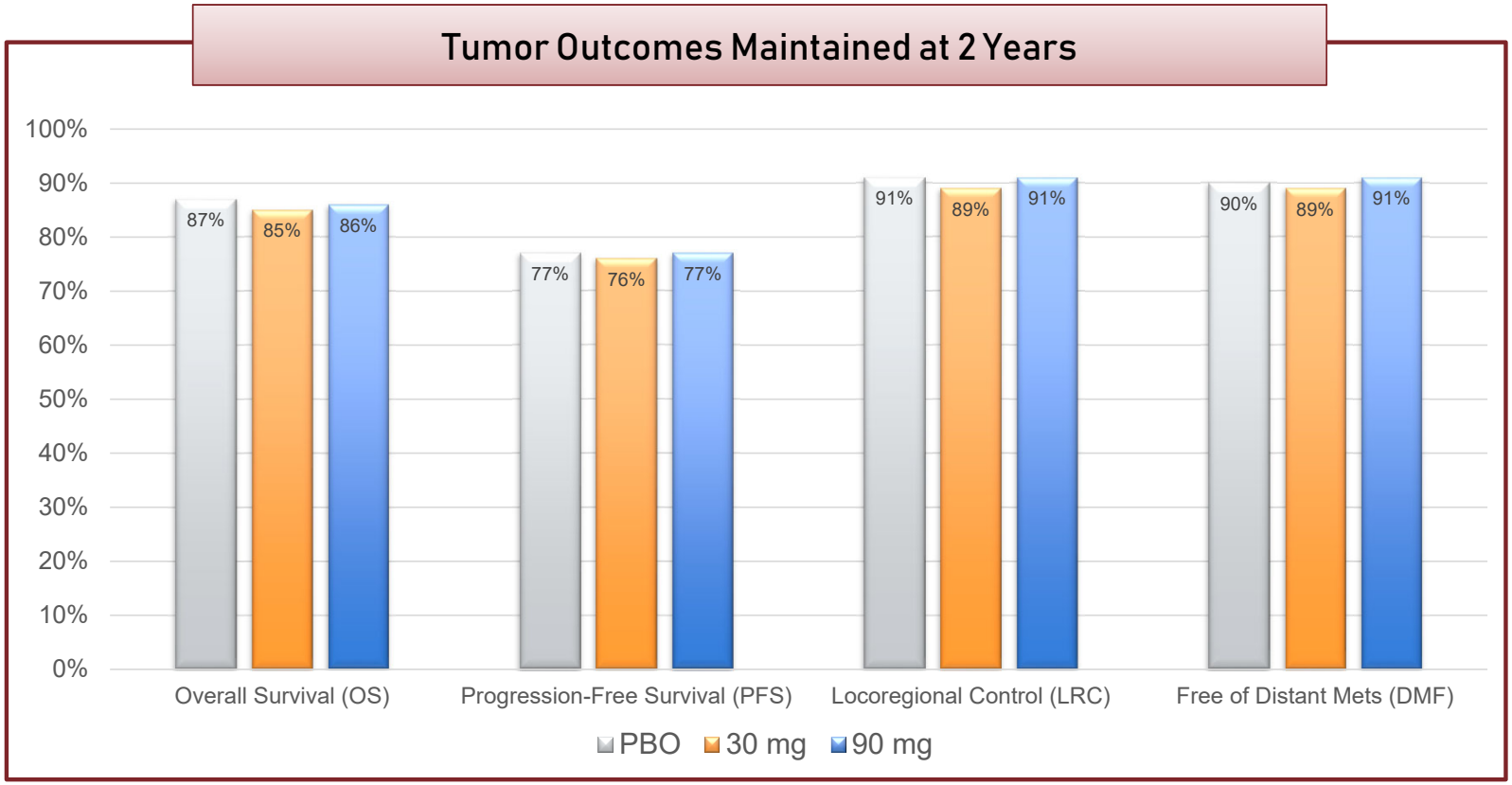
*ITT = Intent-To-Treat population (n=223)*

# Efficacy Parameters Better on 90mg arm Compared to Placebo

*Swimmers plot: each patient who developed at least one SOM episode is represented by a row*



