

[¹⁸F]FDG-PET accurately identifies pathological response early upon neoadjuvant immune checkpoint blockade in head and neck squamous cell carcinoma

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Introduction

- Neoadjuvant immune checkpoint blockade (ICB) with anti-PD-1 or anti-PD-1 + anti-CTLA-4 prior to surgery is safe and effective in resectable HNSCC
- Our recently completed IMCISION phase Ib/IIa trial (NCT03003637, under review) shows that none of the HNSCC patients with a major pathological response (MPR, 90-100% tumor regression) upon neoadjuvant nivolumab (anti-PD-1) or nivolumab with ipilimumab (anti-CTLA-4) has developed an HNSCC relapse
- De-escalation or suspension of functionally impairing and mutilating head and neck surgery in patients with a deep response to neoadjuvant ICB may be possible
- Investigating the feasibility of such neoadjuvant ICB-response-driven treatment adaptation in future HNSCC trials requires a reliable biomarker to identify responding patients prior to surgery

Purpose

- To investigate the utility of [¹⁸F]FDG-PET as an imaging biomarker for pathological response (major or partial) early upon ICB (prior to surgery) in patients with HNSCC

Methods

- 32 patients with stage II–IVb HNSCC were treated with neoadjuvant nivolumab (240mg flat dose, weeks 1 and 3) with or without ipilimumab (1mg/kg, week 1 only) before surgery (week 5, **Figure 1**)
- [¹⁸F]FDG-PET/CT scans at baseline (Pre) and shortly before surgery (On, not mandatory for study participation) were analyzed for SUVmax, SUVmean, metabolic tumor volume (MTV), and total lesion glycolysis (TLG)
- Major and partial pathological responses (MPR and PPR) to immunotherapy were defined based on the residual viable tumor in the resected primary tumor specimen ($\leq 10\%$ and 11-50%, respectively)

