NRG-RTOG 1016: Phase III Trial Comparing Radiation/Cetuximab to Radiation/Cisplatin in HPV-related Cancer of the Oropharynx

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Disclosure for Dr. Trotti

- Employer: Moffitt Cancer Center
- I have no conflicts of interest to disclose.

Background

- HPV-related oropharynx cancer is a distinct and highly curable cancer
- High survival (85%) and local control with treatment
- Can we de-intensify treatment to reduce short and long term toxicity, yet maintain high survival?

- Primary objective of NRG Oncology/RTOG 1016: To determine if cetuximab will result in non-inferior (+/- 5 points) 5-year overall survival (compared to cisplatin), when combined with radiation therapy.

Trial design

REGISTER	Mandatory p16 testing *	STRATIFY	T Stage 1. T1-2 2. T3-4 N Stage 1. N0-2a 2. N2b-3 Zubrod Performance Status 1. 0 2. 1 Smoking History 1. ≤ 10 pack-years 2. > 10 pack-years

Arm 1 (Control):

Accelerated IMRT, 70 Gy/6 weeks + high dose DDP (100 mg/m^2) Days 1, 22 (Total: 200 mg/m^2)

Arm 2 (Investigational)

Accelerated IMRT, 70 Gy/6 weeks + cetuximab (400 mg/m^2) loading dose pre-IMRT, then 250 mg/m^2 weekly during IMRT, + 1 week after IMRT for a total of 8 doses of cetuximab