# Tumor Outcomes Maintained – 2 year follow-up

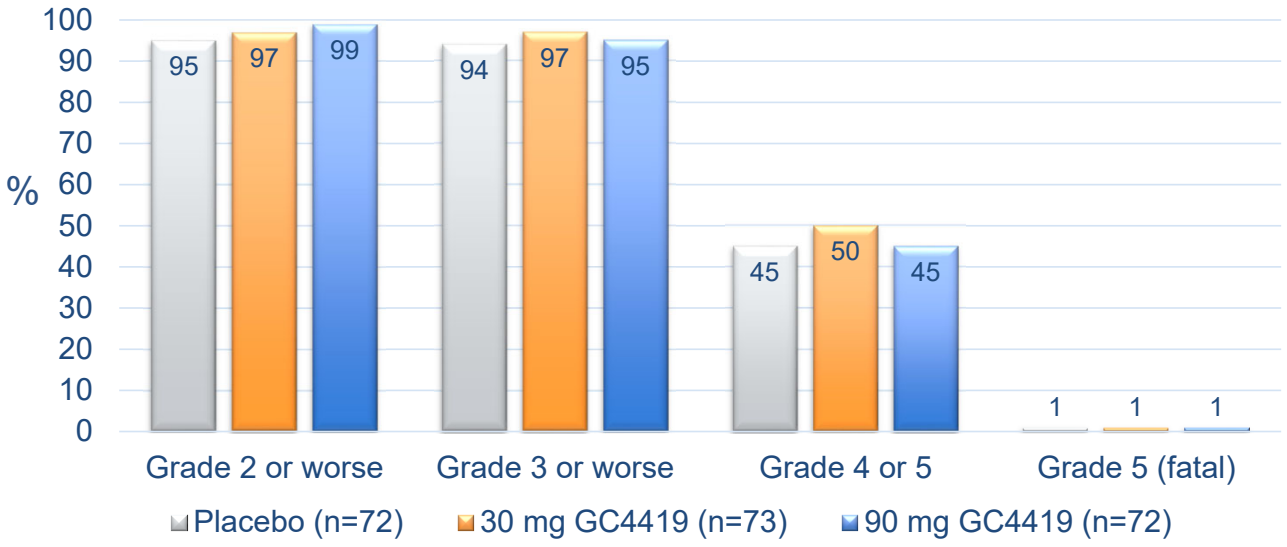



*Final ITT Analysis*

*OS = Overall Survival, PFS = Progression-Free Survival, LRC = LocoRegional Control, DMF = Free of Distant Metastases*

# Safety Summary – Rand. Phase 2b Trial

## Safety Profile of Both GC4419 Doses Comparable to Placebo




GC4419 was well tolerated at both doses

## Most Frequent AE's as expected with Standard Cisplatin – RT Regimen

| Most Frequent AEs (any grade) | Placebo (n=72) | 30 mg GC4419 (n=73) | 90 mg GC4419 (n=72) |
|---|---|---|---|
| Lymphopenia | 89% | 92% | 88% |
| Nausea | 75% | 68% | 82% |
| Fatigue | 69% | 60% | 65% |
| Oropharyngeal pain | 64% | 63% | 61% |
| Constipation | 53% | 59% | 64% |
| Radiation skin injury | 47% | 51% | 53% |
| Vomiting | 47% | 52% | 49% |
| Dysgeusia (taste) | 49% | 55% | 43% |
| Dysphagia | 43% | 42% | 47% |
| Weight decreased | 35% | 40% | 44% |
| Oral candidiasis | 29% | 45% | 43% |
| Leukopenia | 39% | 37% | 39% |

