The importance of window opportunity studies in Head and Neck cancer

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Disclosure

Merck-Serono: Unrestricted Grant to conduct this trial

Boerhinger-Ingelheim: consultant

Window opportunity studies

Baseline biopsies → **investigational drug** → **Surgery**

- **The preoperative setting is increasingly popular for the clinical investigation of new biological drugs**
- **Breast cancer (FDA): pathological response and Ki67**
- **Squamous cell carcinoma of the Head and Neck : erlotinib**

Dowsett M et al, JNCI monogr 2011
Vergez et al , Clin Canccer Res 2010
Thomas et al , Clin Canccer Res 2007

Window opportunity studies: background

- **Targeted agents are often investigated in unselected end-stage cancer patients and by the RECIST criteria**

- **This trial design makes unlikely to fully exploit the antitumour potential of some of these agents**
  - most patients have developed multifactorial resistance
  - translational research is hampered in palliative patient**s**

- **Evaluation of new compounds in the pre-operative window setting :**
  - maximize the chance of observing tumor response
  - collection of biological materials before/after treatment

Issues with window opportunity studies

- Safety
- Not to delay the curative treatment that should start with 3-4 weeks of diagnosis
- The time points for biopsies and imaging must be prospectively pre-defined
- The schedule, dose, and duration of the pre-operative treatment should be standarized and the same for all patients

Primdahl et al, Acta Oncol 2006
Allison et al , Oral Oncol 1998
Jensene AR et al Radiother Oncol 2007

Window opportunity studies with anti-EGFR

- Cetuximab improves overall survival in combination with radiation therapy or chemotherapy
- Only a minority of patients benefit from anti-EGFR mAbs
- Surgery-related release of EGF-like factors might promote cell proliferation leading to tumor recurrence

Bonner et al, NEJM 2006
Vermorken et al , NEJM 2008
Machiels et al, Lancet Oncol 2011
Licitra et al Ann Oncol 2011

Window study with cetuximab in squamous cell carcinoma of the head and neck

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Main inclusion criteria

- **Squamous cell carcinoma of the oral cavity, oro/hypopharynx or larynx**
- **Patients selected for a primary surgical treatment**
- **No active second malignancy during the last five years including head and neck cancer**
- **ECOG 0-1**

Study objectives

Primary objective

- **Surgical safety of pre-operative cetuximab administration**

Secondary objectives

- **Metabolic response by 18FDG-PET/CT after 2 weeks**
- **Imaging: response evaluated by RECIST v1.1 using conventional imaging and by DWI MRI**
- **Translational research**

Study design

1)Safety part (3+3 design, n=12):

- to determine the safe minimum delay between the last cetuximab infusion and surgery

2) Expansion part (n=20) :

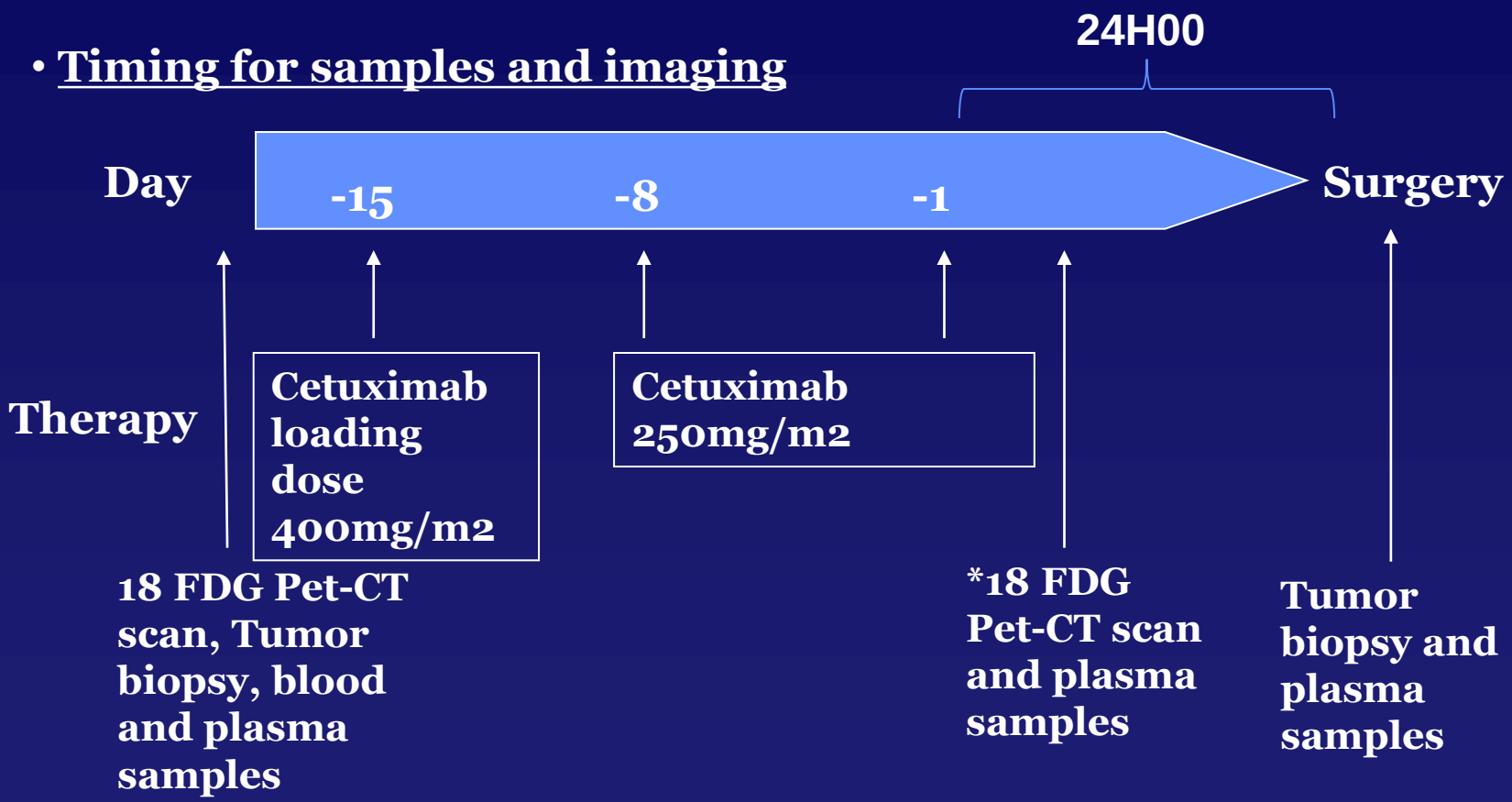
- safety and ^{18}FDG-PET activity (n=20)

