5-Y update of the randomized phase III trial DAHANCA19: Primary (Chemo) RT +/- zalutumumab in HNSCC

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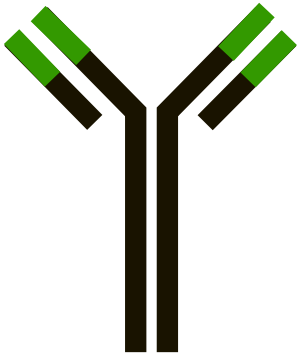
DAHANCA
The Danish Head and Neck Cancer Group

Zalutumumab – preclinical data

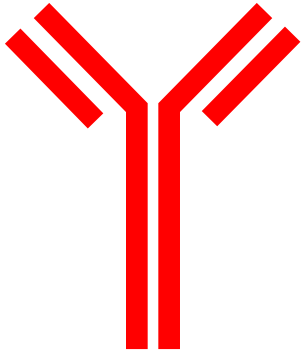
Chimeric



34% Mouse Protein

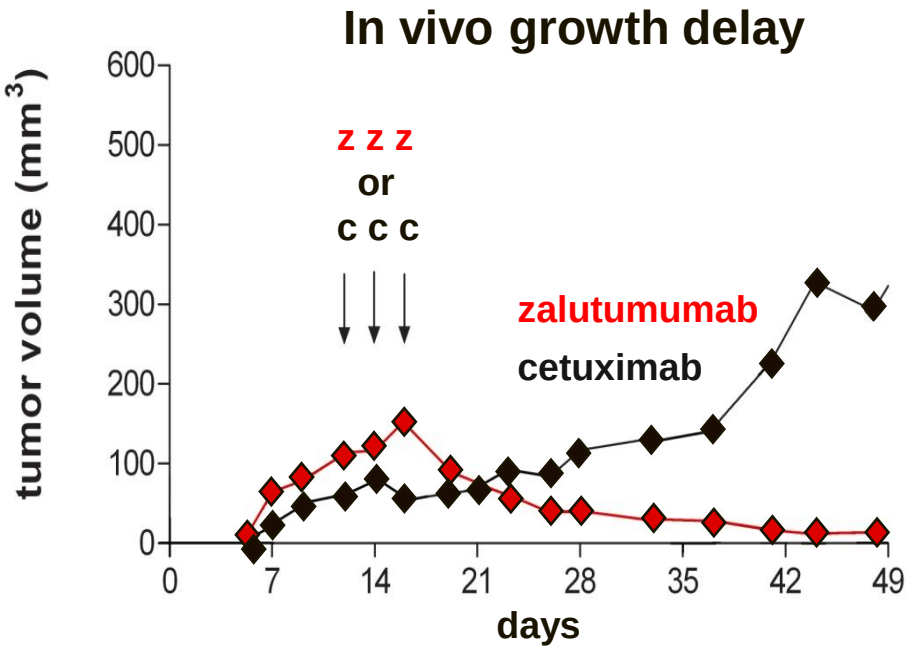
Cetuximab

Fully Human



100% Human Protein

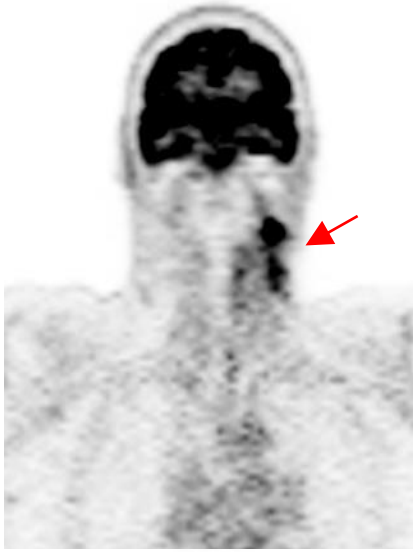
Zalutumumab

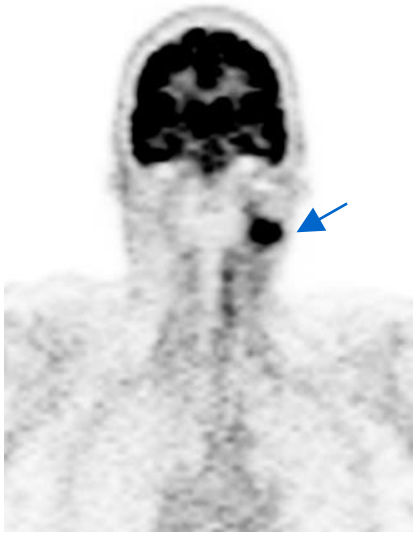


Adapted after Bleeker WK et al, J Immunol 2004

Zalutumumab: phase I-II data (DAHANCA 15)

- Phase I: 0.15-8 mg/kg 28 days follow-up
- Phase II: weekly treatment for 1 month
- FDG-PET/CT 2 mo after 1st dose
- 70% partial remission/stable disease
- Maximal tolerable dose (MTD) not reached





Bastholt L et al, Radiother Oncol 2007

DAHANCA 19: aim

- To determine if addition of the fully human EGFR antibody zalutumumab to primary curative (chemo-) radiotherapy of HNSCC increases:

- Loco-regional failure (primary endpoint)
- Disease specific survival
- Overall survival
- Acute and late toxicity