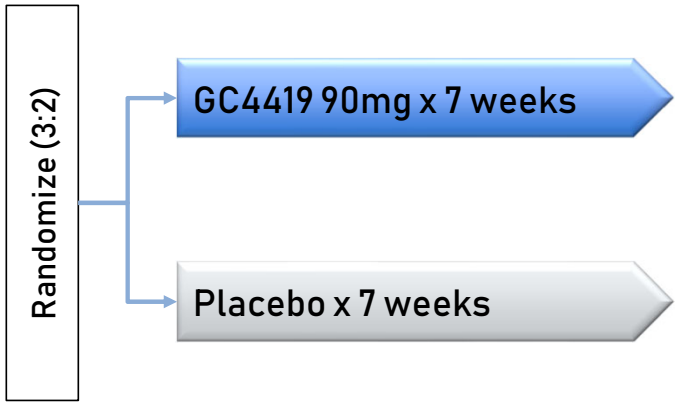
*Anderson et al, JCO, 2019*

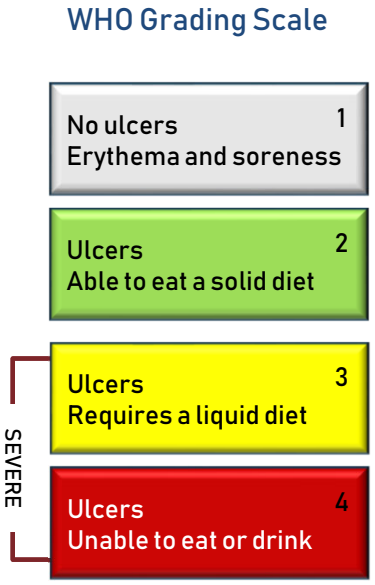
# GT-301: The ROMAN Trial- Phase 3 Confirmatory Trial Enrolling

*Reduction in Oral Mucositis with Avasopasem Manganese (GC4419)*

## Trial Design (n≈365 pts)

| | |
|---|---|
| **Treatment** | • GC4419 90mg or placebo<br>• 60 minute IV infusion, Mon-Fri<br>• Ending <60 mins pre-RT |
| **Population** | • Patients with Head & Neck Cancer<br>• Locally-advanced, squamous cell<br>• Eligible for SoC – 7 weeks IMRT + cisplatin |
| **Stratification Factors** | • Surgery Status: post-op or definitive<br>• Cisplatin Schedule: q3wks or weekly |
| **Endpoints** | • Primary – Reduction in incidence of SOM – WHO Grades 3 & 4 |
| | • Secondary – Reductions in severity of SOM and number of days of SOM experienced<br>• Tumor outcomes* – LRC, DM-free, PFS, OS |






**LRC = locoregional control, DM-free = free of distant mets, PFS = Progression-Free Survival, OS = Overall Survival*

# RT-related Mucositis Beyond Head and Neck Cancer

**Mucositis of Esophagus**

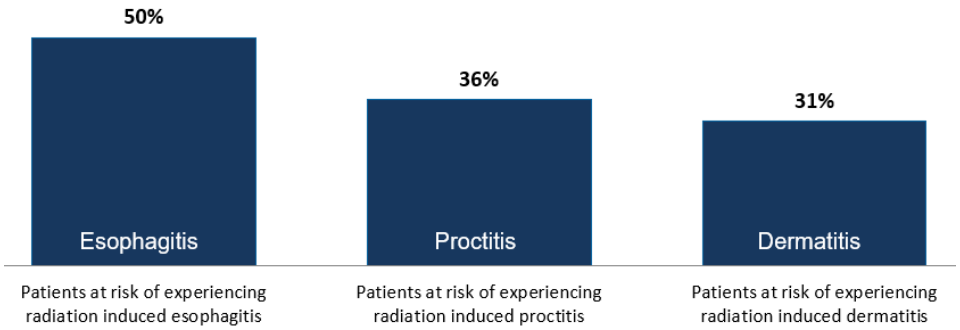
Radiotherapy-related Esophagitis in Lung Cancer

- Galera's HNC trials seen by radiation oncologists as supportive for esophagitis[1]
- ~50,000 lung cancer patients are treated with RT, 50% get ≥ Grade 2 esophagitis[2]
- Effects: inability to swallow, severe pain, ulceration, bleeding & hospitalization

**Compendial Listing**

Phase 2 to support Compendial Listing post-Approval for SOM

- Single-arm Phase 2a trial in 60 patients w/ locally-advanced lung cancers
- Standard IMRT to ≥ 5 cm of esophagus (30 fractions, 2Gy/day x5 for 6 weeks)
- Post approval for SOM in HNC, plan to seek compendial listing in U.S.