(P_o=0.10, P_1=0.35, α=0.1 and β= 0.10; Simon, 4 patients out of 19 should have PET response).

3) Control group (n=5) : 5 untreated patients were recruited as control

Expansion part of the study

- **Timing for samples and imaging**



+ inclusion of 5 « control » patients: same time points for Pet-CT and tissue samples but without preoperative administration of Cetuximab.

* 18 FDG Pet-Ct scan was performed strictly 2H00 after Cetuximab

Patient characteristics

Patient Characteristics	*N*
No of patients included	37
Sex	
Female	10
Male	27
Primary tumor location	
Oral cavity	32
Larynx	4
Hypopharynx	0
Oropharynx	1
Human Papillomavirus	
p16 positive	2
p16 negative	35

Patient characteristics

Patient Characteristics	*N*
Clinical staging T	
cT1	7
cT2	25
cT3	3
cT4	2
Clinical staging N	
cN0	33
cN1	3
cN2b	1
cN2c	0

Safety

N=32	Grade 1-2	Grade 3-4
Rash	29 (66%)	3 (9%)
Diarrhea	1 (3%)	0%
Calcemia	12 (37.5%)	0%
Magnesium	2 (6%)	0%
Phosphorus	5 (16%)	0%
Stomatitis	2 (6%)	0%
Nail changes	1 (3%)	0%

18FDG-PET results

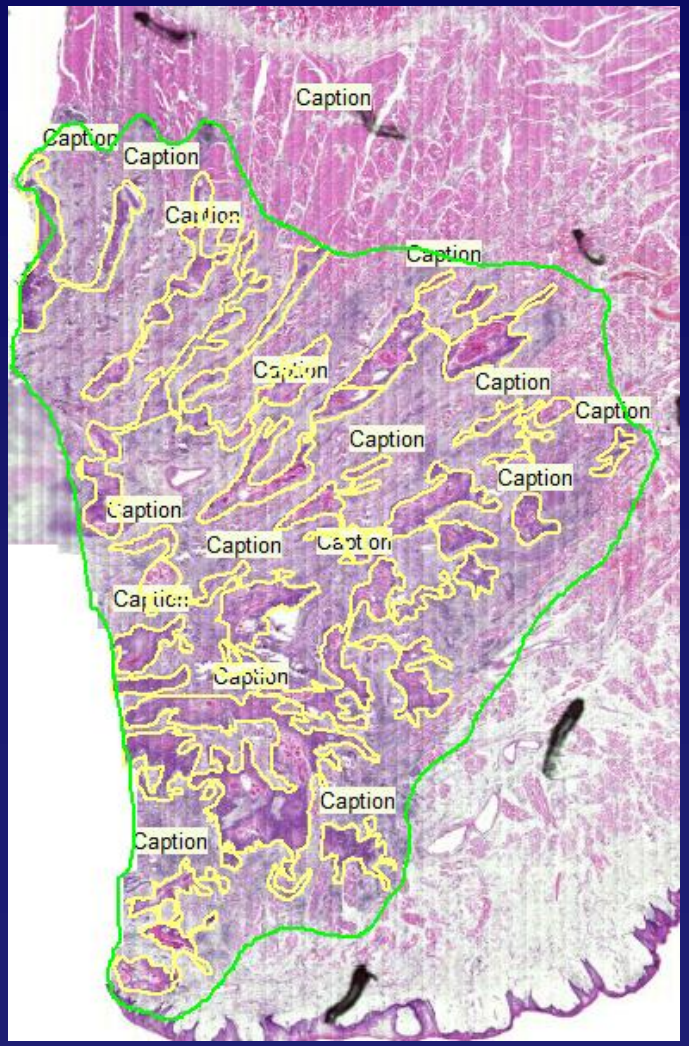
	Safety part N=12	Expansion part N=20	Control N=5
Number of evaluable patients	10	19	5
ΔSUVmax > + 25%	0	0	0
ΔSUVmax between +25% and -25%	2 (20%)	1 (5%)	5 (100%)
ΔSUVmax between -25% and -50%	2 (20%)	8 (42%)	0
ΔSUVmax between -50% and -75%	6 (60%)	8 (42%)	0