DAHANCA 19: eligibility criteria

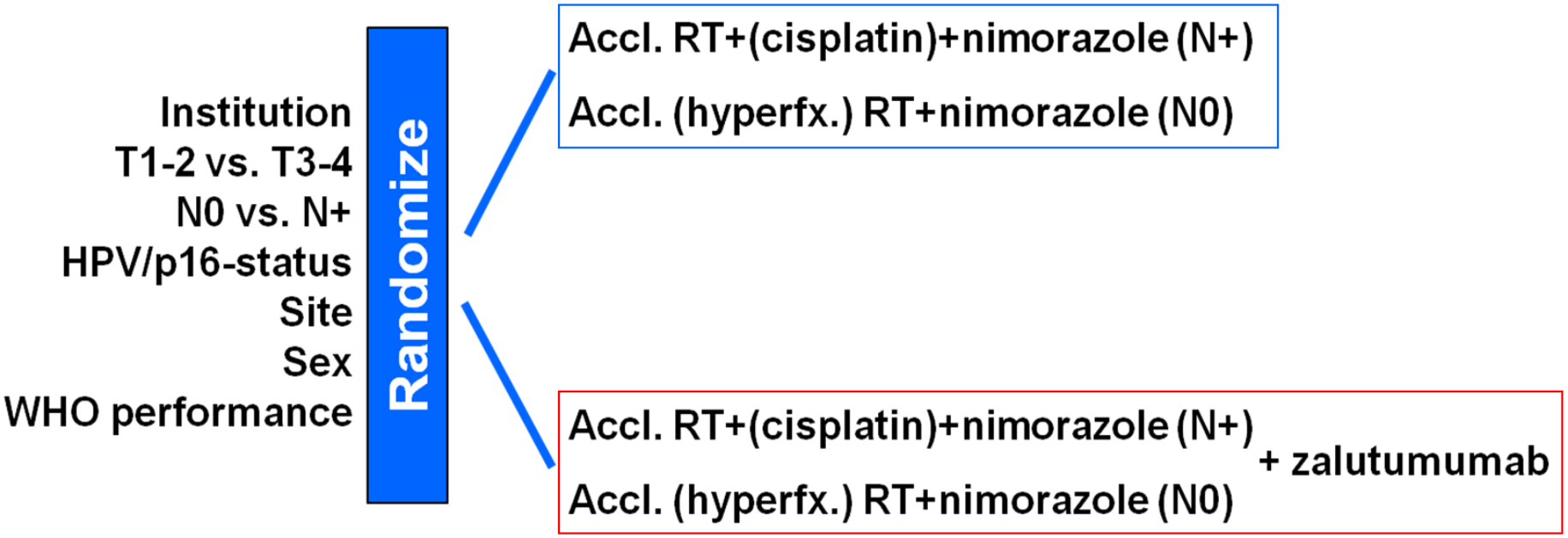
- Squamous cell carcinoma
- Larynx, oropharynx, hypopharynx and oral cavity
- T1-4, N0-3, M0
- Excluding st. I larynx and st. I-II glottic larynx cancer
- Known HPV/p16 status
- Performance 0-2
- No primary surgery
- Compliant and physically fit to therapy

DAHANCA 19: treatment

- Intensity-modulated radiotherapy (IMRT)
- Accelerated fract. RT 66-68 Gy, 2 Gy/fx, 6 fx/wk

  (or hyper-fract. RT 76Gy, 1.35 Gy BID, 10 fx/wk to N-neg. pts. (optional))
- Cisplatin, weekly, 40 mg/m2, to N-pos. patients
- Nimorazole 1.200 mg/m2, 90 min. prior to RT
- Zalutumumab 8 mg/kg, starting 1 week before treatment and weekly during treatment

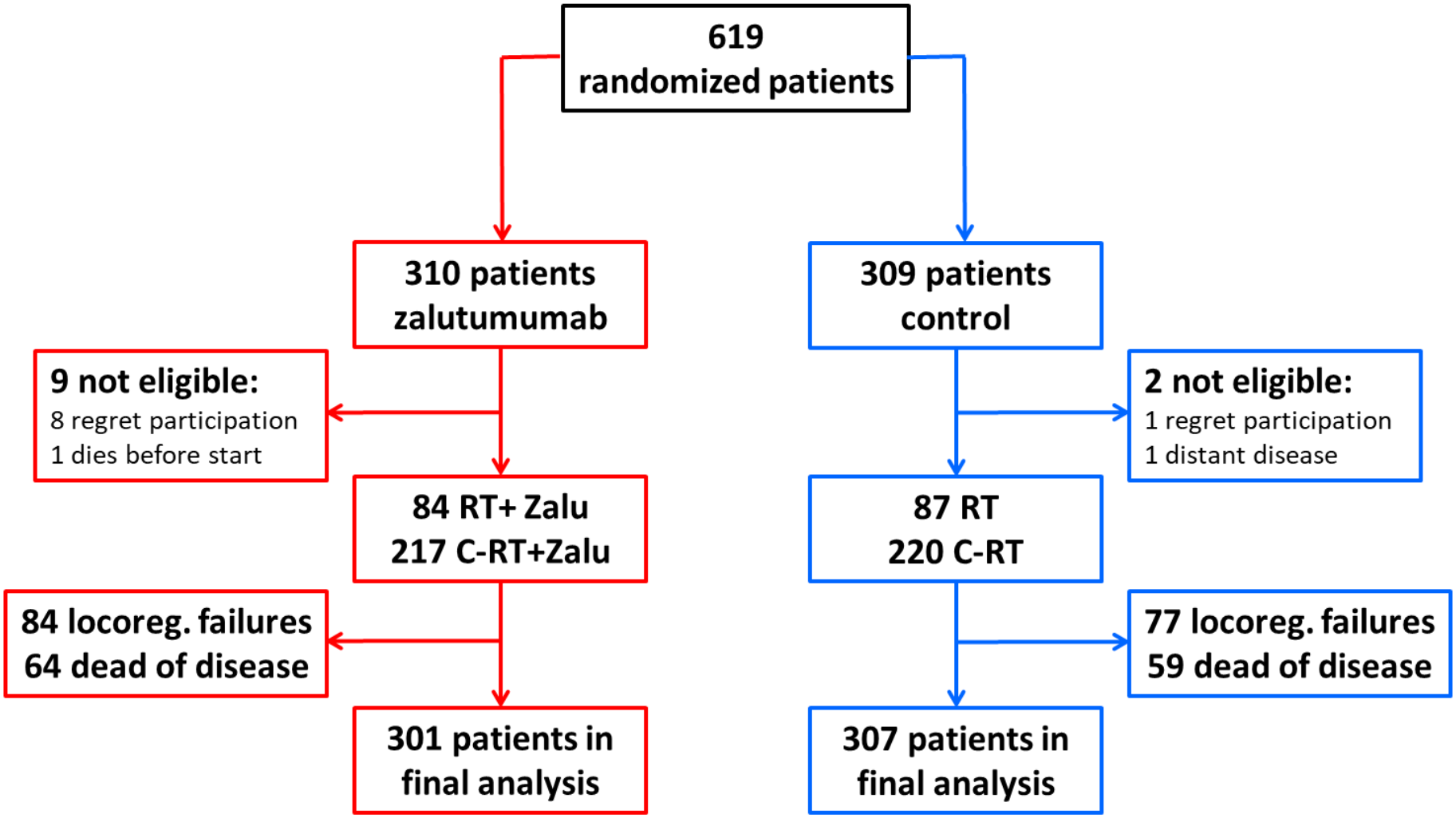
DAHANCA 19: trial design



DAHANCA 19: Patient accrual and status

- Accrual period: November 2007 to June 2012
- All H&N cancer centres in Denmark + Oslo, Norway
- 619 patients (~40% of potential eligible population)
- Date of evaluation: November 1st. 2017
- Median observation time: 58 months (1-107 months)