Market Research Question
Patients with Other Conditions[1]

Given the demonstrated ability of Product X to prevent radiation-induced toxicities in the oral mucosa, please indicate how you might use (maximum %) Product X for the following radiation associated conditions?

[1] *Galera Market Research (150 Radiation Oncologists)*
[2] *NCI or RTOG grading scales*

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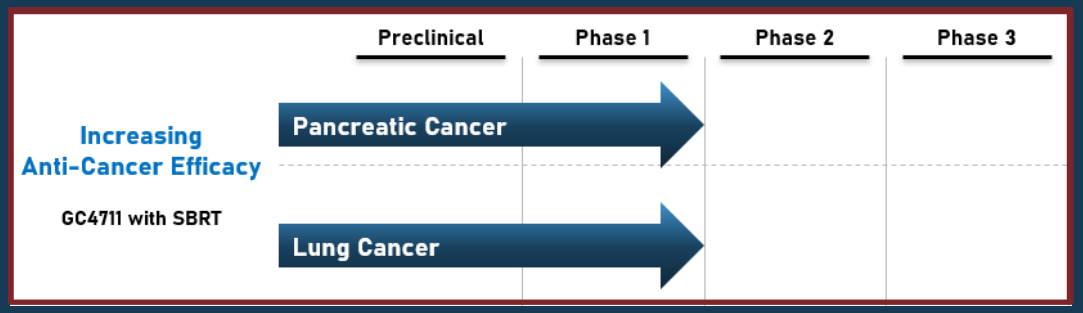



# Increasing Anti-Cancer Efficacy with SBRT

# GC4419 + SBRT Pilot Phase 1b/2a in Pancreatic Cancer

**Pancreatic Cancer**

Locally-Advanced Pancreatic Cancer (LAPC)

- 3rd leading cause of cancer death in US – 45,750 deaths in 2019
- One year survival is 20% & 5-year survival is ~5%
- Placebo-controlled, Adaptive Trial: Escalating SBRT Dose (LO-ET Method[1]) both arms

**48 Patient Pilot Trial**

Screened After 6 months of induction Chemo

R

SBRT + GC4419 x 5 doses

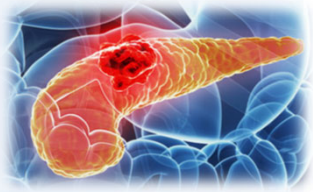
SBRT + Placebo x 5 doses

Evaluated at 2, 3, 6 & 12 months

1° Objective is MTD of SBRT (at 12 months)

2° Objectives include

- Progression-Free Survival (PFS)
- Overall Response Rate at 90 days



**Trial status as of August 2019**

Single-Center: 19 patients treated

- Numerical differences in favor of GC4419 arm in PFS, local tumor response rate & overall response rate
- Data is preliminary, not yet audited, & subject to change
- Now Multi-Center, targeting 29 more patients

*SBRT = Stereotactic Body Radiation Therapy, C Taniguchi & J Herman (MD Anderson),*

[1]*LO-ET = Late-Onset Efficacy-Toxicity (*Jin IH, Liu S, Thall PF, Yuan Y. J Am Stat Assoc 2014;109:525-36)

# GC4711 + SBRT Combination in NSC Lung Cancer

**GC4711**

GC4711 – SBRT Clinical Candidate

- Same mechanism of action as GC4419, with IV & oral forms
- NCE with new IP & lyophilized drug product
- Completing Phase 1 in healthy volunteers: 15-minute infusion

**NSCLC**

Non-Small Cell Lung Cancer (NSCLC)

- Leading cause of cancer death in US – 142,670 deaths in 2019
- SBRT commonly used for smaller peripheral tumors
- Lung toxicity limits use in larger or centrally-located tumors

**Pilot Study**

Phase 1b/2a in NSCLC with GC4711 + SBRT

- 1st Stage: 5 fractions of SBRT +/- GC4711
- 2nd Stage: 5 fractions of SBRT + checkpoint inhibitor +/- GC4711
- Endpoints include safety, acute pneumonitis ($DLCO_2$) & PFS

