A Phase 2, Randomized Trial (CONCERT-2) of Panitumumab Plus Radiotherapy Compared With Chemoradiotherapy in Patients With Unresected, Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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Disclosures

- Dr. Jordi Giralt has no disclosures

Introduction

- Concomitant chemoradiation is the standard treatment in patients with non-resectable locally advanced squamous cell carcinoma of the head and neck
- Radiotherapy (RT) given concomitantly with cetuximab has demonstrated longer disease-free progression and overall survival versus radiotherapy alone[1]
- There is no formal comparison between the combination of RT with cisplatin versus RT with EGFR inhibitors
- Panitumumab is a fully human IgG2 mAb targeting the EGFR
- Preclinical studies with panitumumab and radiation showed enhanced effect[2]

1.Bonner et al. Lancet Oncol 11:21-28, 2010
2.Kruser et al. Int J Radiat Oncol Biol Phys 72:534-542, 2008

Objectives

Primary Endpoint

- Local-regional control (LRC) rate at 2 years in patients receiving chemoradiotherapy (CRT) alone vs panitumumab plus radiotherapy (PaRT)

Other Key Endpoints

- Progression-free survival (PFS)
- Overall survival (OS)
- Duration of local-regional control
- Objective response
- Safety
- Exploratory biomarker endpoints

