Safety and Efficacy of Cisplatin plus 5-FU and Cetuximab in HPV-positive and HPV-negative Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck (R/M SCCHN): Analysis of the Phase III EXTREME Trial

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Disclosures

- Advisory Board (Merck KGaA)

Background

- Analyses of data from retrospective cohorts[1] and randomized trials have established HPV status as an important prognostic factor in locally advanced SCCHN[2,3]
- To date, the role of HPV status in the R/M setting has been explored only in the phase III SPECTRUM trial[4]
- This retrospective analysis of the phase III EXTREME trial explored both the prognostic and the predictive value of HPV status in R/M SCCHN:
  - *The clinical trial reported that the addition of cetuximab to platinum/5-FU significantly improved response rate, overall survival and progression-free survival compared with platinum/5-FU alone*[5]

HPV, human papillomavirus; R/M, recurrent and/or metastatic; SCCHN, squamous cell carcinoma of the head and neck

[1]Weinberger PM et al. J Clin Oncol 2006;24:736–47;
[2]Ang KK et al. N Engl J Med 2010;363:24–35;
[3]Rischin D et al. J Clin Oncol 2010;28:4142–8;
[4]Vermorken J et al. Eur J Cancer 2011;47(Suppl 2):25 LBA;
[5]Vermorken JB et al. N Engl J Med 2008;359:1116–27

Methods

- p16 IHC status is a useful surrogate marker of HPV status in oropharyngeal squamous cell carcinoma[1]
- We used immunohistochemical detection of p16INK4A (p16) to determine HPV status (CINtec® Histology Kit)
  - p16 positivity was considered to be strong and diffuse nuclear staining in >70% of tumor cells
- Primary overall survival analysis data were used

IHC, immunohistochemistry

[1]Weinberger PM et al. J Clin Oncol 2006;24:736–47;
[2]Vermorken J et al. Eur J Cancer 2011;47(Suppl 2):25 LBA

Sample Size

- Tumor tissue evaluable for p16 analysis was available from:
  - 196/222 (88.3%) patients in the chemotherapy + cetuximab arm
  - 185/220 (84.1%) patients in the chemotherapy alone arm

Baseline Patient and Disease Characteristics

Characteristic,%	ITT n=442	p16 evaluable n=381	p16 non-evaluable n=61
Sex, male	90.3	90.0	91.8
Age <65 years	82.6	82.7	82.0
KPS ≥80	88.2	87.1	95.1
Primary tumor site			
Oropharynx	33.7	35.7	21.3
Hypopharynx	14.0	13.9	14.8
Larynx	25.1	24.1	31.1
Oral cavity	19.9	19.2	24.6
Other	7.2	7.1	8.2
Extent of disease			
Locoregional recurrence only	53.4	54.3	47.5
Metastatic ± locoregional recurrence	46.6	45.7	52.5

KPS, Karnofsky performance score; ITT, intention-to-treat

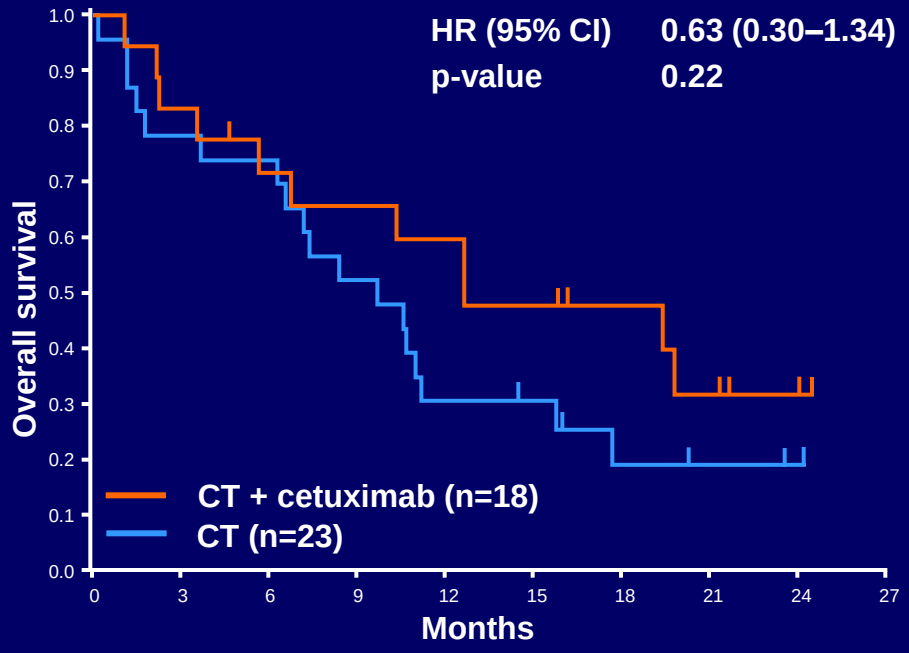
Baseline Patient and Disease Characteristics: ITT and p16 Evaluable