*[1] 2019 SEER Data*

*[2] DLCO = diffusing capacity of the lung for carbon monoxide*

Galera Therapeutics, Inc

# Commercial Considerations

# Large Commercial Opportunity Addressing Clear Unmet Need

Galera Therapeutics, Inc

## 220 Rad Oncs in market research

**5% of Rad Oncs**

Galera's quantitative market research to date includes ~5% of US radiation oncologists

Support significant, rapid uptake of GC4419 for oral mucositis

## SOM clear unmet need

**70% get SOM**

Rad Oncs report severe oral mucositis is most burdensome side effect of HNC RT treatment

70% of patients get SOM (Grades 3 & 4) with standard-of-care RT & 20-30% get Grade 4

## SOM common & costly

**~$32,000**

Current approaches inadequate – while frequently used, only 1 in 5 believe they are useful

Patients with OM incur ~$32,000 more in medical expenses in first 6 months from start of RT

## OM data representative for all mucositis

**4,000 Rad Oncs**

~2,500 radiotherapy sites in US
~60% of patients are treated in ~500 centers[1]

Market research suggests rad oncs view OM data as representative of efficacy in esophagitis

## Targeted salesforce In U.S.

**~40 Reps**

Focused commercial infrastructure


Evaluating options for commercialization outside U.S.

*Rad Oncs = Radiation Oncologists, SOM = Severe Oral Mucositis*

[1] *Medicare Claims Analysis by Galera in 2019*

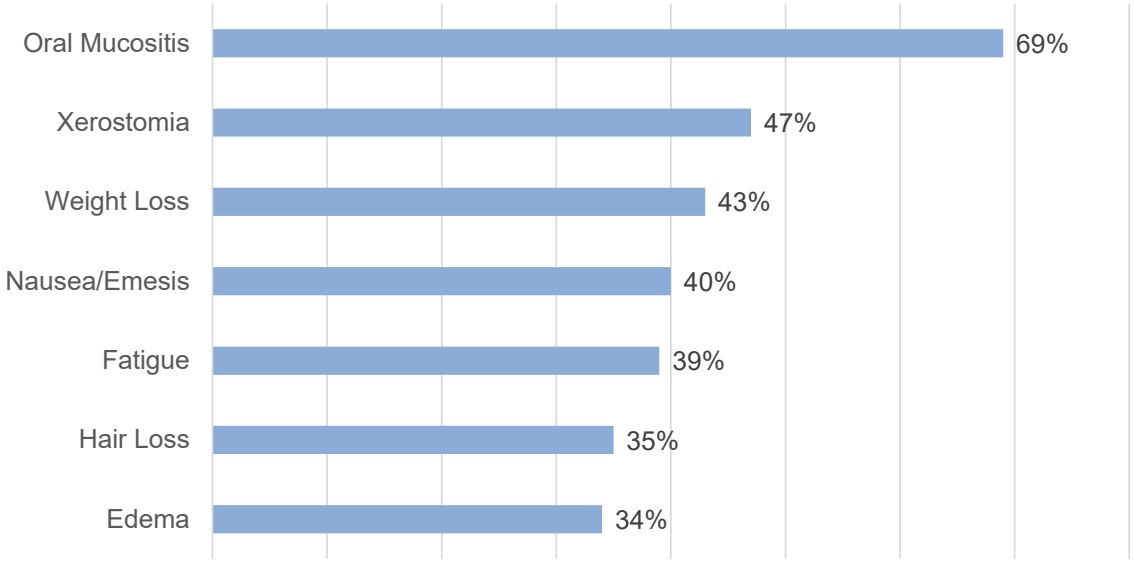
# Oral Mucositis Most Burdensome Side Effect of RT in HNC

*Physicians are aware of the problem of Oral Mucositis*

RT-Related Side Effects

Patients receiving radiation with chemo or targeted therapy

- Oral mucositis deemed worst (69%) side effect
- Rad. Oncs agree that SOM is huge issue both for them & their patients