According to EORTC:
80% of patients in the Cetuximab arm had a partial response

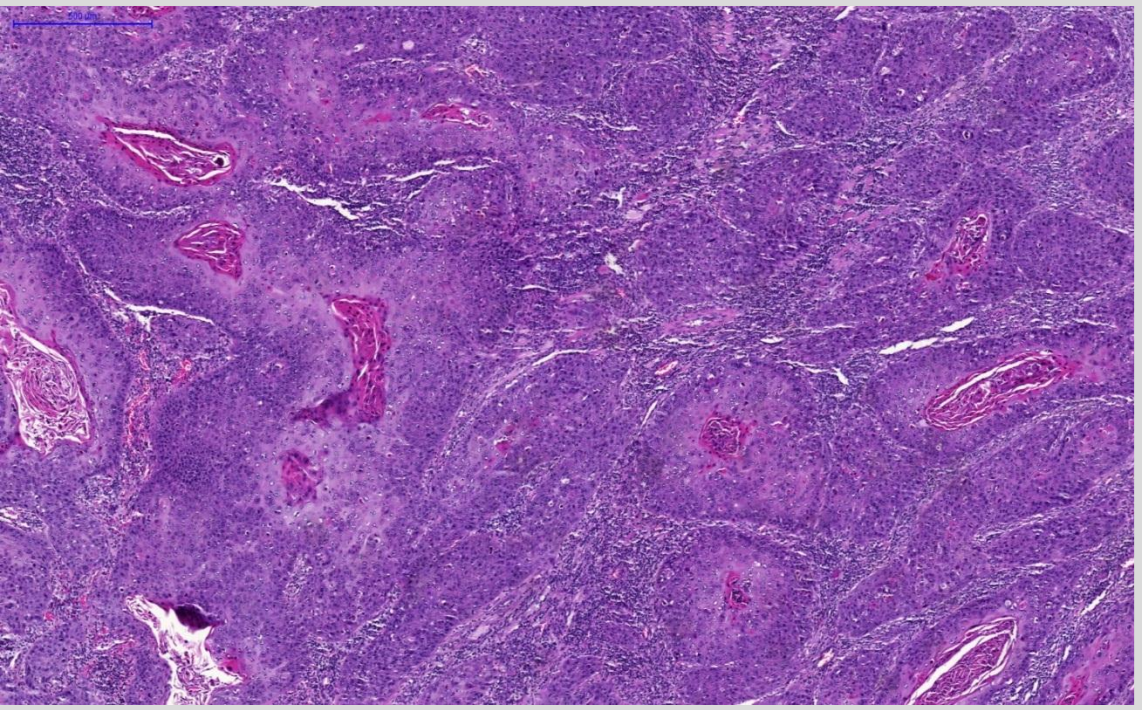
ΔSUV_{max} = % of SUVmax modification between two PET studies)

Young et al, Eur J Cancer 1999

Pathological response on the resected specimen

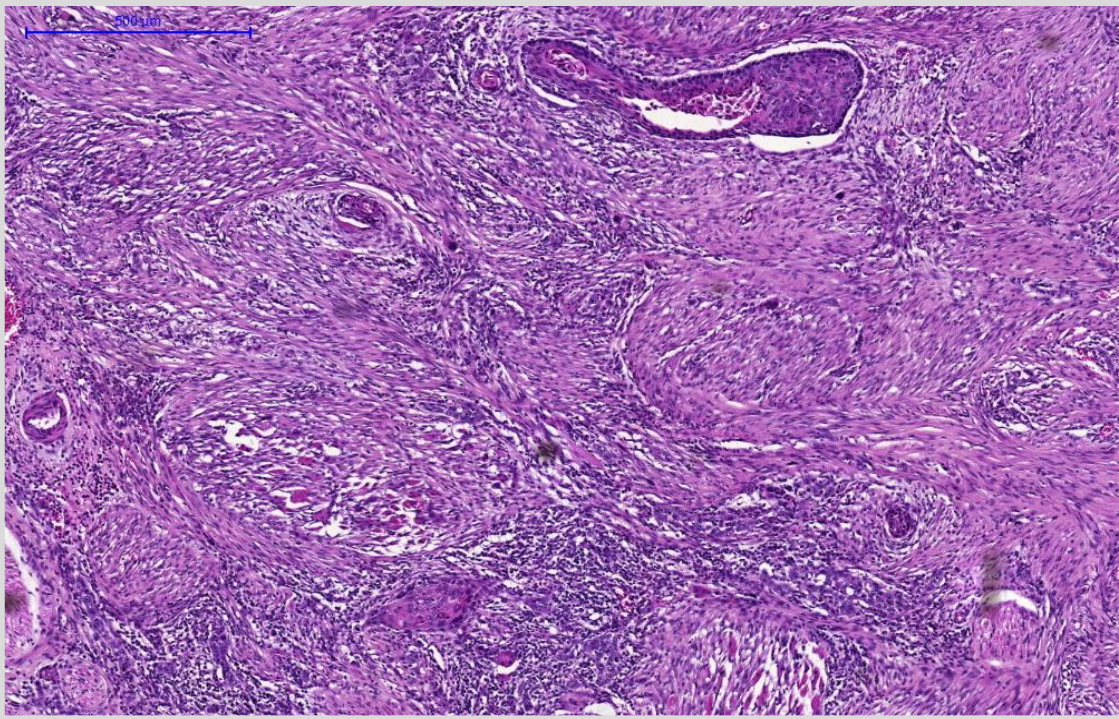


Residual tumor cellularity (%) was the surface occupied by tumor cells divided by the surface of the whole tumor