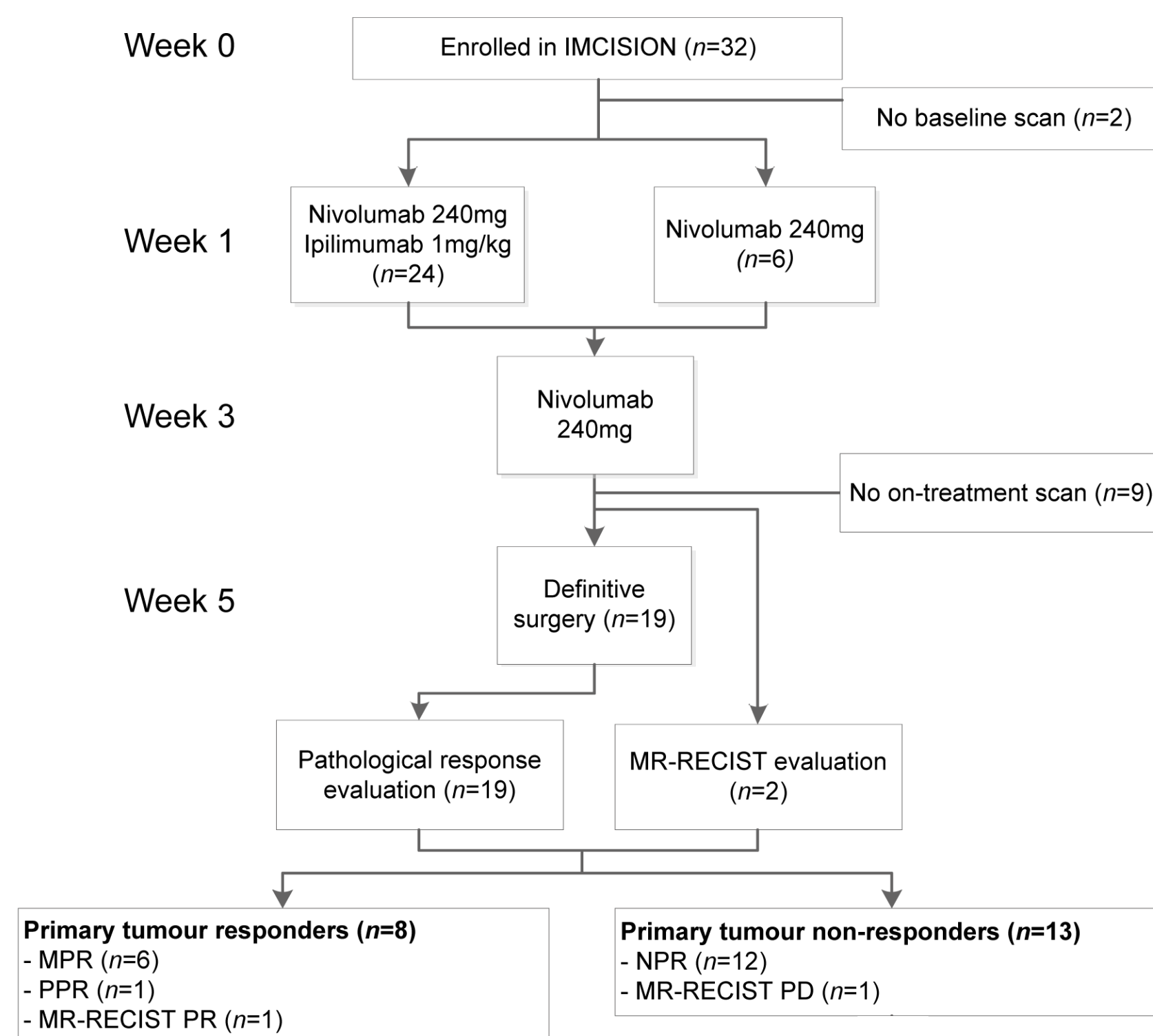


Figure 1: IMCISION treatment timeline, [¹⁸F]FDG-PET/CT availability and response to neoadjuvant ICB.

- Response for the 2 pathologically unevaluable, [¹⁸F]FDG-PET-analyzable patients was determined per MRI-RECIST v.1.1 (**Figure 1**)

Results

- 21 IMCISION patients (**Figure 1**, **Table 1**) were analyzable per [¹⁸F]FDG-PET: 6 had MPR, 1 had PPR, and 12 had no pathological response (NPR). One pathologically unevaluable patient had PR per MRI-RECIST, one had RECIST-progressive disease
- The on-treatment scan was made a median of 3 days (IQR 0) prior to surgery

	Total (n=21)	Responders (n=8)	Non-responders (n=13)
Age, median (range)	66 (22-78)	59 (51-76)	66 (22-78)
Sex, n (%)			
Male	12 (57)	6 (75)	6 (46)
Female	9 (43)	2 (25)	7 (54)
Tumour site, n (%)			
Oral cavity	18 (86)	7 (88)	11 (85)
Oropharynx	3 (14)	1 (13)	2 (15)
Tumour HPV status, n (%)			
Positive	1 (5)	1 (13)	0
Negative	20 (95)	7 (88)	13 (100)
cT-stage, n (%)			
2	3 (14)	3 (38)	0
3	9 (43)	2 (25)	7 (54)
4	9 (43)	3 (38)	6 (46)
cN-stage, n (%)			
0	12 (57)	4 (50)	8 (62)
1	5 (24)	3 (38)	2 (15)
2	4 (19)	1 (13)	3 (23)
Neoadjuvant ICB			
Nivolumab	3 (14)	0	3 (23)
Nivolumab + ipilimumab	18 (86)	8 (100)	10 (77)

Table 1: Baseline characteristics of IMCISION patients evaluable per [¹⁸F]FDG-PET.