"Literally everyone suffers from it, even at low radiation levels"

*Radiation Oncologist*
*Large Hospital*

"Oral mucositis is our biggest concern by far, especially with head & neck cancer patients"

*Radiation Oncologist*
*Large Clinic*

*BluePrint Market research, Jan 2018 Q1.On a scale of 1 to 7, where 1 is Not Burdensome" and 7 is "Extremely Burdensome Please indicate how burdensome each of the following side effects are on your head and neck cancer patients receiving radiation therapy in combination with chemotherapy or targeted therapy.*

# Topical Agents Perform Poorly in Efficacy Attributes

*Physicians seek therapy to prevent/reduce the toxicity of radiation*

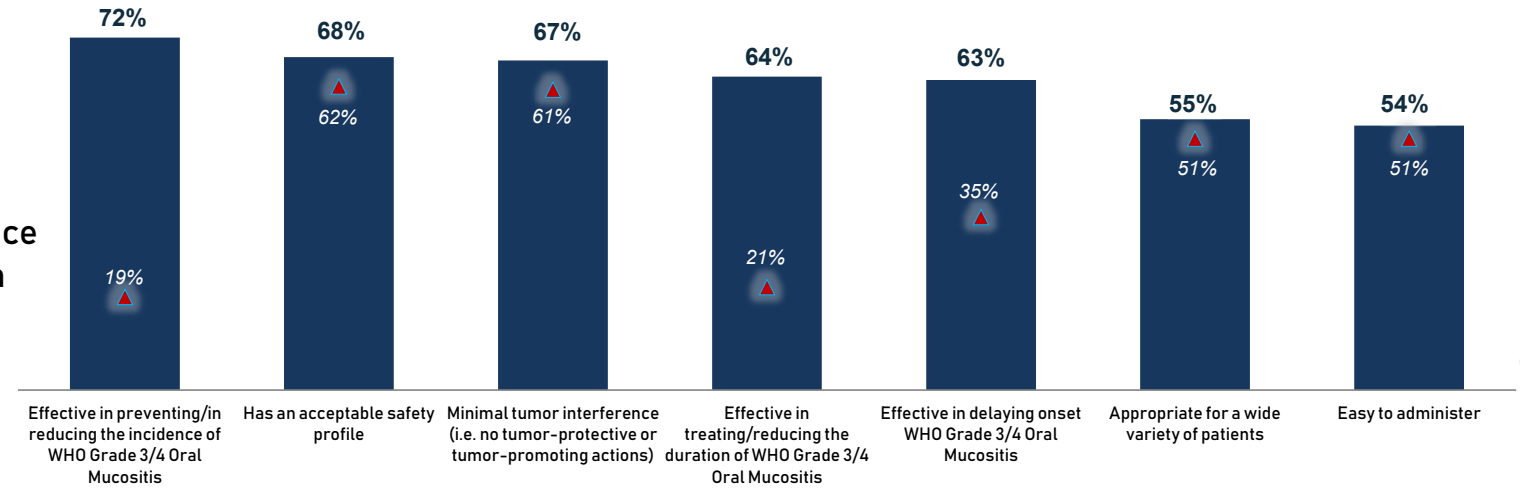
Product Performance

Product Attribute Importance & Topical Performance

- Efficacy in preventing/reducing OM is most important product attribute
- Only 19-21% MDs believe topical agents perform well in preventing or reducing mucositis

**Product Importance**

Rated in importance when choosing an oral mucositis treatment




**Topical Performance**

Rated on usefulness for treating oral mucositis

*Galera Market Research (150 U.S. Radiation Oncologists)*
*% MDs that rated these attributes as a 6 or 7 on a 7-point scale*

# OM Substantially Increases Medical Expenses in Patients with HNC

*Health economic analysis of patients with HNC receiving RT or chemo/RT*

High Cost Of Oral Mucositis

Identified patients with locally advanced Head & Neck Cancer, treated with RT +/-chemo

- Longitudinal claims analysis[1] assessing costs over a six month period
- Compared healthcare expenses of patients with & without oral mucositis
- Included both in-patient and out-patient expenses associated with a claim