DAHANCA 19: Elegible patients



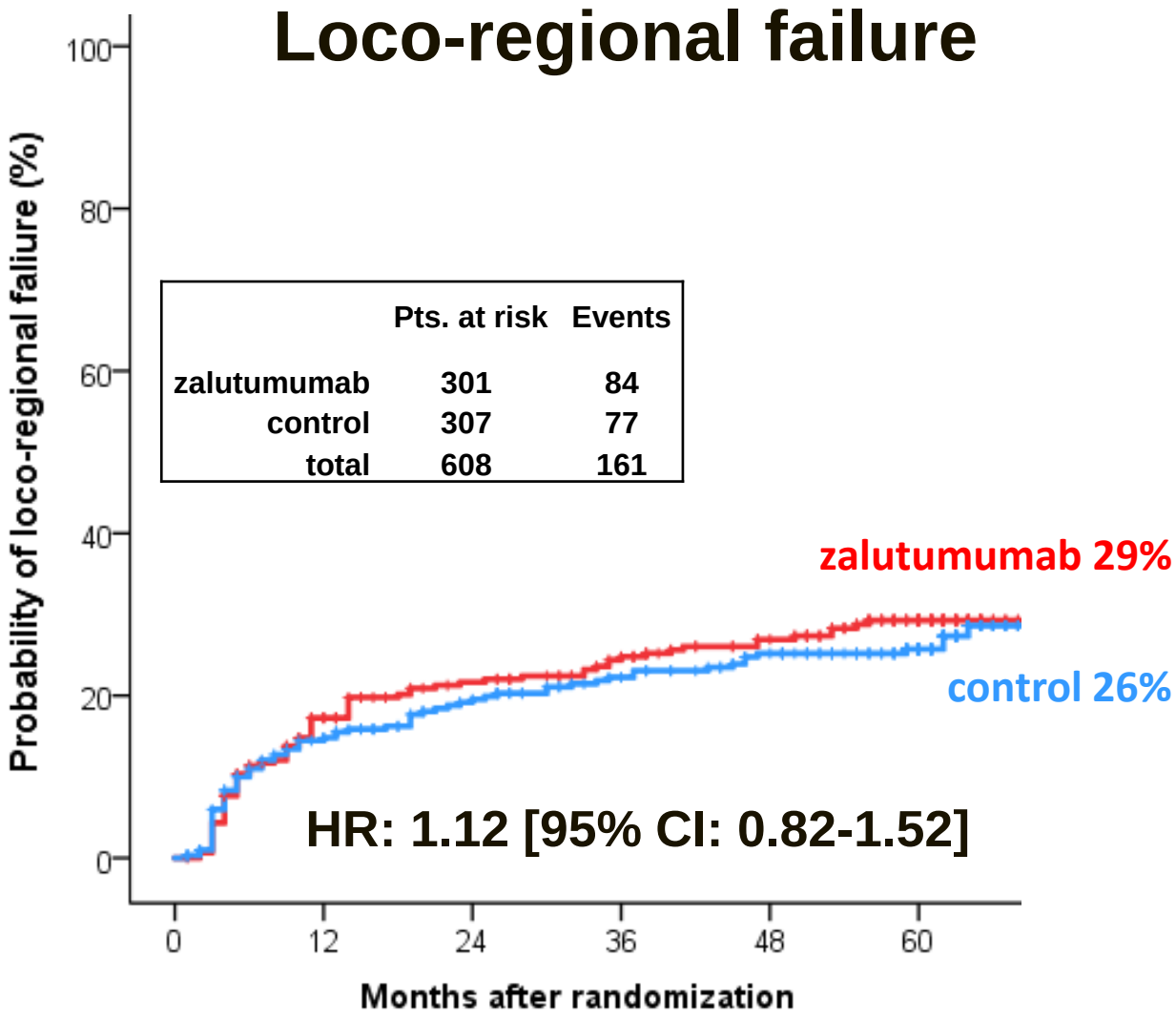
DAHANCA 19: patient/tumour characteristics

	Total (n=608)	Zalutumumab (n=301)	Control (n=307)
Age (median years)	59 (31-84)	58 (31-79)	59 (38-84)
Male	497 (82%)	245 (81%)	252 (82%)
WHO 0-1	592 (97%)	292 (97%)	300 (98%)
Smoking (≥10 PY)	466 (77%)	224 (74%)	242 (79%)
Oral cavity	24 (4%)	11 (4%)	13 (4%)
Oropharynx	424 (70%)	211 (70%)	213 (69%)
Hypopharynx	74 (12%)	36 (12%)	38 (12%)
Larynx	87 (14%)	44 (14%)	43 (14%)
Stage I-II	61 (10%)	28 (9%)	33 (11%)
Stage III-IV	548 (90%)	274 (91%)	274 (89%)
HPV/p16+ (all pts.)	333 (55%)	166 (55%)	167 (54%)
HPV/p16+ (oroph.)	312 (74%)	154 (73%)	158 (74%)

DAHANCA 19: treatment and compliance

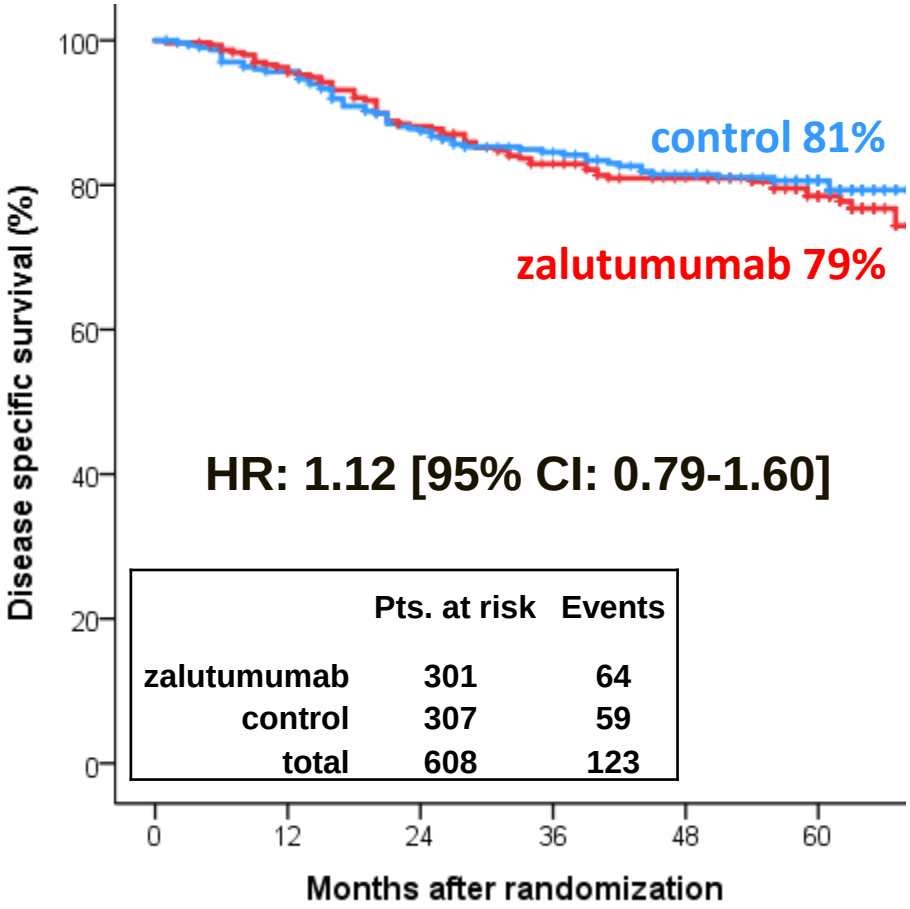
	Total (n=608)	Zalutumumab (n=301)	Control (n=307)
RT ≥ 66 Gy	601 (99%)	302 (100%)	301 (98%)
Weekly platinum	433 (71%)	216 (72%)	217 (71%)
≥ 5 series*	327 (76%)	149 (69%)	178 (82%)
Nimorazole	589 (97%)	291 (97%)	298 (97%)
Full compliance	406 (69%)	195 (67%)	211 (71%)
Zalutumumab (mean doses)		5.5 (1-7)	