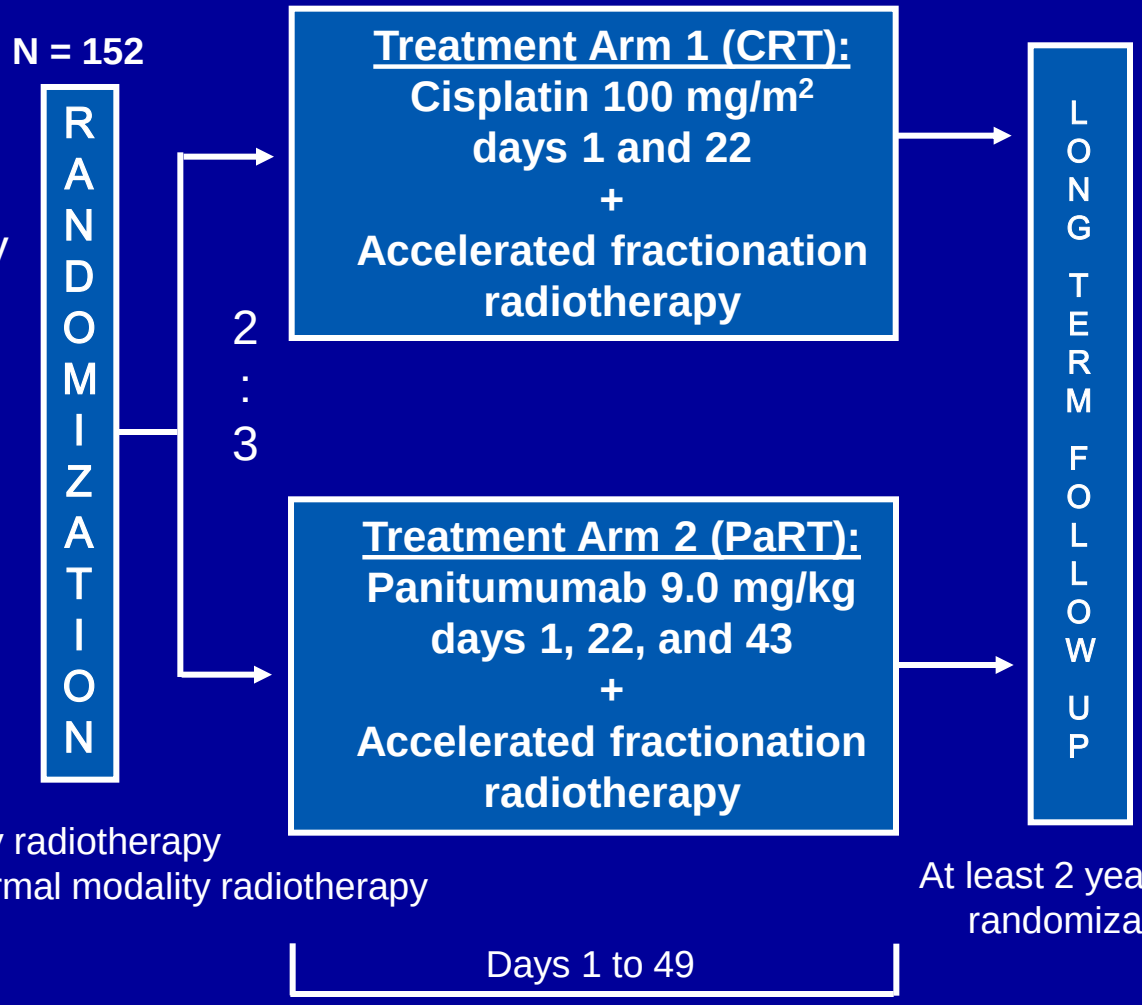
Key Eligibility Criteria

- Histologically or cytologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx
- Stage III or Stage IVa-b disease (M0)
- ECOG performance status of 0 or 1
- Bidimensionally measurable disease ≥ 10 mm in at least 1 dimension
- ≥ 18 years of age
- Adequate hematologic, renal, hepatic, and metabolic function
- No prior anti-EGFR inhibitor therapy, surgery for SCCHN, radiotherapy in the planned field, or systemic chemotherapy for SCCHN

CONCERT-2 Study Schema

Stratification factors:

- Site of primary tumor: hypopharynx / oral cavity vs oropharynx / larynx
- RT delivery modality: IMRT* vs 3D-CRT**
- Nodal status: N0 vs N+
- Tumor stage: T1-3 vs T4



*IMRT = intensity-modulated modality radiotherapy
**3D-CRT = three-dimensional conformal modality radiotherapy

Amgen Trial 20062079; ClinicalTrials.gov identifier NCT00547157

Study Timeline and Statistical Objectives

Overview of Study Timeline

- First patient enrolled: 30-Nov-2007
- Enrollment period: 24 months
- Last patient enrolled: 16-Nov-2009

Statistical Objectives

- No formal hypothesis testing planned
- The treatment effect of PRT compared to CRT (and 95% confidence intervals) was estimated for all efficacy endpoints
- P-values are descriptive only

Baseline Demographics and Disease Characteristics

		CRT (n = 61)	PaRT (n = 90)
Sex – %	Male	90	80
	Female	10	20
Age – %	< 65 years	84	83
	≥ 65 years	16	17
Tobacco use – %	Never	3	7
	Current	46	43
	Former	51	41
ECOG PS – %	0	66	63
	1	34	34
Primary site – %	Oropharynx	46	50
	Oral cavity	11	12
	Hypopharynx	18	14
	Larynx	25	23

Baseline Demographics and Disease Characteristics (cont'd)

		CRT (n = 61)	PaRT (N = 90)
T stage – %	T1	5	8
	T2	16	18
	T3	43	39
	T4	36	36
Nodal stage – %	N0	11	12
	N1	23	21
	N2	61	64
	N3	3	2
HPV status* – %	Positive (+)	15	17
	Negative (-)	49	50
	Unevaluable	36	33
Median index lesion area – mm^2		1352	1562