Pts with OM incur ~$32,000 more of medical expenses within first 6 months of start of RT

[1] *Navigant analysis; 40 million member years*

# Physicians View Oral Mucositis Data as Potentially Applicable to Other Radiation-Related Toxicities

Other RT-related Mucositis

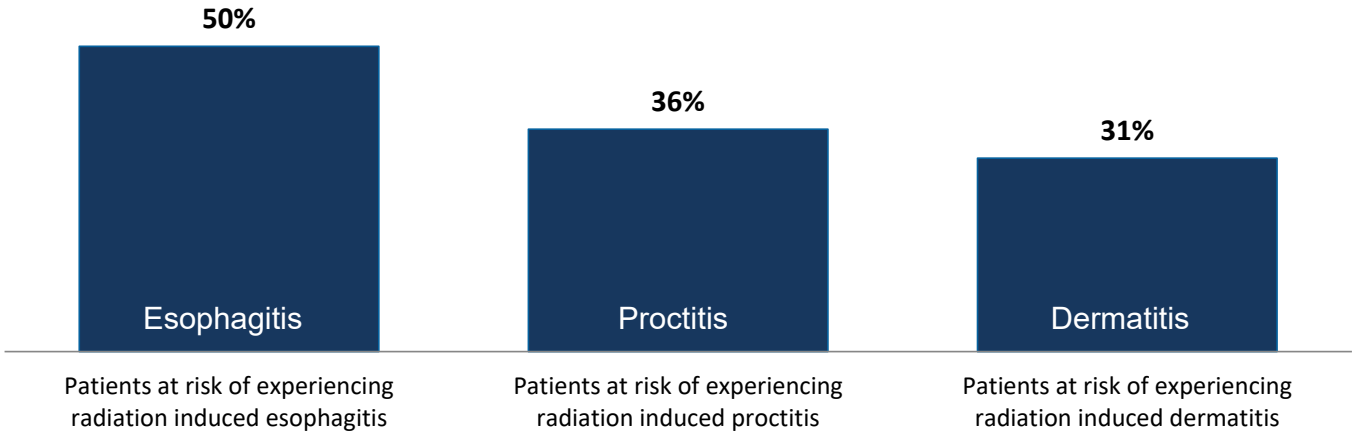
GC4419 for other RT-related Toxicities

- Over 50% cancer patients will get RT at some time in their treatment
- Several major cancers treated with RT (lung, prostate, breast)
- Largest potential usage for radiation induced esophagitis (out of conditions below)

Question
Patients with Other Conditions

Given the demonstrated ability of Product X to prevent radiation-induced toxicities in the oral mucosa, please indicate how you might use (maximum %) Product X for the following radiation associated conditions?

Potential Usage in Other Radiation Associated Conditions
*Maximum % of Patients with Other Conditions*