DAHANCA 19: primary endpoint

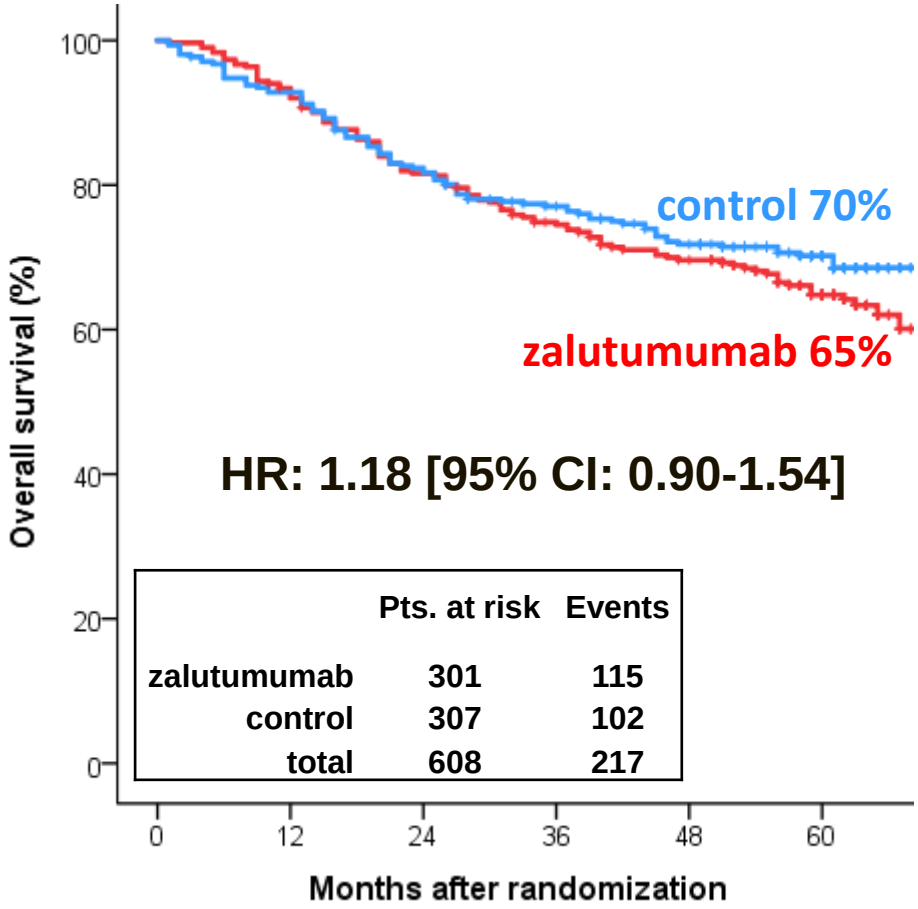


DAHANCA 19: secondary endponints

Disease specific survival



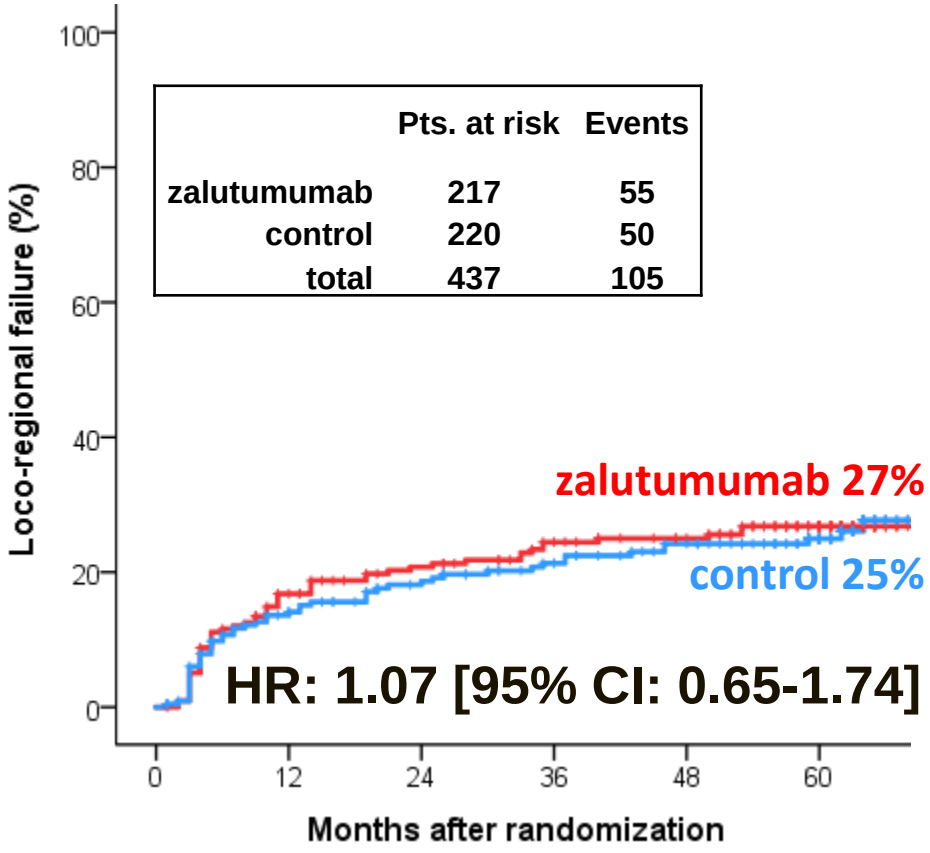
Overall survival



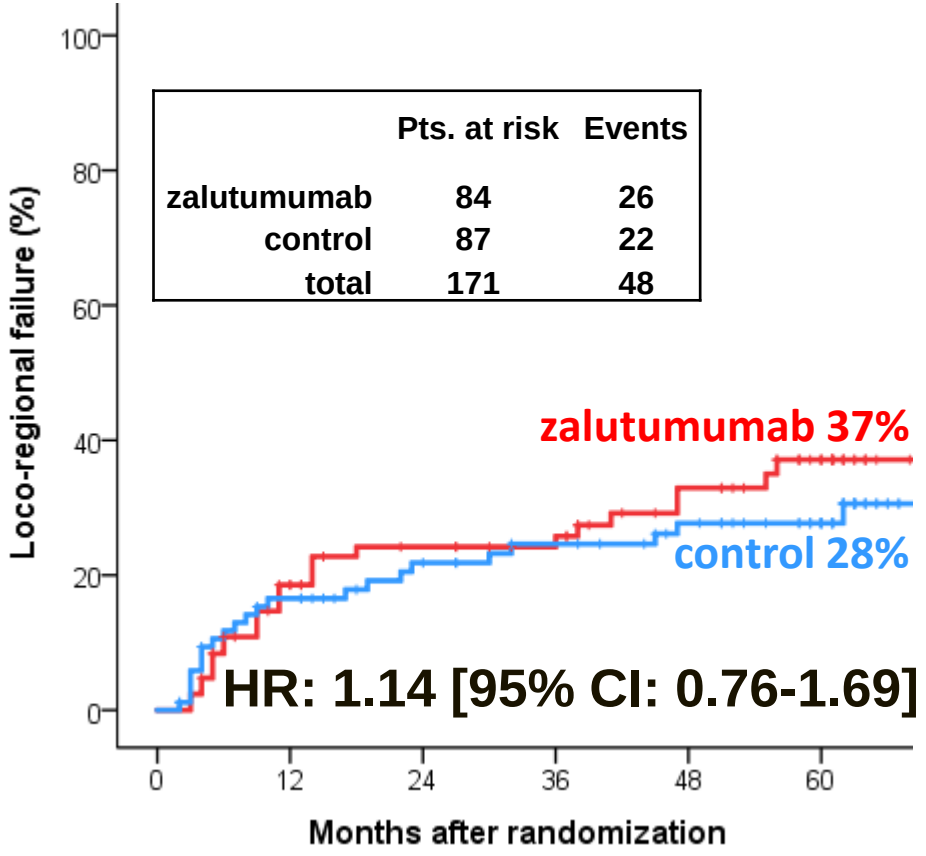
DAHANCA 19: C-RT vs. RT

Loco-regional failure

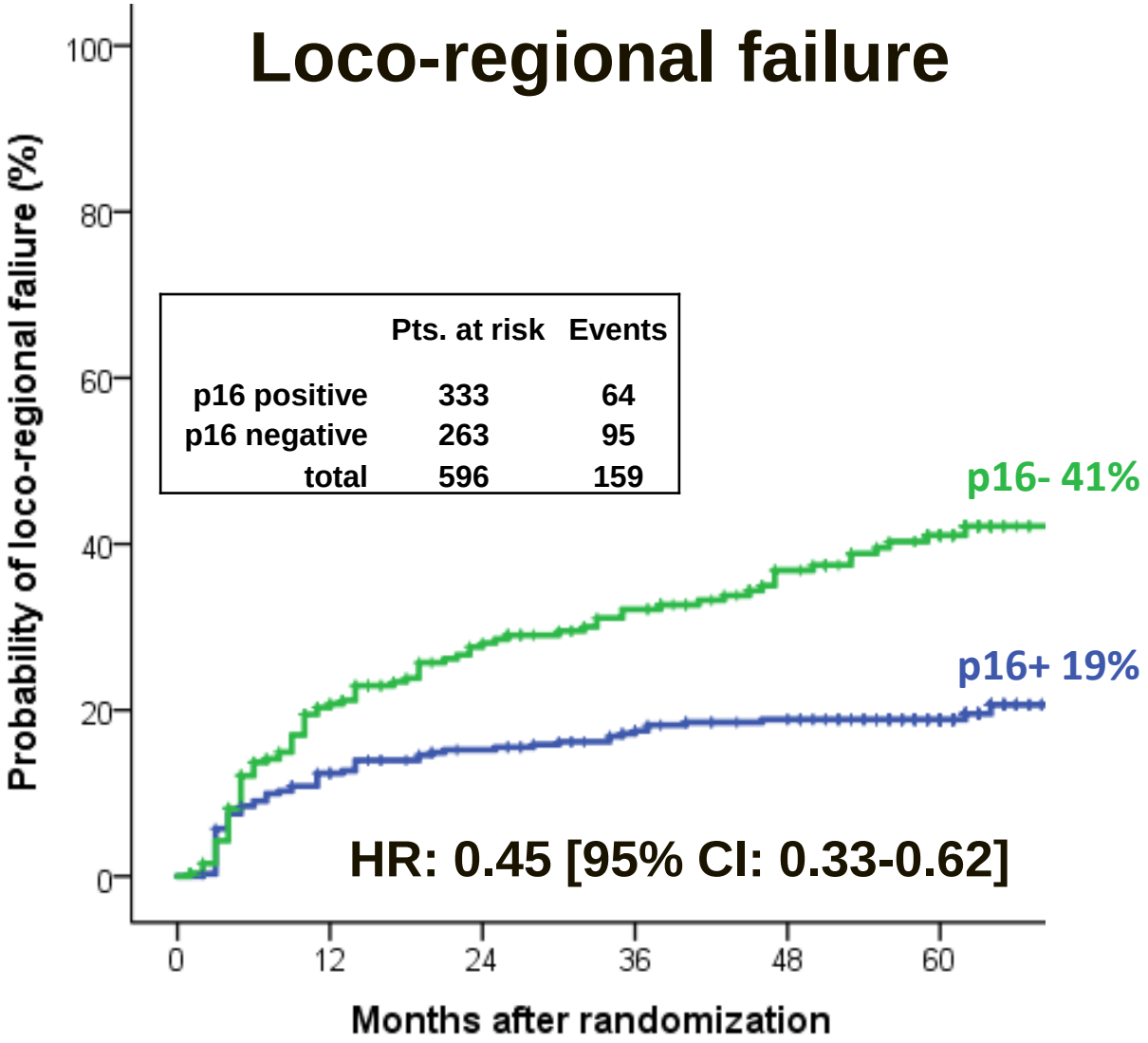
C-RT



RT



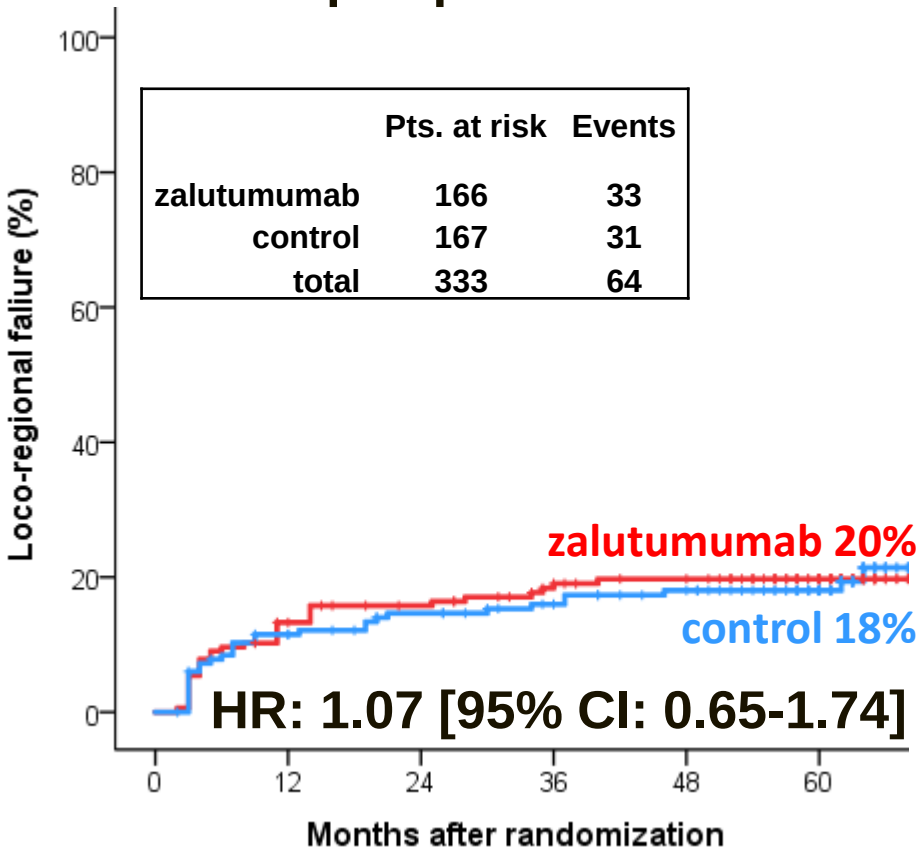