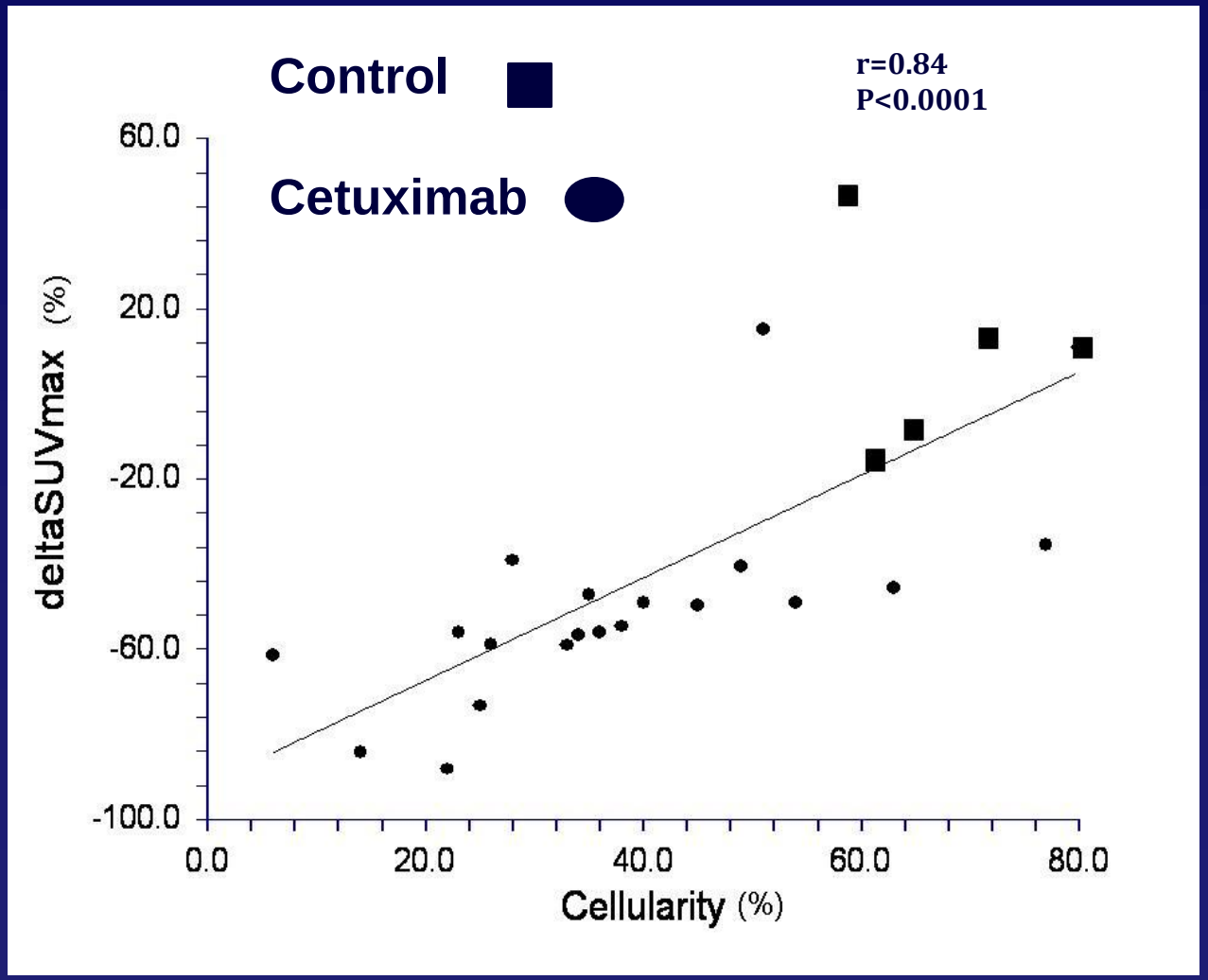


Treatment naive tumour

Tumour after Cetuximab infusion