- All primary tumor median metabolic parameters decreased in responding patients after neoadjuvant ICB (**Table 2**, **Figures 2–3**), but SUVmax showed pseudo-stable or pseudoprogressive disease (**Figure 4**)
- MTV and TLG were able to identify primary tumor ICB response with 95% accuracy (**Table 3**)
- 14 lymph nodes in 7 patients had an increase in SUVmax (median 2.1) after neoadjuvant ICB, while no tumor was present in the corresponding neck dissection specimen (**Figure 5**)
- Patients with a primary tumor TLG decrease after neoadjuvant ICB did not develop HNSCC relapse (median FU 24 months after surgery), but there was no significant OS benefit (**Figure 6**)

Metabolic parameter	Responders (n=8)	Non-responders (n=13)	P-value
Baseline, median (IQR)			
SUVmax	14.5 (9.6)	14.5 (11.1)	0.8
SUVmean	9.5 (7.2)	9.3 (7.6)	0.3
MTV	1.5 (10.3)	6.2 (7.8)	0.2
TLG	14.3 (74.7)	36.0 (136.3)	0.2
On-treatment, median (IQR)			
SUVmax	9.6 (9.4)	17.8 (15.1)	0.06
SUVmean	7.2 (10.8)	10.1 (7.9)	0.2
MTV	0.6 (1.8)	11.6 (20.8)	< 0.001
TLG	6.1 (19.7)	86.4 (334.4)	< 0.001
%Δ, median (IQR)			
%ΔSUVmax	-33.3 (62.6)	6.9 (36.4)	0.05
%ΔSUVmean	-14.7 (98.6)	3.2 (29.5)	0.002
%ΔMTV	-73.7 (60.0)	84.6 (147.8)	< 0.001
%ΔTLG	-77.3 (53.7)	108.0 (206.0)	< 0.001

Table 2: Median values of primary tumor metabolic parameters at both time points and their %change, per response category.

Metabolic parameter	AUC	Threshold	Sensitivity	Specificity	Accuracy
%ΔSUVmax	0.760	-25%	1	0.63	0.86
%ΔSUVmean	0.901	-8.5%	1	0.71	0.90
%ΔMTV	0.978	-12.5%	0.92	1	0.95
%ΔTLG	0.978	-12.5%	0.92	1	0.95

Table 3: Performance of the %change in primary tumor metabolic parameters as tests for ICB response.