DAHANCA 19: influence of HPV/p16



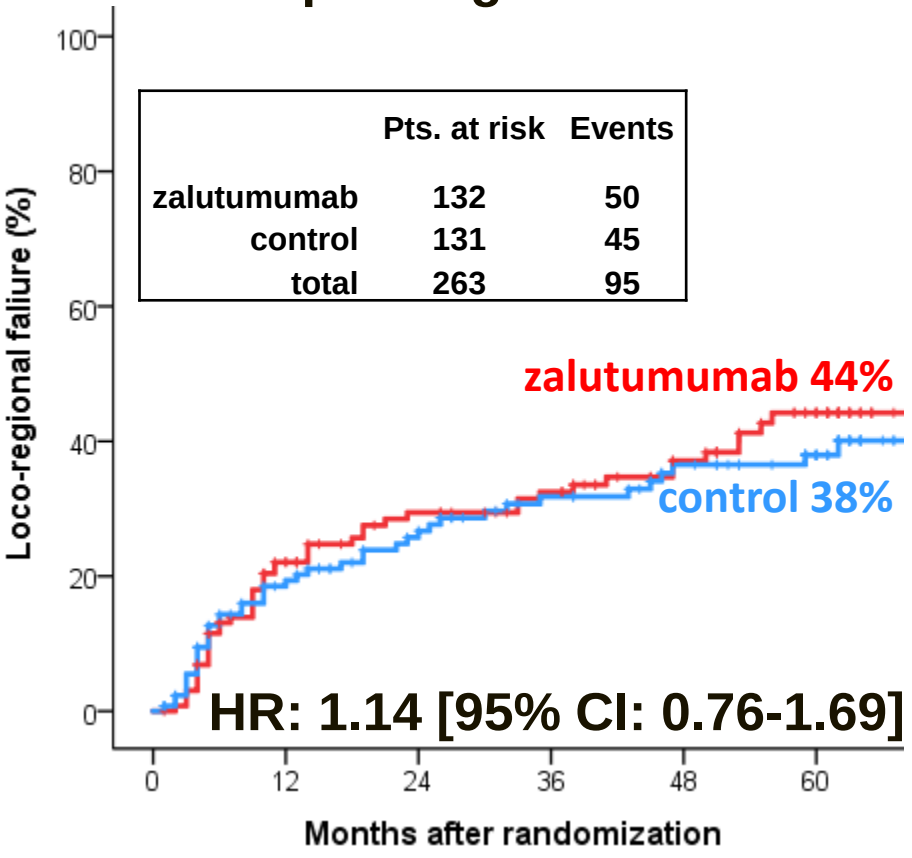
DAHANCA 19: HPV/p16 and zalutumumab

Loco-regional failure

p16 positive



p16 negative



DAHANCA 19: Cox proportional hazard analysis

	Loco-regional faliure	Disease specific death	Overall death
Male vs. female	1.09 [0.72-1.65]	1.36 [0.80-2.29]	**1.52 [1.01-2.28]**
WHO 0 vs. 1-2	**0.67 [0.46-0.97]**	**0.47 [0.31-0.70]**	**0.62 [0.45-0.83]**
T I-II vs. T III-IV	0.75 [0.54-1.04]	**0.43 [0.29-0.64]**	**0.45 [0.34-0.61]**
N0 vs. N+	**0.51 [0.32-0.83]**	**0.42 [0.24-0.71]**	**0.61 [0.42-0.88]**
Oropharynx vs. other sites	0.81 [0.55-1.19]	1.17 [0.77-1.78]	1.12 [0.81-1.54]
HPV/p16+ vs. HPV/p16-	**0.44 [0.29-0.65]**	**0.40 [0.25-0.64]**	**0.37 [0.26-0.53]**
C-RT vs. RT alone	0.84 [0.56-1.26]	0.84 [0.54-1.31]	0.80 [0.57-1.12]