*Galera Market Research (150 U.S. Radiation Oncologists)*

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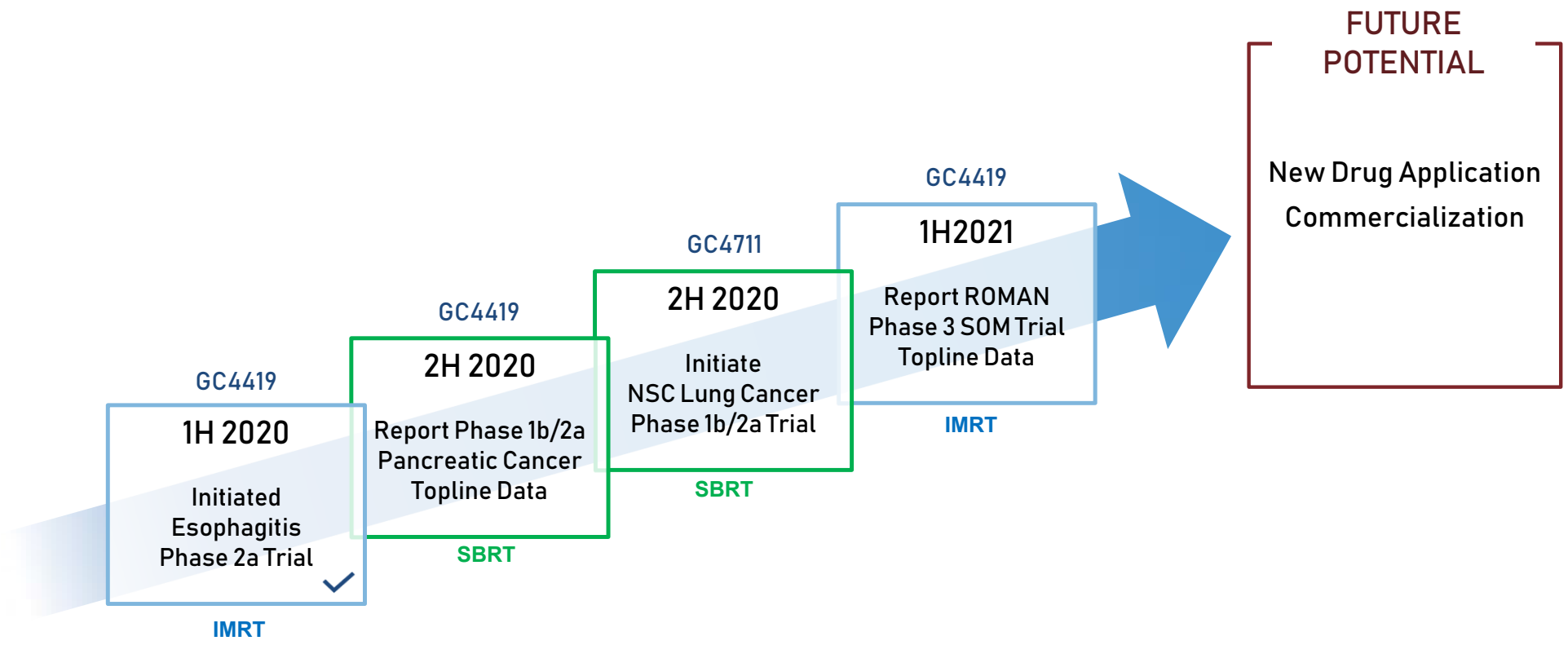
# Summary

# Near-term Potential Catalysts to Drive Future Value



# Transforming Radiotherapy With Dismutase Mimetics

## Reducing Toxicity

Rapid elimination of Superoxide ($O_2^{\bullet}$)

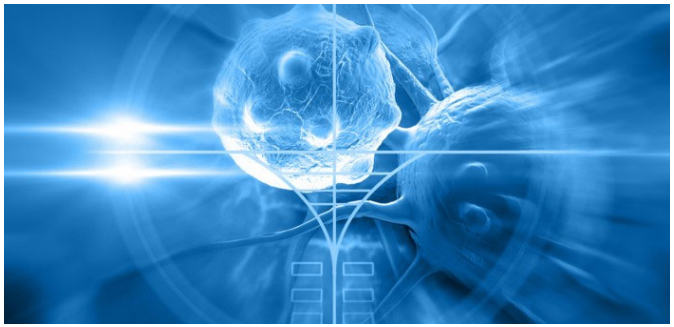
Severe Oral Mucositis in Head & Neck Cancer

Esophagitis in NSC Lung Cancer

IMRT

Other IMRT-related Toxicities

**Normal tissue toxicity limits optimal radiotherapy treatment of tumor**

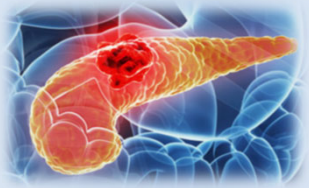


Over half of cancer patients receive radiotherapy as part of their care[1, 2]

## Increasing Anti-Cancer Efficacy

Increase $H_2O_2$ in tumors

Locally-Advanced Pancreatic Cancer



Centrally-Located NSC Lung Cancer

Other SBRT-Treated Tumors

SBRT

**Radiotherapy is standard-of-care for many local tumors but need remains for greater efficacy**

[1] *Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment… Cancer. 2005;104:1129-1137*

[2] *Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer. 2011;11:239-253*