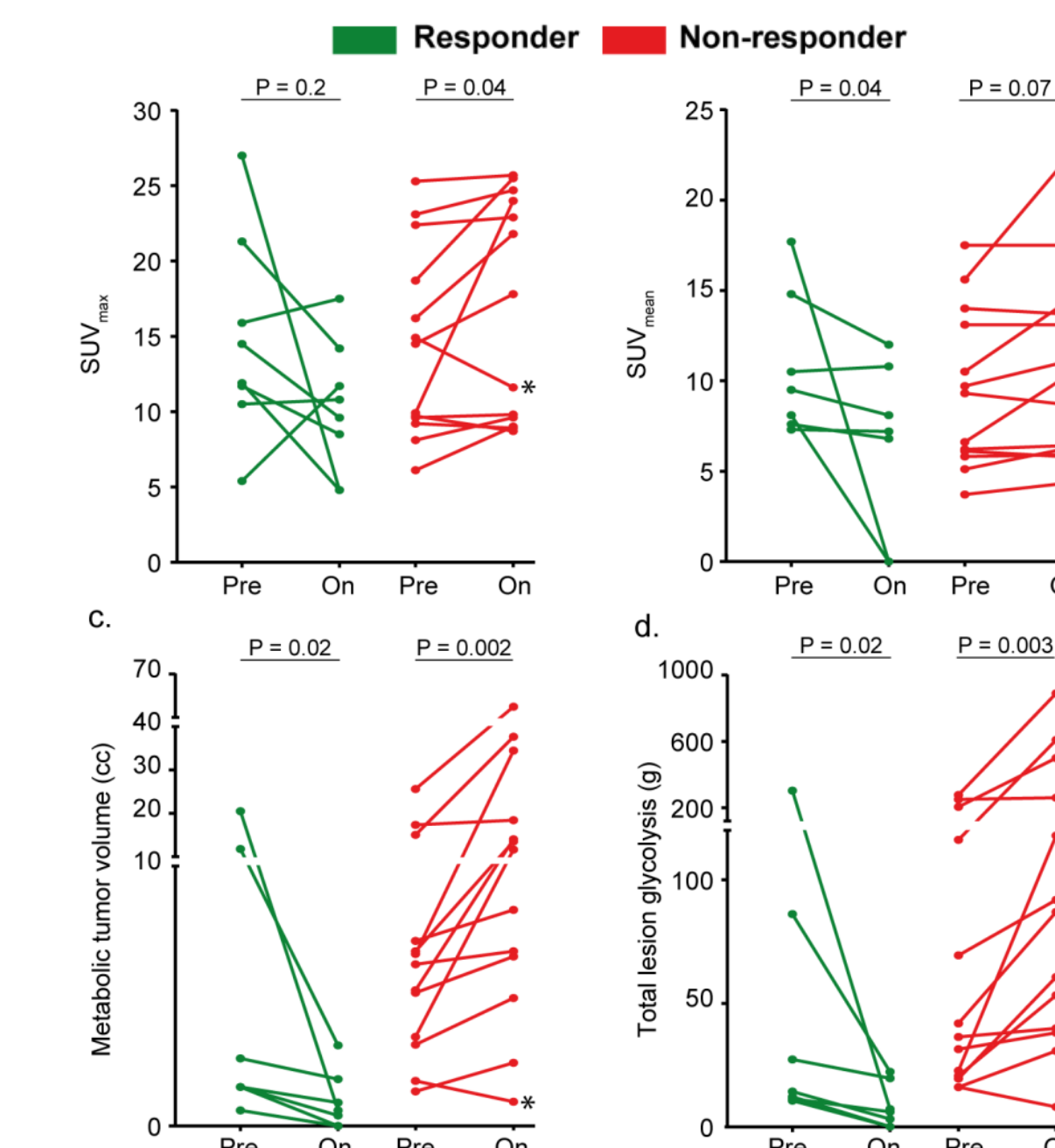


Figure 2: Change in individual primary tumor SUVmax, SUVmean, MTV and TLG from baseline to on-treatment, per ICB response category.