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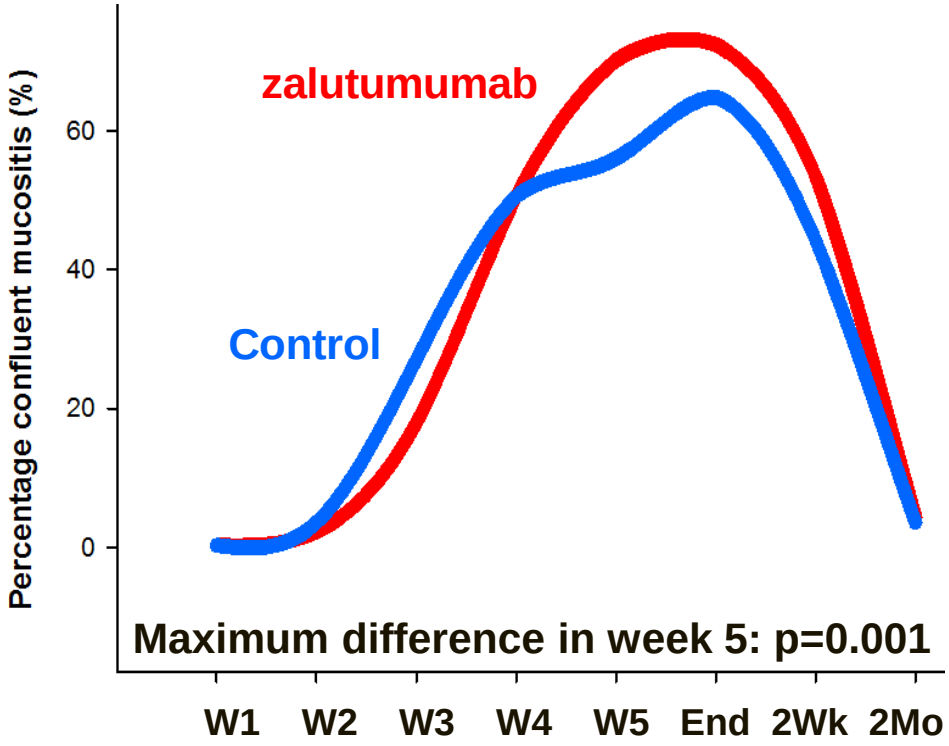
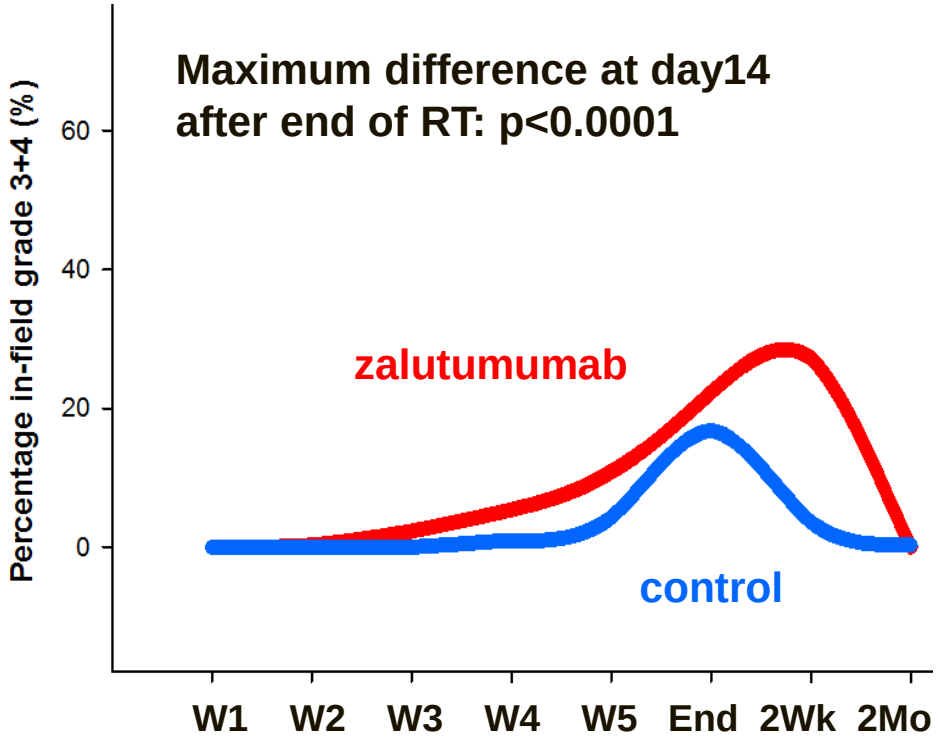
C-RT vs. RT alone	0.84 [0.56-1.26]	0.84 [0.54-1.31]	0.80 [0.57-1.12]
Zalutumumab vs. control	**1.07 [0.78-1.47]**	**1.14 [0.80-1.63]**	**1.20 [0.91-1.58]**