Correlation between ΔSUV_{max} and Tumor cellularity



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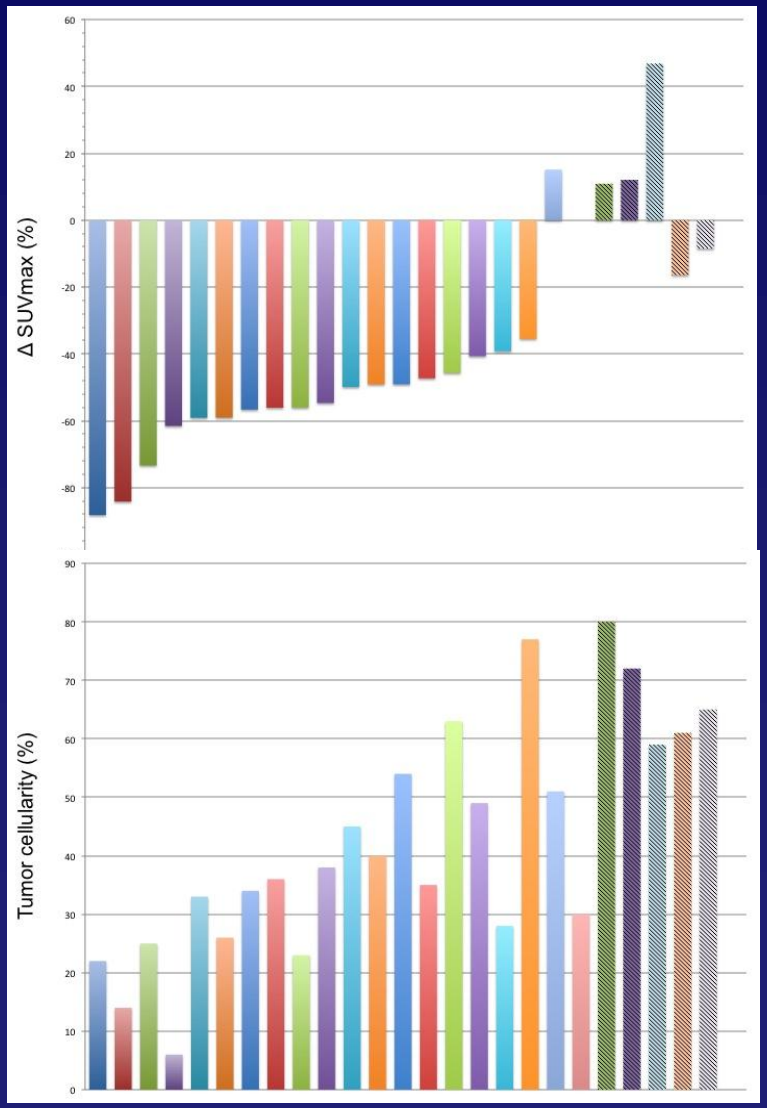
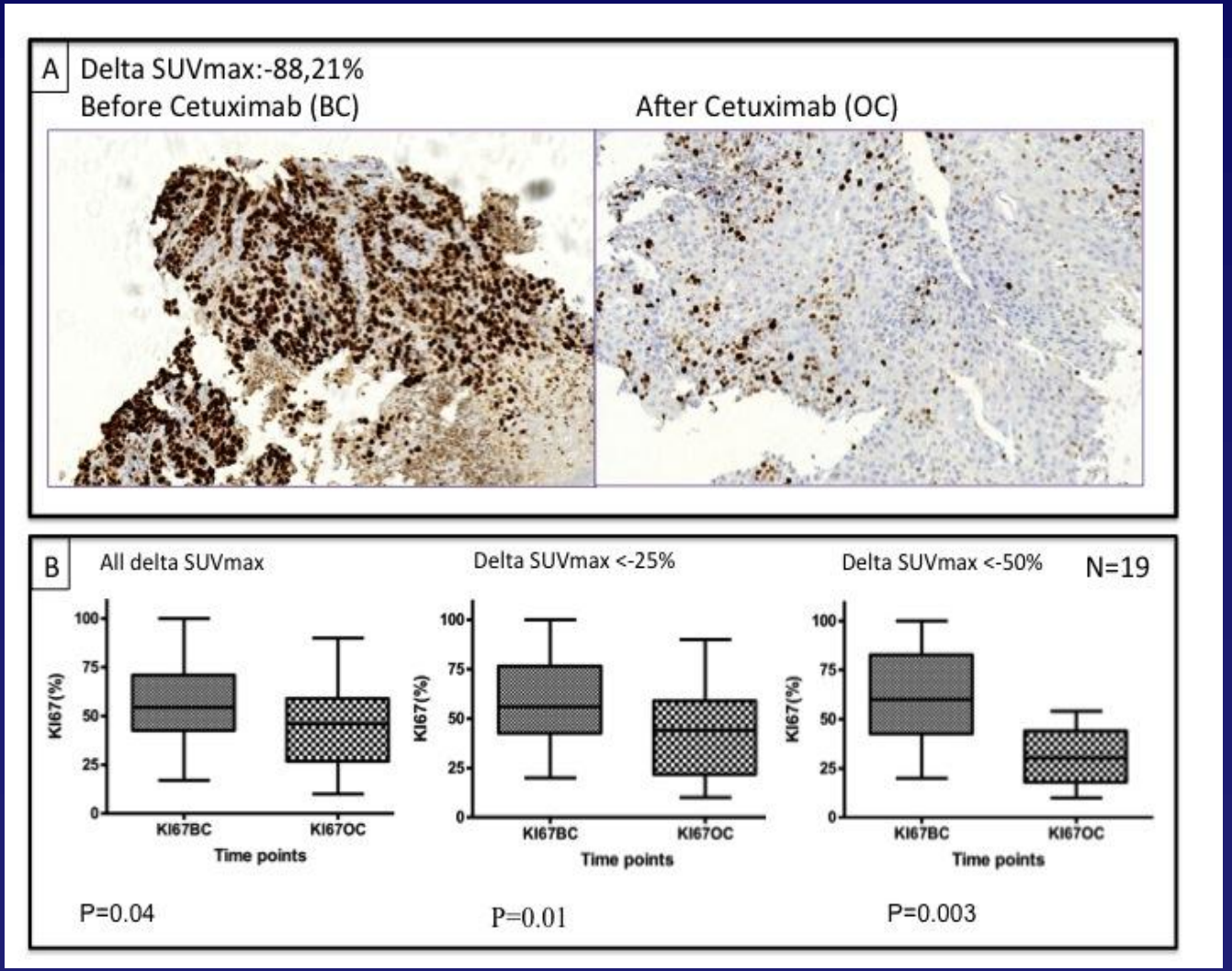
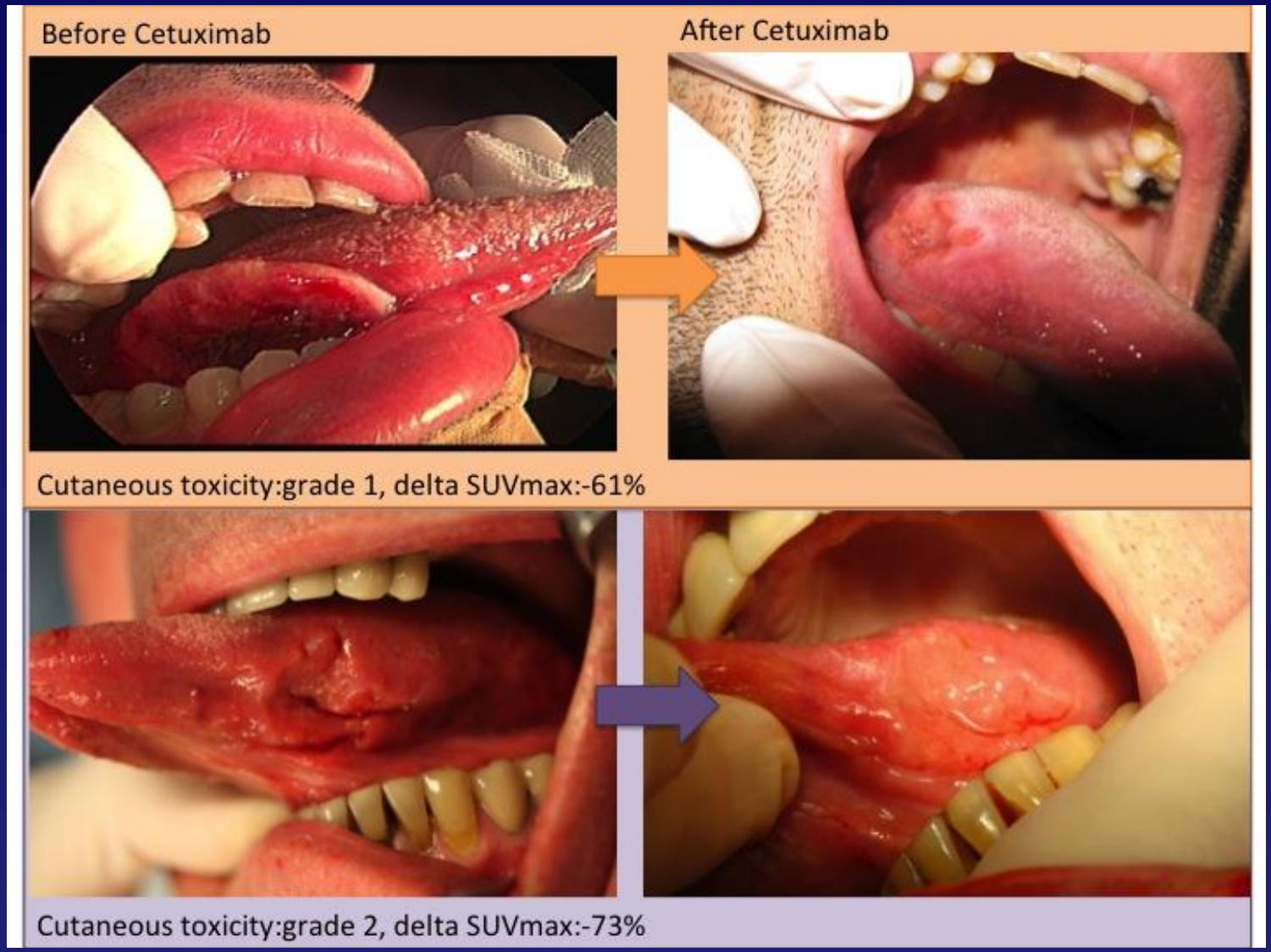