*HPV status was determined retrospectively using archival tumor specimens

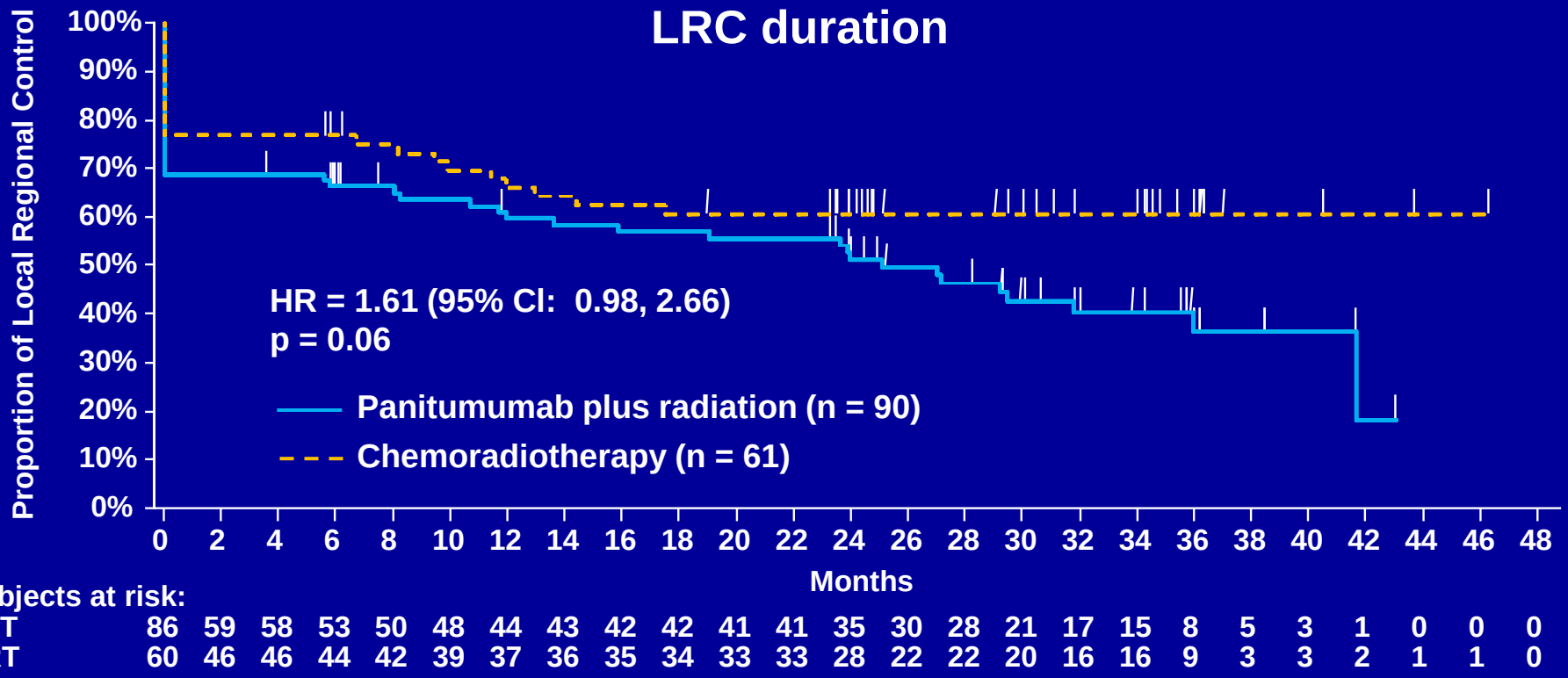
Treatment Received

Treatment parameter	CRT (N = 62)	PaRT (N = 89)
Median relative dose intensity - %		
Cisplatin	99	-