DAHANCA 19: acute morbidity

Confluent mucositis

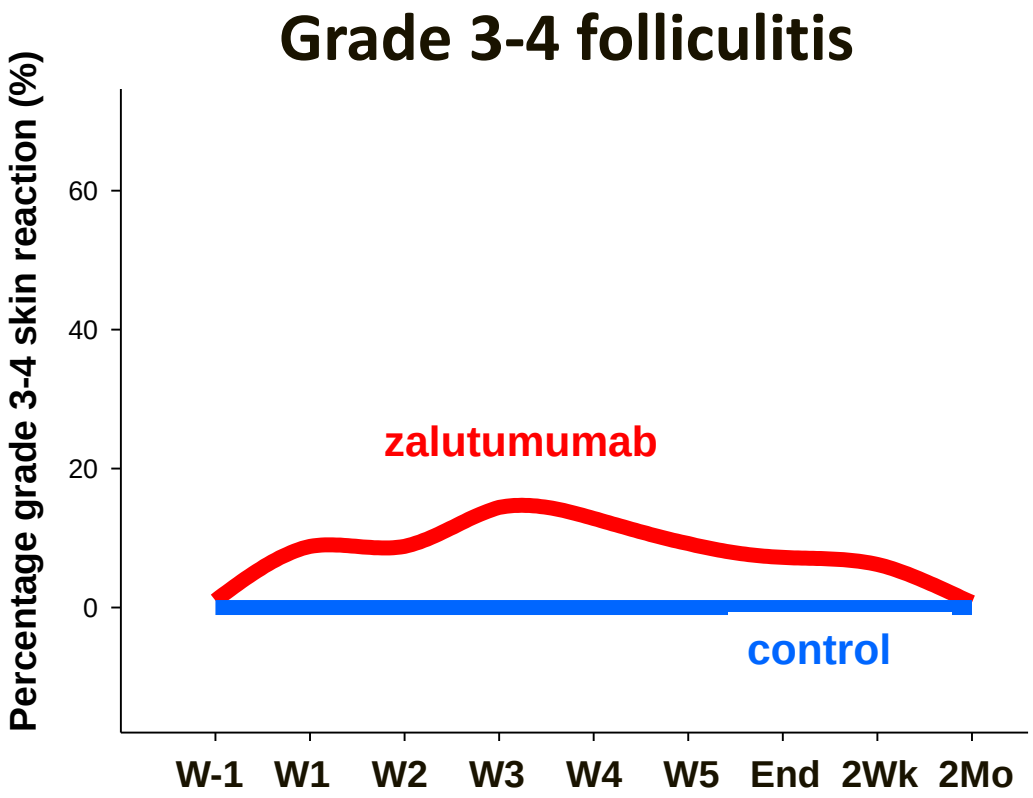


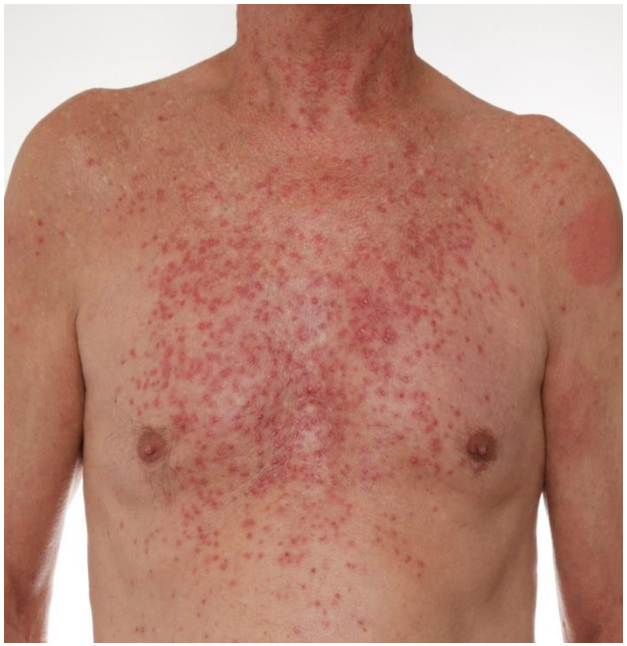
Grade 3-4 in-field reaction



Need for tube-feeding at end of treatment:
No difference (50% vs. 48%)

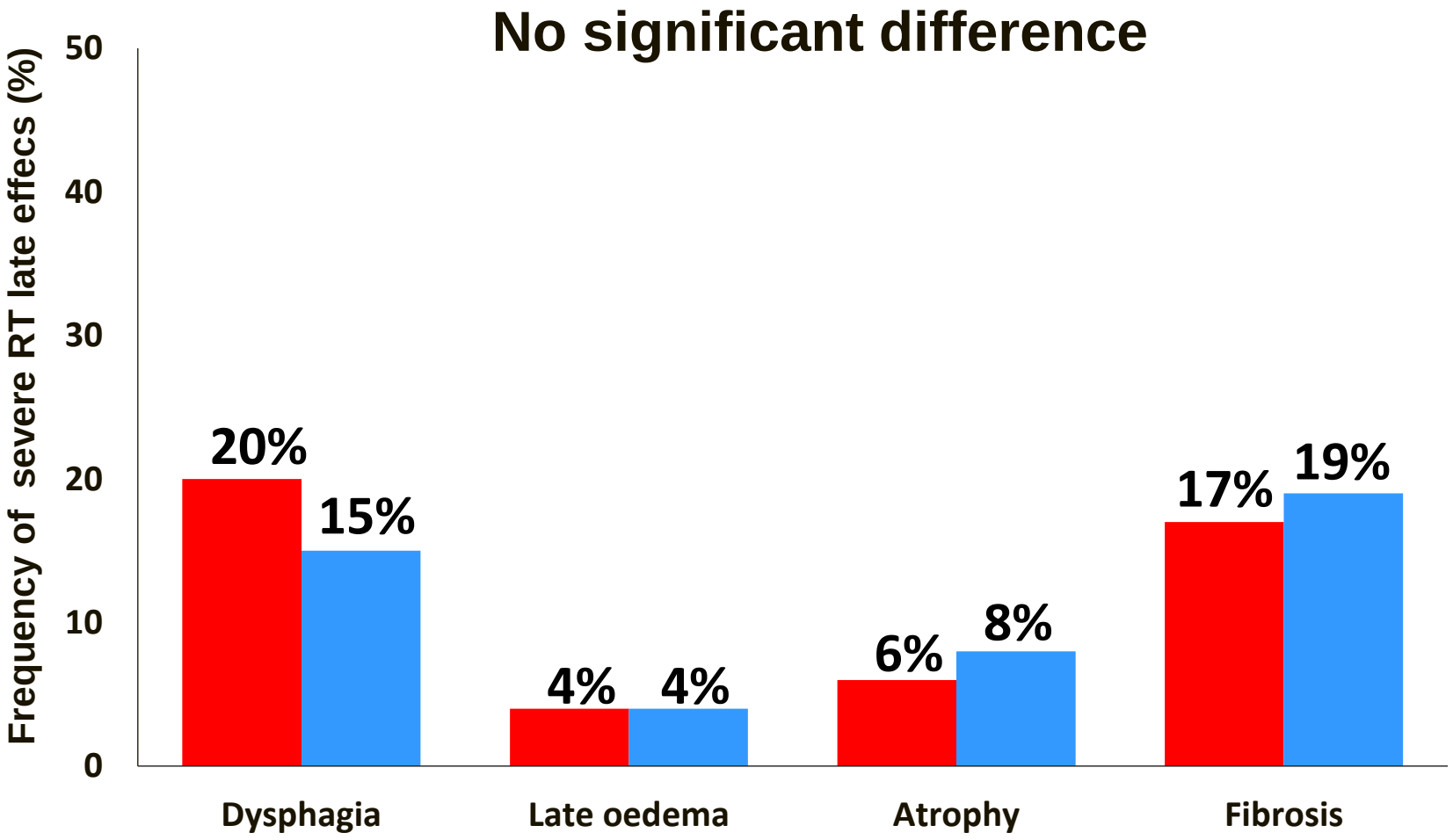
DAHANCA 19: folliculitis





- 94% in the zalutumumab-arm developed a skin rash
- 29% experienced grade 3-4 rash
- 11% ceased zalutumumab due to rash

DAHANCA 19: severe late RT effects



DAHANCA 19: conclusions

- Addition of zalutumumab to accelerated (chemo-) RT for HNSCC did not alter loco-regional failure, disease specific nor overall survival at 5 years
- Response to zalutumumab was not related to tumour HPV/p16 status or administration of concomitant cisplatin
- Zalutumumab did not influence compliance to RT
- Treatment with zalutumumab was well tolerated