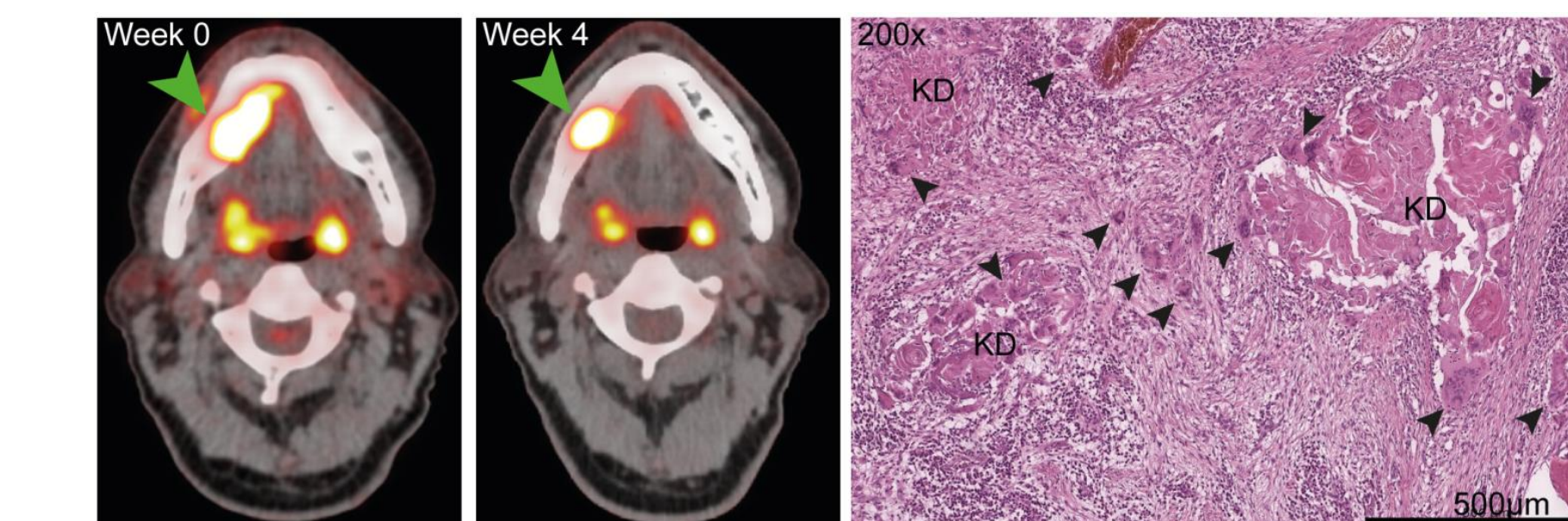


Figure 4: Scans of a patient with a right anterior floor-of-mouth tumor showing an increase in SUV from 15.9 to 17.5 (+10%), but a TLG decrease from 27.3 to 19.7 (-28%). The primary tumor resected specimen showed a PPR with 70% of the tumor bed taken up by keratinous debris (KD) and multinucleated giant cells (arrows).

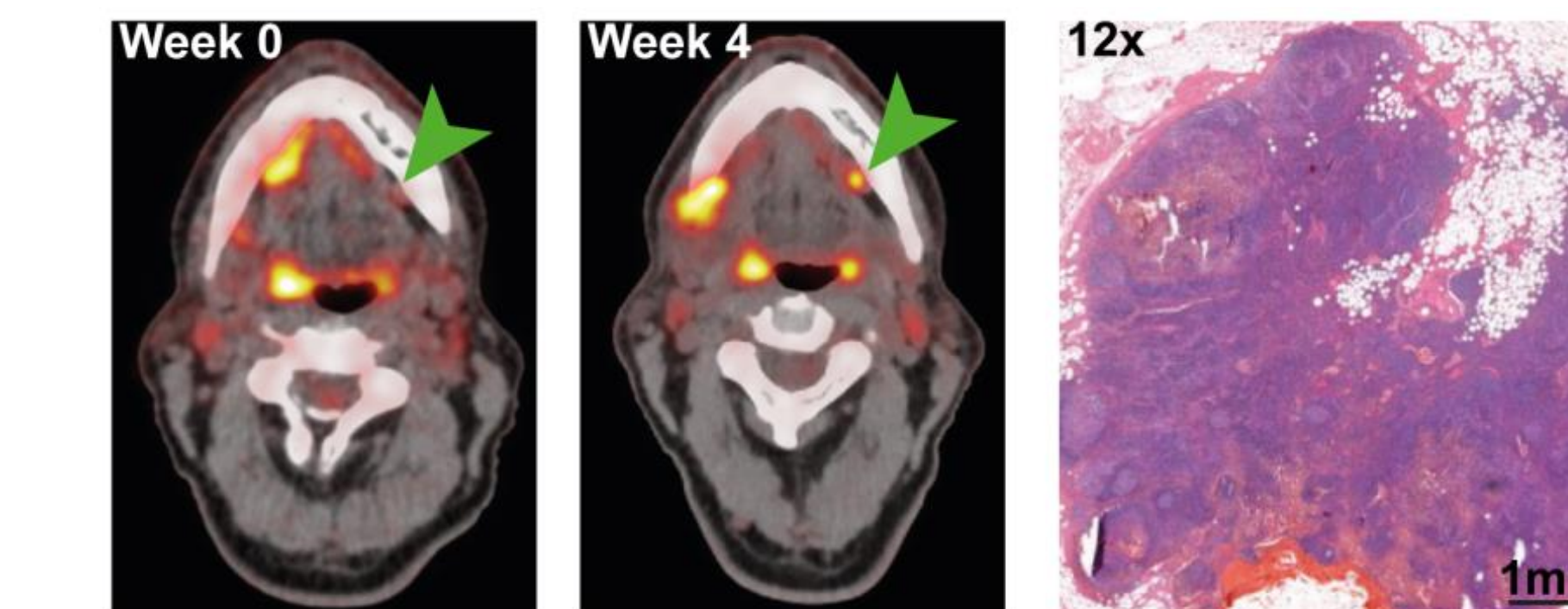


Figure 5: The same patient shown in **Figure 4** had a 1.9 SUVmax increase in a contralateral level 1 lymph node. Pathological assessment (right panel) of the neck dissection revealed no contralateral lymph node metastases.