Panitumumab	-	100
Radiotherapy* – %		
IMRT	53	54
3D-CRT	47	46
Total Dose ≥ 66 Gy	97	96
RT major deviations	0	0
Treatment interruptions > 10 days	0	7

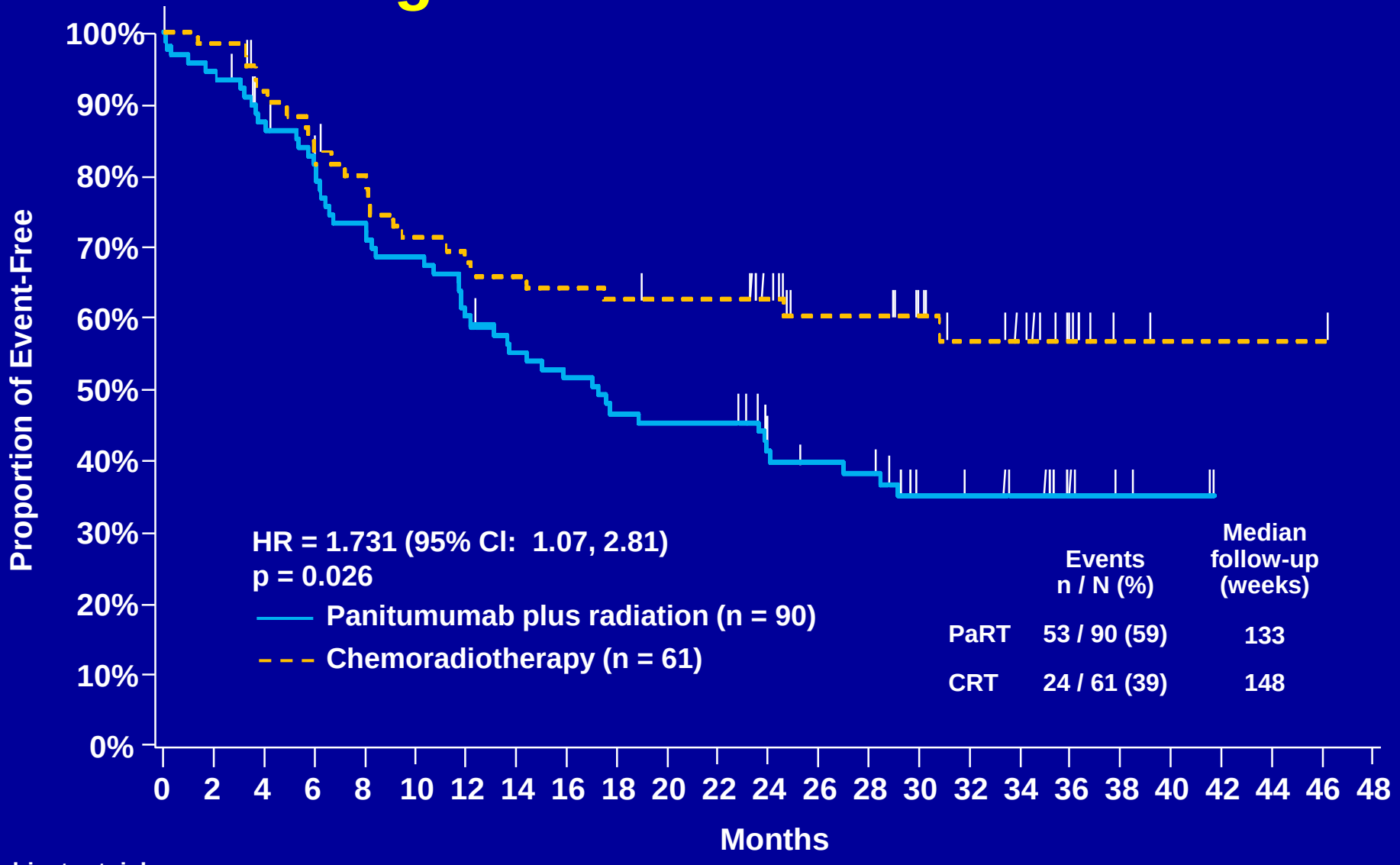
*Radiotherapy quality assurance was performed