Characteristic, %	ITT		p16+		p16−	
	CT + cetuximab n=222	CT n=220	CT + cetuximab n=18	CT n=23	CT + cetuximab n=178	CT n=162
Sex, male	88.7	91.8	88.9	82.6	88.2	93.2
Age <65 years	82.4	82.7	83.3	95.7	82.0	81.5
KPS ≥80	87.8	88.6	83.3	95.7	87.6	85.8
Primary tumor site						
Oropharynx	36.0	31.4	44.4	69.6	36.5	29.0
Hypopharynx	12.6	15.5	22.2	8.7	11.8	16.0
Larynx	26.6	23.6	16.7	8.7	27.0	24.1
Oral cavity	20.7	19.1	16.7	4.3	20.8	19.8
Other	4.1	10.5	0	8.7	3.9	11.1
Extent of disease						
Locoregional recurrence only	53.2	53.6	33.3	52.2	55.6	55.6
Metastatic ± locoregional recurrence	46.8	46.4	66.7	47.8	44.4	44.4

CT, chemotherapy

Overall Survival by p16 Status

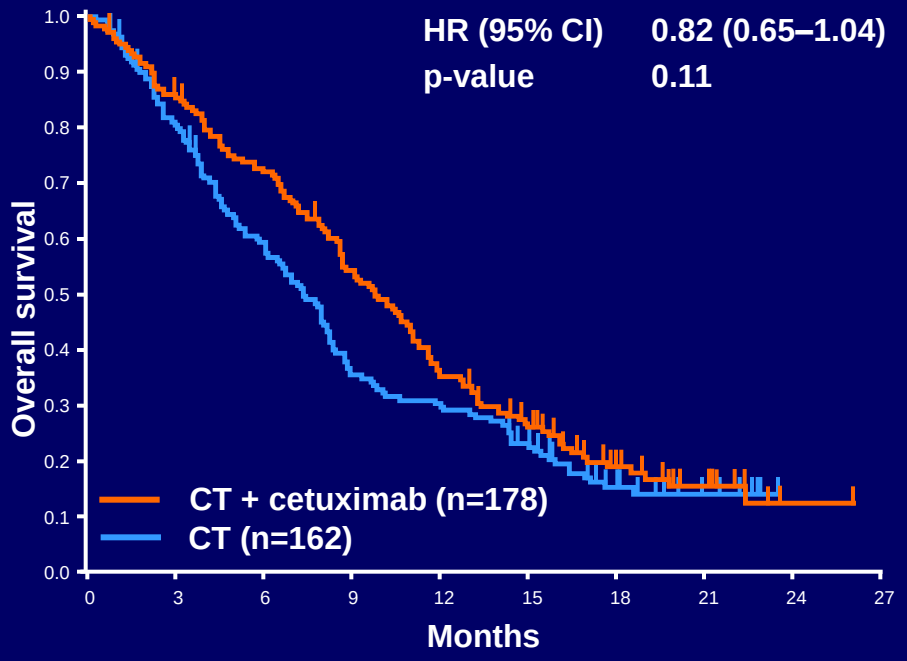
p16+ patients



Number of patients at risk

18	15	12	11	10	8	6	4	1	0
23	18	17	12	7	6	3	2	1	0

p16− patients