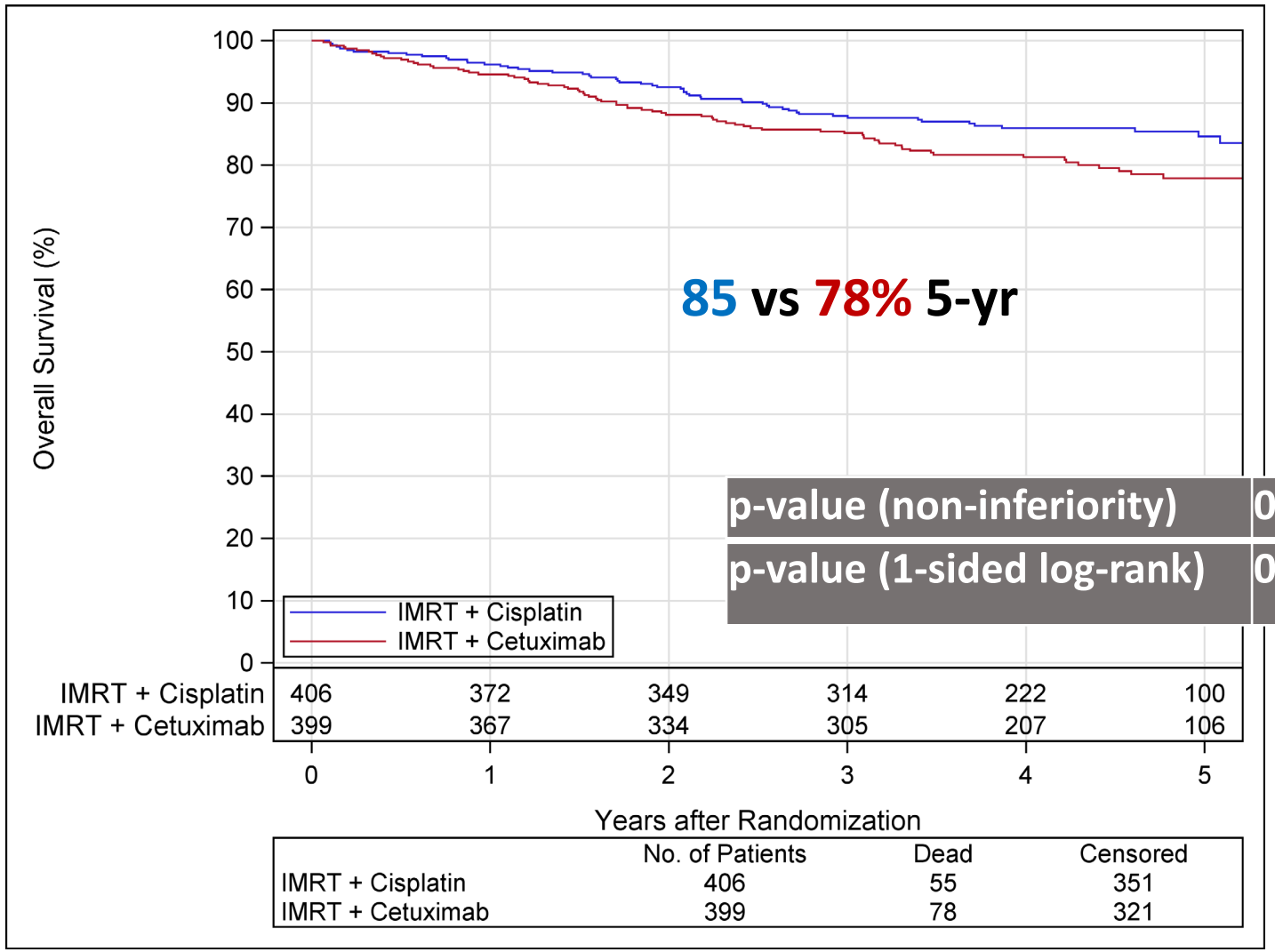
*Centralized RTOG lab test

Outcomes at five years post-treatment

	Cisplatin (%)		Cetuximab (%)	
Overall Survival	85	vs	78	(p=0.02)
Progression-Free Survival	78	vs	67	(p<0.001)
Locoregional Failure	10	vs	17	(p<0.001)
Distant Metastasis	9	vs	12	(p=0.09)

Hazard ratio (cetuximab/cisplatin): 1.45 (p=0.02)
1-sided 95% upper confidence bound: 1.94