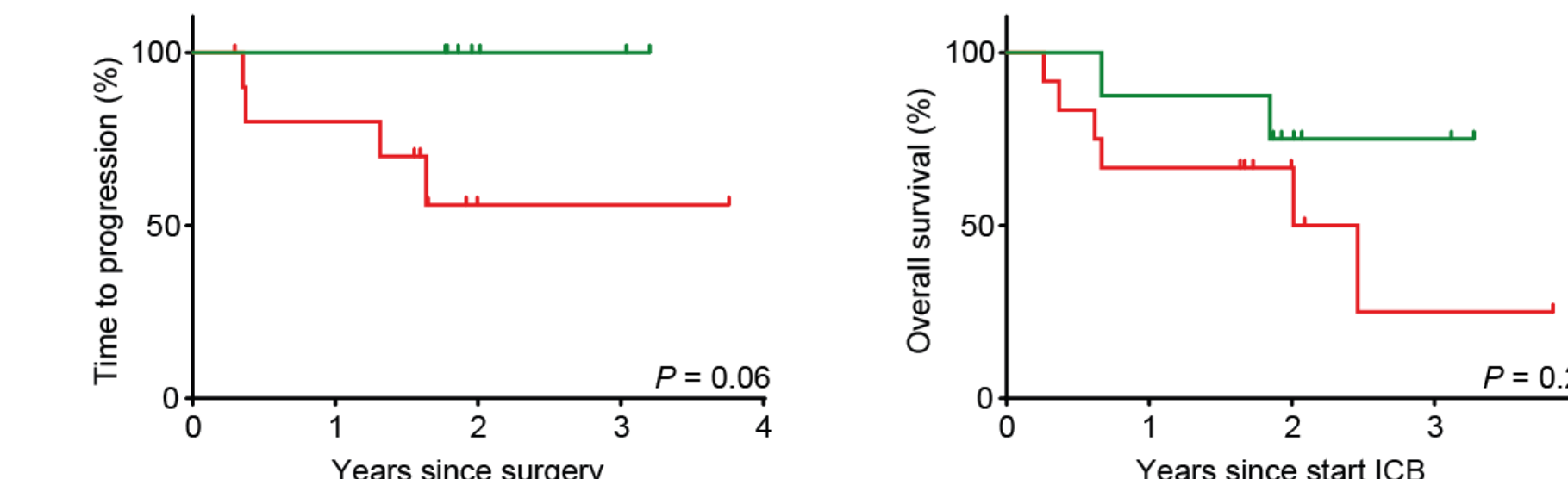


Figure 6: Kaplan-Meier survival estimates for time to progression (left) and overall survival (right). Green line indicates a TLG decrease, red line a stable or increased TLG after neoadjuvant ICB.