Local-Regional Control

KM estimate – % (95% CI)	CRT (N = 61)	PaRT (N = 90)	Difference PaRT vs CRT
LRC at 24 months (Primary Endpoint)	61 (47 – 72)	51 (40 – 62)	-9 (-23 to 9)



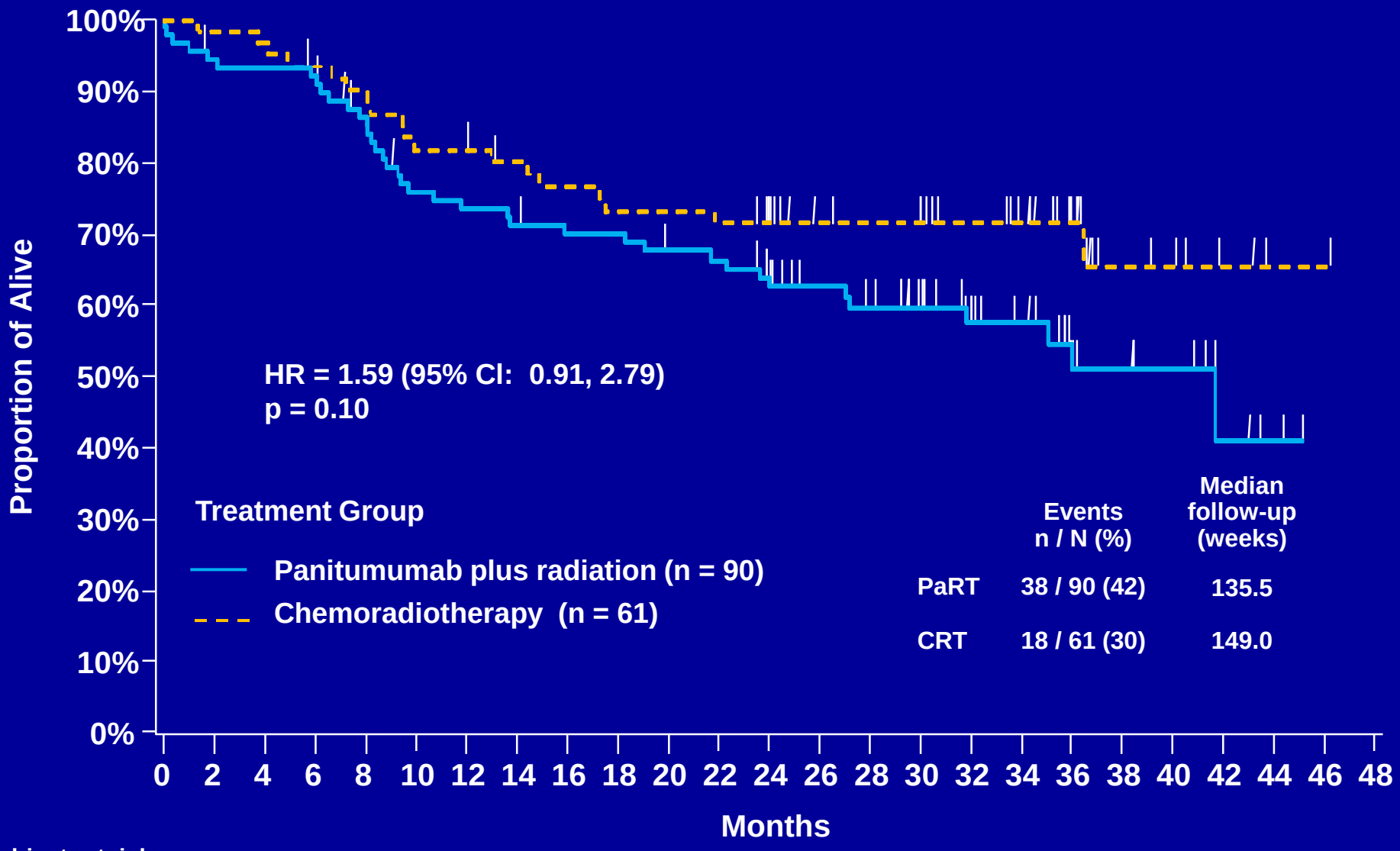
Progression-free Survival



Subjects at risk:

PRT	90	84	75	69	61	57	50	45	42	38	37	37	28	26	25	16	15	13	6	3	2	0	0	0	0
CRT	61	60	54	49	46	41	39	38	37	36	35	35	30	24	24	20	16	14	8	2	1	1	1	1	0

Overall Survival



Subjects at risk:

PRT	90	84	83	82	74	64	62	60	58	58	55	54	48	43	40	33	26	22	13	11	8	4	2	0	0
CRT	61	60	59	56	54	49	49	46	44	42	42	41	37	32	31	31	26	23	15	7	6	3	1	1	0

Adverse Events by Grade

	CRT (N = 62)	PaRT (N = 89)
Patients with any adverse event – %	**100**	**100**
Worst grade of 3	**61**	**71**
Worst grade of 4	**16**	**9**
Worst grade of 5*	**3**	**6**
Any serious	**40**	**34**
Patients with adverse event leading to permanent discontinuation – %	**5**	**16**

*On-treatment fatal adverse events included:

1 pneumonia and 1 cardio-respiratory arrest in the CRT arm (3% total), and

2 sudden deaths, 1 pneumonia, 1 septic shock, and 1 death NOS in the PaRT arm (6% total)