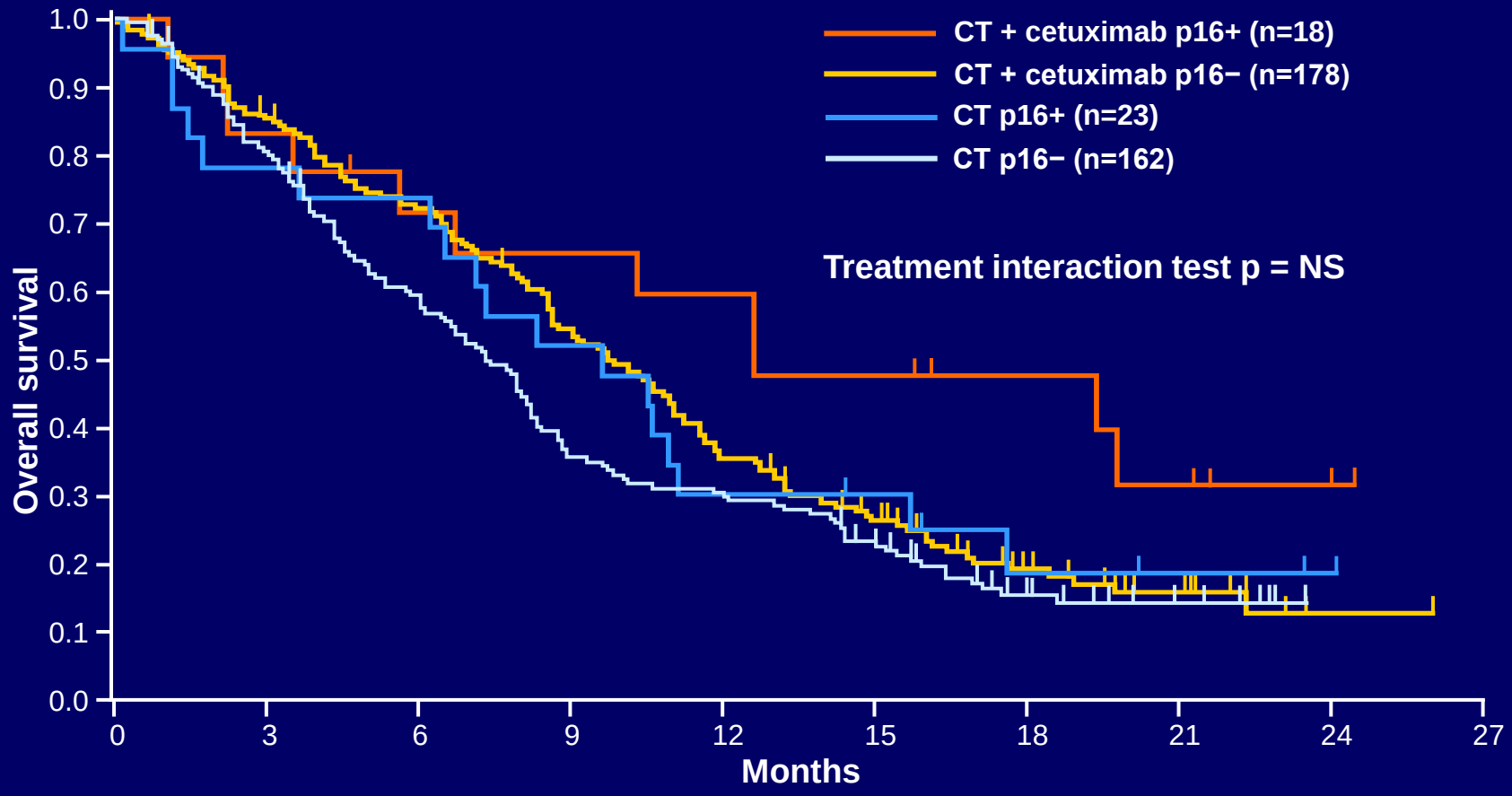


Number of patients at risk

178	150	126	93	61	40	19	10	1	0
162	128	92	56	47	33	15	6	0	0

HRs are CT + cetuximab vs CT
CI, confidence interval; HR, hazard ratio

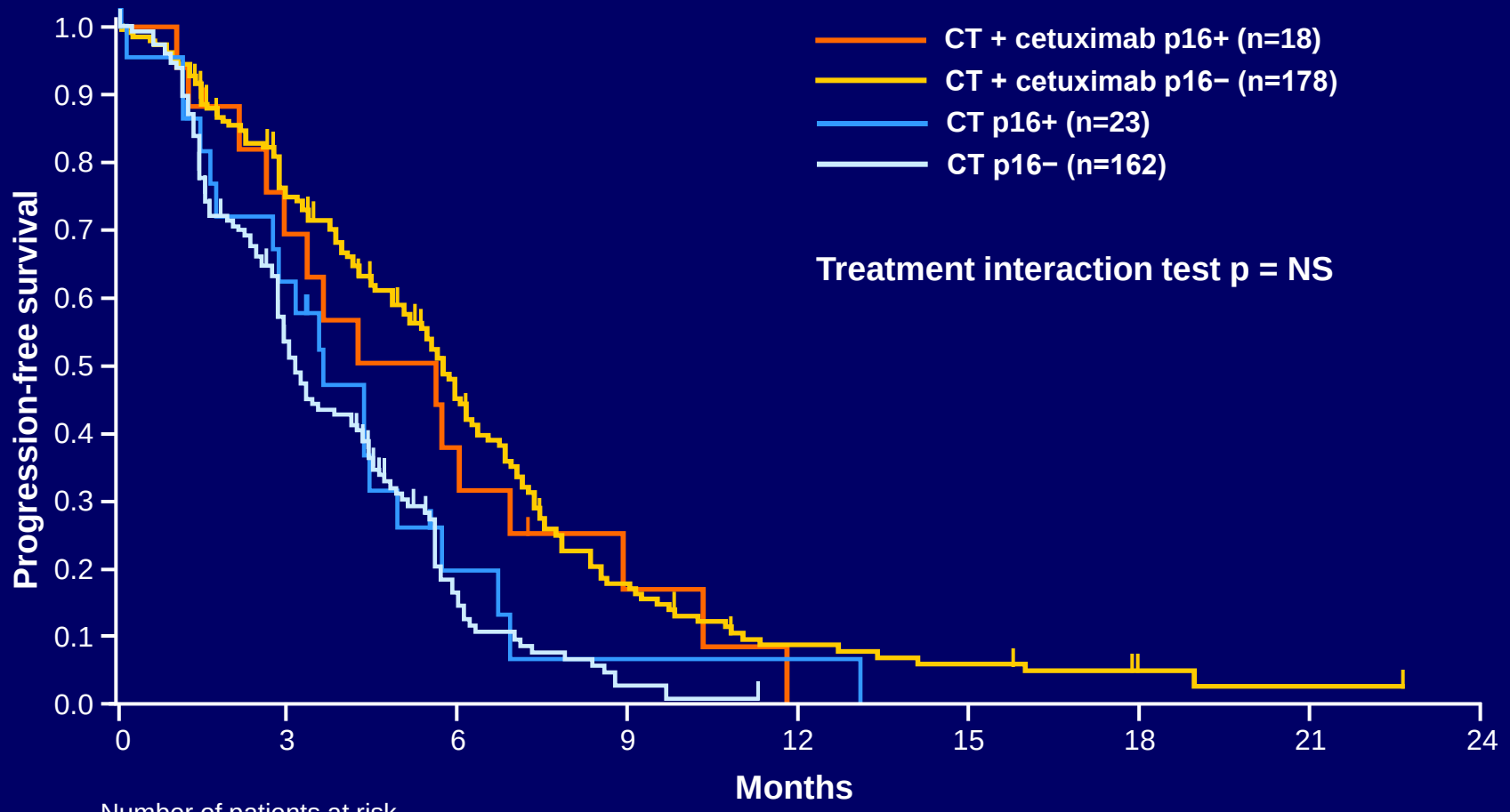
Overall Survival: Interaction



Number of patients at risk

18	15	12	11	10	8	6	4	1	0
178	150	126	93	61	40	19	10	1	0
23	18	17	12	7	6	3	2	1	0
162	128	92	56	47	33	15	6	0	0