Overall survival

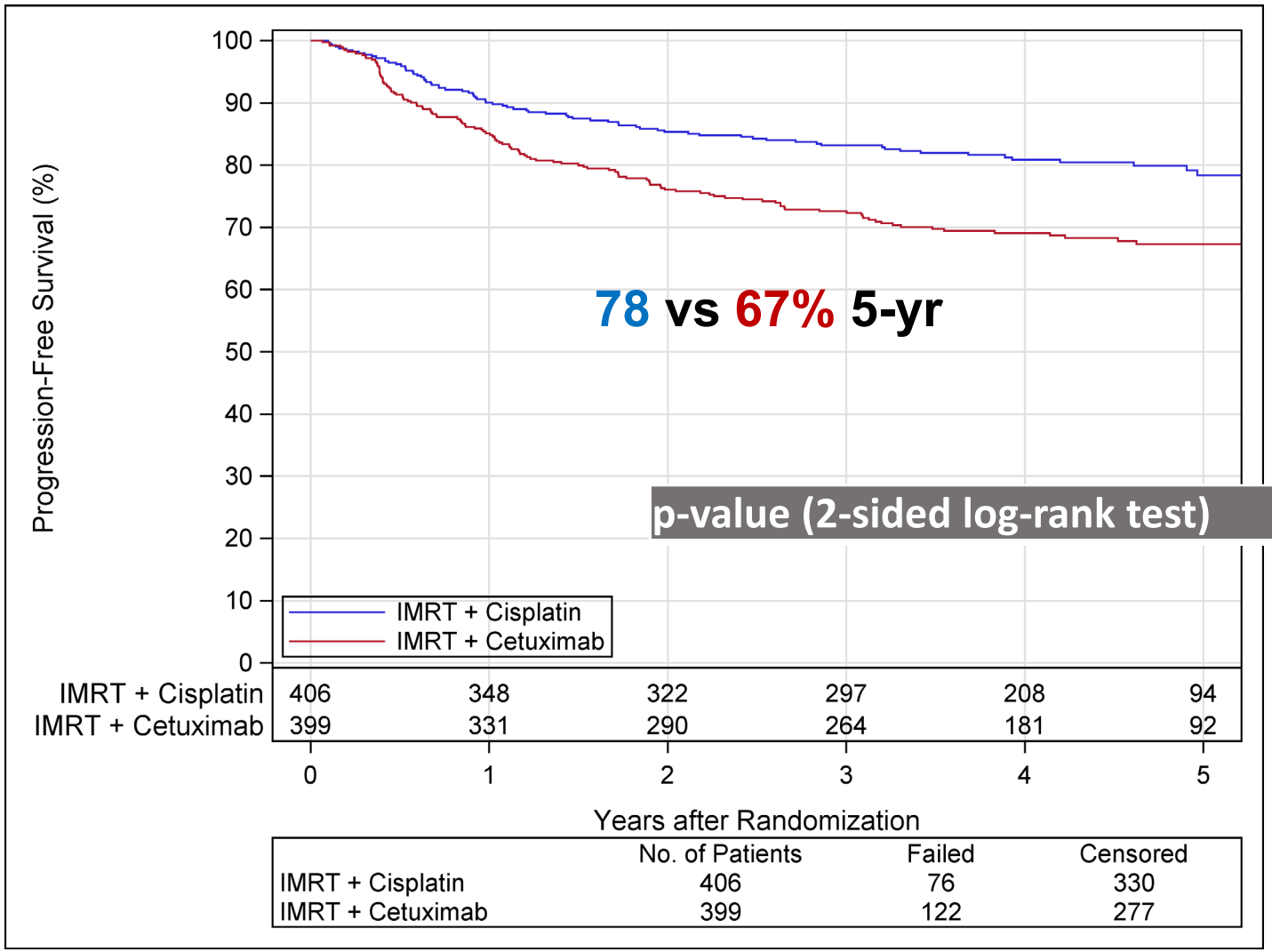


Cisplatin

Cetuximab

p-value (non-inferiority)	0.51
p-value (1-sided log-rank)	0.02

Progression-free survival

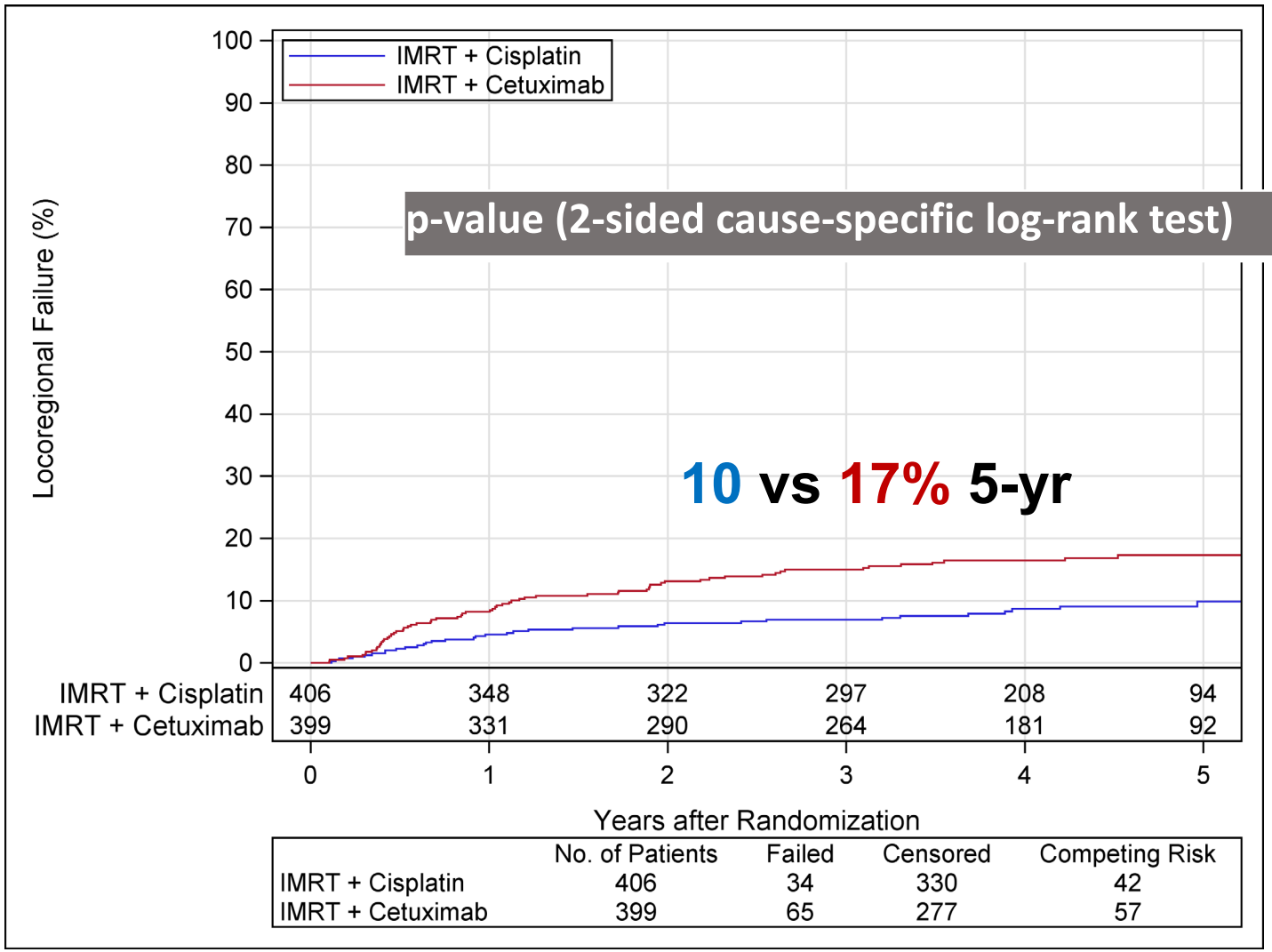


Cisplatin

Cetuximab

p-value (2-sided log-rank test)	<0.001

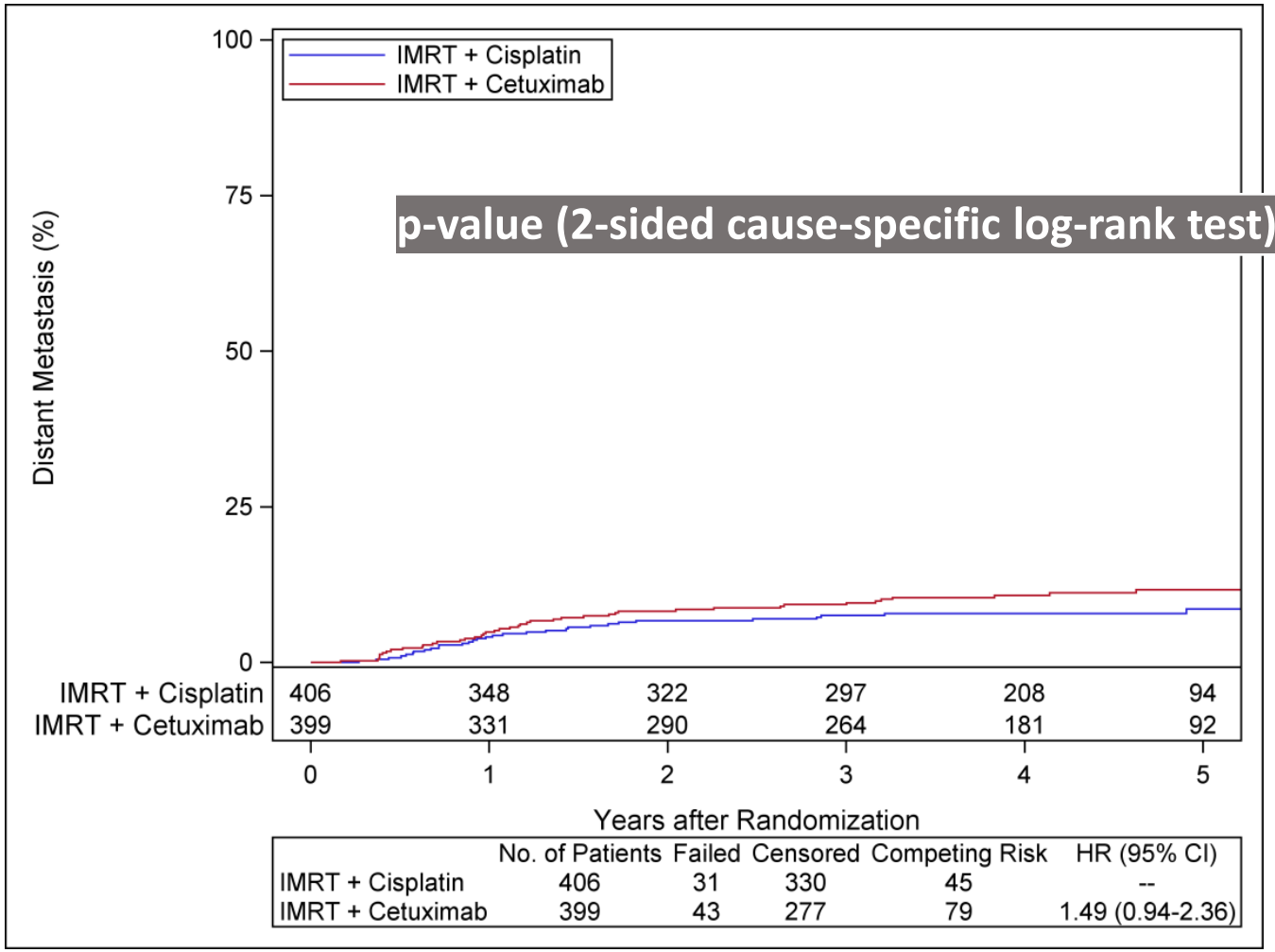
Locoregional failure



Cetuximab

Cisplatin

Distant metastasis



p-value (2-sided cause-specific log-rank test)	0.09

Cetuximab

9 vs 12% 5-yr

Cisplatin

Acute toxicity

	Cisplatin	Cetuximab		
Mean raw T-score (Acute Toxicity Burden/T-score captures *all* grade 3-4 acute adverse events)	3.19	2.35	40% increased acute toxicity	p<0.001
Grade 3-4 overall (standard "worst grade" method)	81.7%	77.4%	no significant difference	p=0.16

Late toxicity

	Cisplatin	Cetuximab		
Mean raw A-score (Late Toxicity Burden/A-score captures *all* grade 3-4 acute adverse events)	0.38	0.27	40% higher late toxicity (n.s.)	p=0.12
Grade 3-4 overall (classical)	20%	17%	no significant difference	p=0.19

Conclusions

- Non-inferiority of cetuximab was NOT demonstrated
  - Cisplatin had better OS, PFS, LRC
  - Acute “Toxicity Burden” 40% worse with cisplatin
  - Late “Toxicity Burden” not significantly different

- RTOG 1016 establishes the first standard of care (no prior phase III trials) in HPV-related oropharynx cancer

  Accelerated IMRT radiation therapy 70Gy/6 weeks + 100mg/m2 Cisplatin x 2

- Outcomes are very good in this population (85% 5 year OS), albeit with moderate to high acute toxicity burden