Individual data

Ki67 and 18FDG PET-scan



Clinical modifications

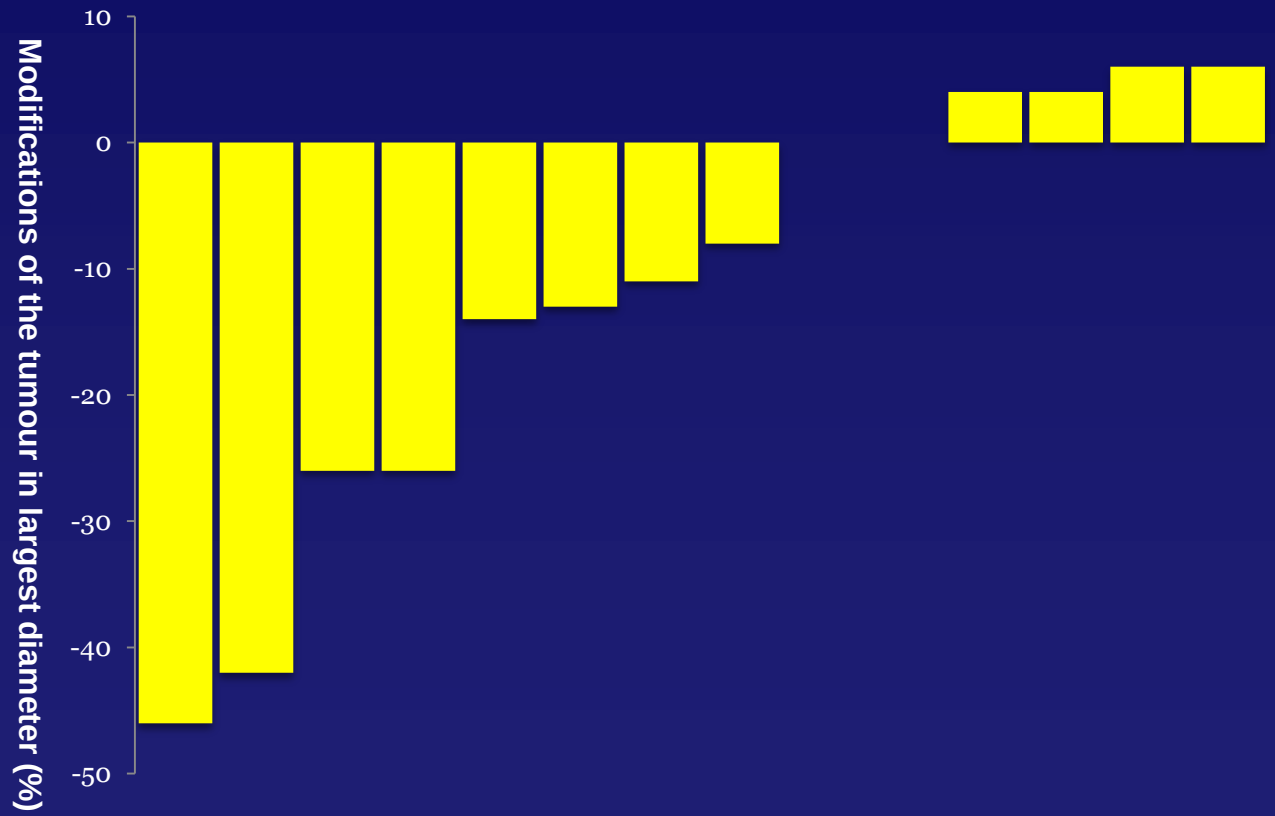


4 out of 32 patients

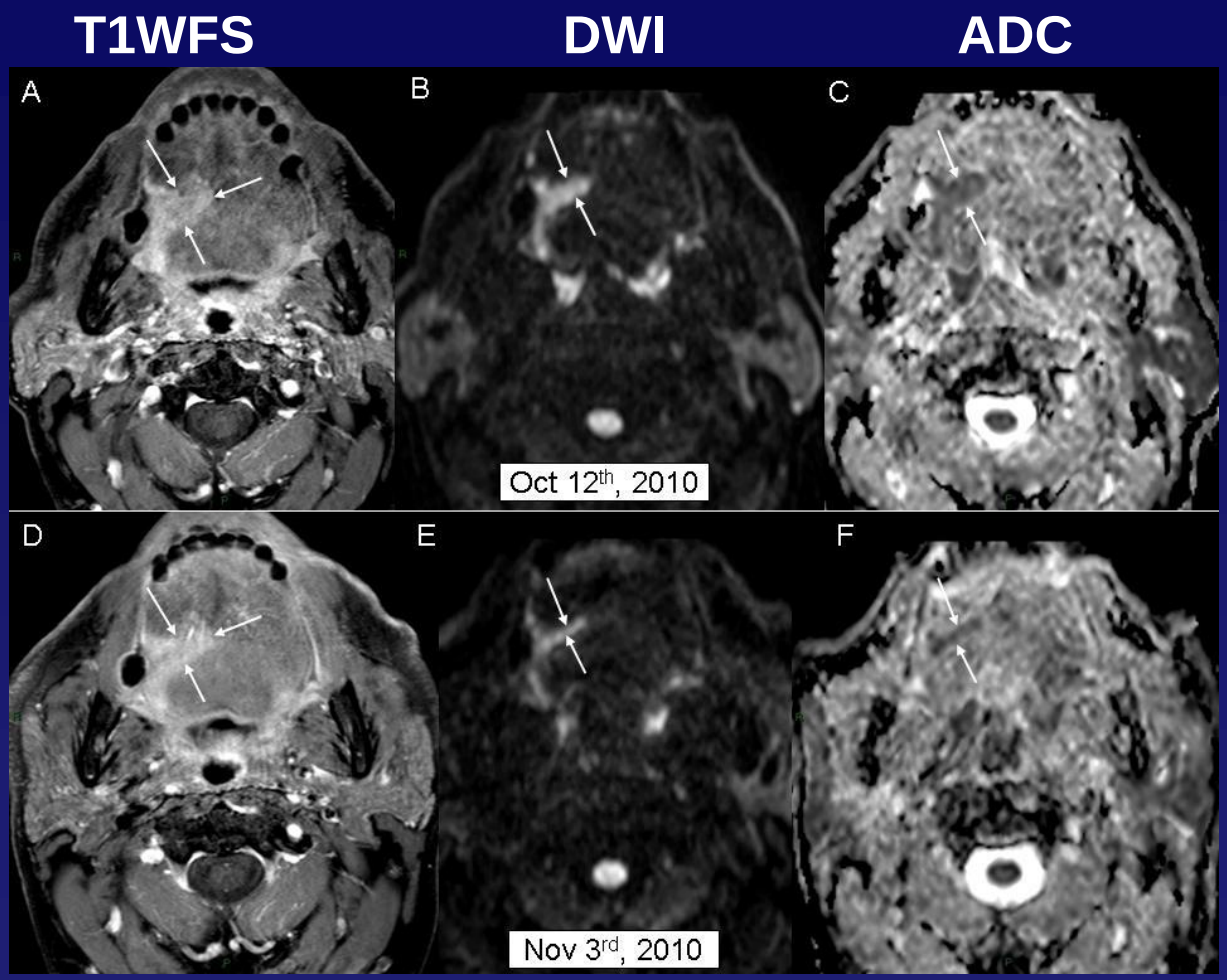
All the patients

CT-scan/MRI modifications

14/20 pts had measurable lesions on imaging



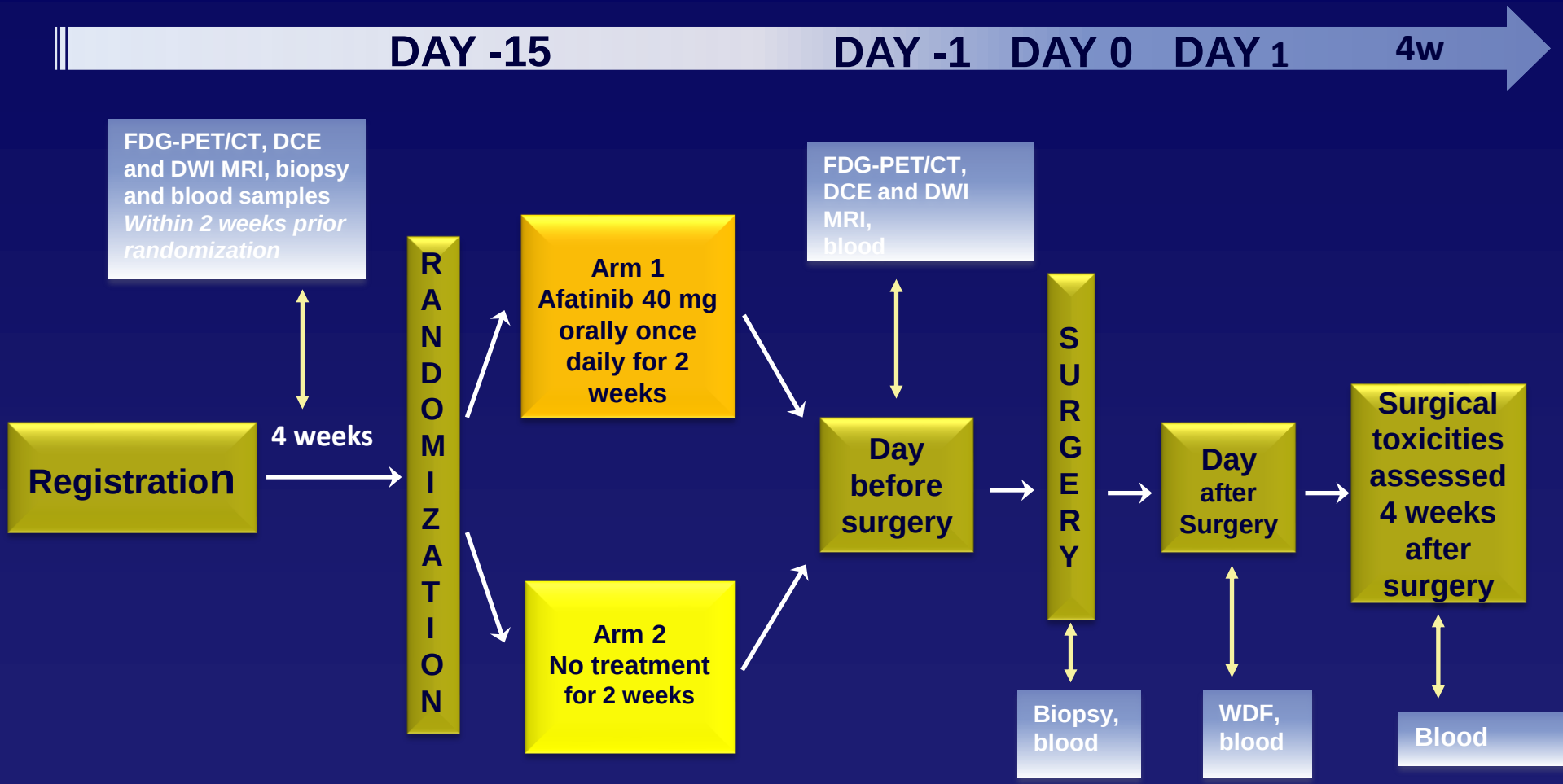
Diffusion-Weighted MRI modifications



Conclusions

- The preoperative setting is attractive to investigate new drugs
- Endpoints for window study should be defined for SCCHN
- Feasible and safe in SCCHN
- Further analyses are performed: pharmacodynamics
  (Schmitz et al. ESMO2012)

EORTC Platform



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