Progression-free Survival: Interaction



Number of patients at risk

18	11	5	2	0	0	0	0	0
178	110	58	22	9	6	3	1	0
23	13	3	1	1	0	0	0	0
162	69	17	3	0	0	0	0	0

Predictive Effect

HPV status	Overall survival		Progression-free survival		Objective response rate	
	CT + cetuximab	CT	CT + cetuximab	CT	CT + cetuximab	CT
p16− (n=340)						
Median (months) / Rate	9.7	7.3	5.7	3.1	36.5%	17.3%
HR*/ Odds ratio†	0.82*		0.49*		2.75†	
95% CI	0.65–1.04		0.38–0.63		1.66–4.58	
p-value	0.11		<0.0001		<0.0001	
p16+ (n=41)						
Median (months) / Rate	12.6	9.6	5.6	3.6	50.0%	21.7%
HR*/ Odds ratio†	0.63*		0.73*		3.60†	
95% CI	0.30–1.34		0.36–1.47		0.93–13.95	
p-value	0.22		0.38		0.06	

HRs and odds ratios are CT + cetuximab vs CT

Prognostic Effect

Treatment	Overall survival		Progression-free survival		Objective response rate	
	p16+	p16−	p16+	p16−	p16+	p16−
CT + cetuximab (n=196)						
Median (months) / Rate	12.6	9.7	5.6	5.7	50.0%	36.5%
HR*/ Odds ratio†	0.59*		1.17*		1.74†	
95% CI	0.32–1.10		0.69–2.01		0.66–4.60	
p-value	0.09		0.56		0.26	
CT (n=185)						
Median (months) / Rate	9.6	7.3	3.6	3.1	21.7%	17.3%
HR*/ Odds Ratio†	0.83*		0.87*		1.33†	
95% CI	0.50–1.36		0.53–1.43		0.46–3.88	
p-value	0.45		0.59		0.60	

HRs and odds ratios are p16+ vs p16−

Summary of Adverse Events

	ITT*		p16+		p16−	
Patients, %	**CT + cetuximab n=219**	**CT n=215**	**CT + cetuximab n=18**	**CT n=22**	**CT + cetuximab n=175**	**CT n=159**
Any AE	99.5	96.7	100	90.9	99.4	97.5
Treatment-related	99.1	90.7	100	81.8	98.9	90.6
Any SAE	50.2	47.4	55.6	54.5	49.1	47.2
Treatment-related	29.2	27.0	33.3	31.8	29.7	27.7
Cetuximab-related	10.5	N/A	16.7	N/A	10.3	N/A
Grade 3/4 AEs	81.7	76.3	88.9	77.3	80.0	77.4
Treatment-related	68.5	58.1	83.3	54.5	67.4	59.7
AEs leading to death	15.5	15.3	16.7	18.2	13.7	14.5
Treatment-related	3.2	5.6	0	4.5	2.9	5.7
Cetuximab-related	0.5	N/A	0	N/A	0.6	N/A

*Safety population
AE, adverse event; N/A, not applicable; SAE, serious AE

Conclusions

- Globally, 88.3% of patients receiving CT + cetuximab were evaluable for p16 as a surrogate marker for HPV in EXTREME, with 9.2% of R/M SCCHN patients having p16+ tumors
- All subgroups were comparable regarding demographics and baseline characteristics
- Patients, independent of tumor p16 status, benefited from the addition of cetuximab to platinum-based chemotherapy
- The data suggest that p16 expression may be a positive prognostic factor in R/M SCCHN
- No new safety findings in any of the subgroups
- These results do not confirm the findings of the SPECTRUM trial* presented at ESMO 2011[1]

*In the SPECTRUM trial, p16 positivity required uniform staining in >10% of tumor cells

[1]Vermorken J et al. Eur J Cancer 2011;47(Suppl 2):25 LBA

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