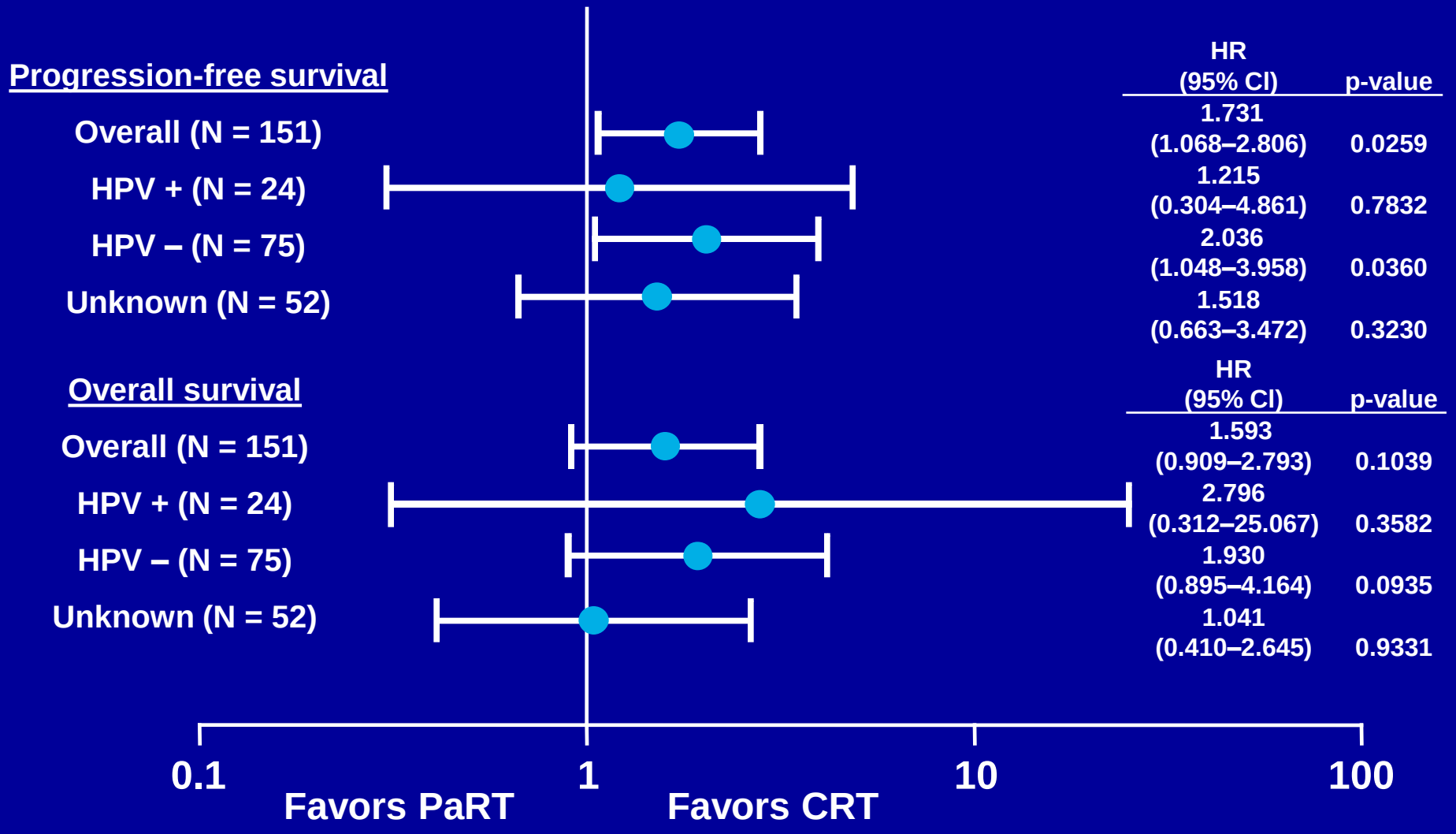
Selected Grade 3 or Higher Adverse Events

Any grade ≥3 adverse event – %	CRT (N = 62)	PaRT (N = 89)
Mucosal toxicity		
Mucosal inflammation	40	38
Odynophagia	19	9
Dysphagia	32	39
Skin toxicity		
Dermatitis	0	16
Radiation skin injury	11	24
Rash	0	9
Other		
Neutropenia	13	0
Febrile neutropenia	8	0
Dehydration	6	3

Baseline Characteristics by HPV Status

		HPV+ (n = 24)	HPV- (N = 75)
Tobacco use – %	≤ 10 pack-years	13	8
	> 10 pack-years	79	85
T stage – %	T1-3	71	59
	T4	29	41
Nodal stage – %	N0-1	8	38
	N2-3	88	62
Primary site – %	Oropharynx	83	37
	Other	17	63
Median index lesion area – mm^2		1540	1760

Forest Plot for PFS and OS by HPV Status



Summary

- There is a trend in favor of the CRT arm compared with the PaRT arm for LRC and OS
  - Median not reached in all measures of efficacy in the CRT arm
  - HR for PFS was 1.731, p-value 0.026 in favor of CRT arm
- Toxicity severity was similar in both arms
  - Increased rates of skin toxicity in PRT arm
  - Increased rates of neutropenia, febrile neutropenia in CRT arm
- Efficacy trends seen were also seen by HPV status
  - Trends favored the CRT arm in the HPV negative group
  - No differences seen between arms in HPV positive group, low sample size limits interpretability

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Objective Response (Central Review)

Best overall response by 6 months - n (%)	CRT (N = 60)	PRT (N = 90)
Complete response	7 (12)	13 (14)
Partial response	39 (65)	52 (58)
Stable disease	6 (10)	5 (6)
Disease progression	3 (5)	4 (4)
Unable to evaluate	2 (3)	8 (9)
Not done	3 (5)	8 (9)
Patient overall response	46 (77)	65 (72)
Odds ratio (95% CI)	0.79 (0.34 – 1.79) p = 0.57	