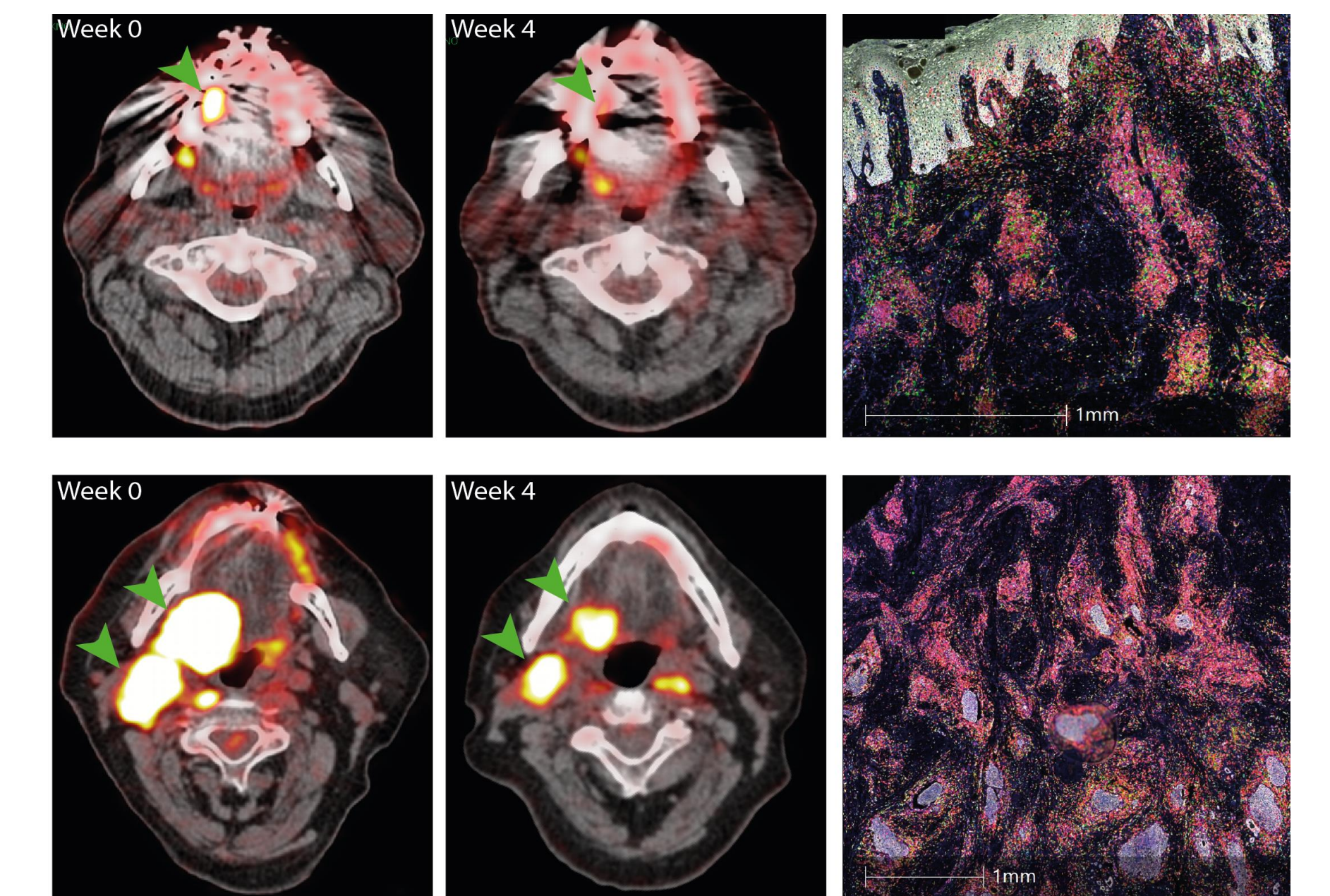


Figure 3: Scans of 2 patients with a profound decrease in [¹⁸F]FDG-avidity after two courses of neoadjuvant ICB (green arrows); multiplex-stained pathology (right panels) revealed both patients had primary tumor MPR.

Conclusions

- Primary tumor response assessment using [¹⁸F]FDG-PET-based TLG and MTV accurately identifies pathological responses early upon neoadjuvant ICB in HNSCC, prior to surgery
- Pseudoprogession / ICB-flare-up at the cervical lymph nodes in the absence of HNSCC metastases is seen in 7 of 21 (33%) patients
- Irrespective of cervical lymph node pseudoprogession, patients with a decrease in TLG are unlikely to develop an HNSCC relapse
- Early on-treatment [¹⁸F]FDG-PET may, upon validation, select HNSCC patients for response-driven treatment adaptation in future trials

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