How new drugs are changing the role of surgery in melanoma

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Disclosures

- Honorarium:
  - Amgen
  - Bristol-Meyers-Squibb
- Travel support:
  - Amgen
  - Bristol-Meyers-Squibb
  - Roche

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Case 1: 24 year old female

- November 2014
- Referred by peripheral dermatologist because of pT4b (Breslow 5.0 mm, ulcerated) melanoma of the right scapular region
- S100 = 0.09 µg/l, LDH = 149 (U/l)
- Planned for re-excision + SN biopsy

Agreed? Other suggestions?

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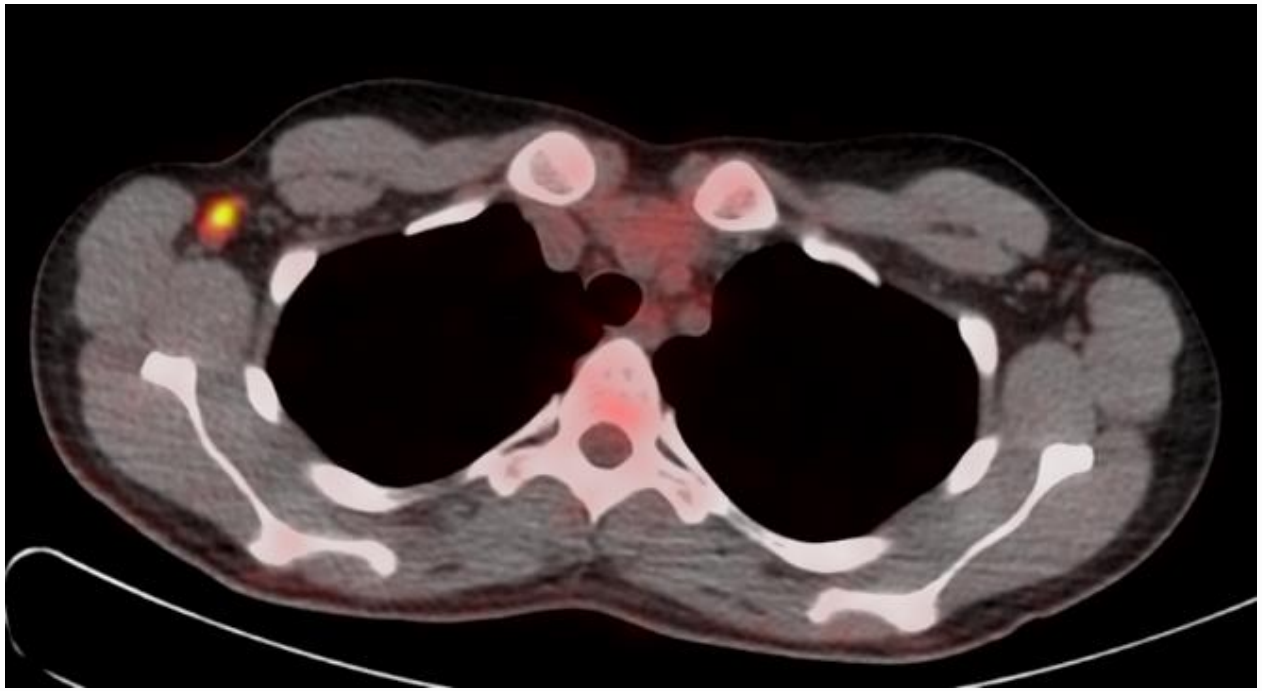
PET-CT on Christmas Eve 2014

- Suspicion of axillary metastasis, no other mets



What would you do?

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Case Continued

- Brain-MRI: no mets
- Cytology +
- Axillary dissection on 15-1-2015

- *Pathology: 21/34 lymph nodes involved, no extracapsular extension, largest 14 mm, top node is negative*

How would you proceed?

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MDT

Extra Information / Considerations:

- BRAF V600E + → Adjuvant therapy (study)?
- Radiotherapy: no survival benefit expected
  - Reduction of regional in field recurrence rate
  - Henderson et al. Lancet Oncol ANZMTG trial
- Repeat imaging in 6 weeks?

Decision for last option

Agreed? Other suggestions?

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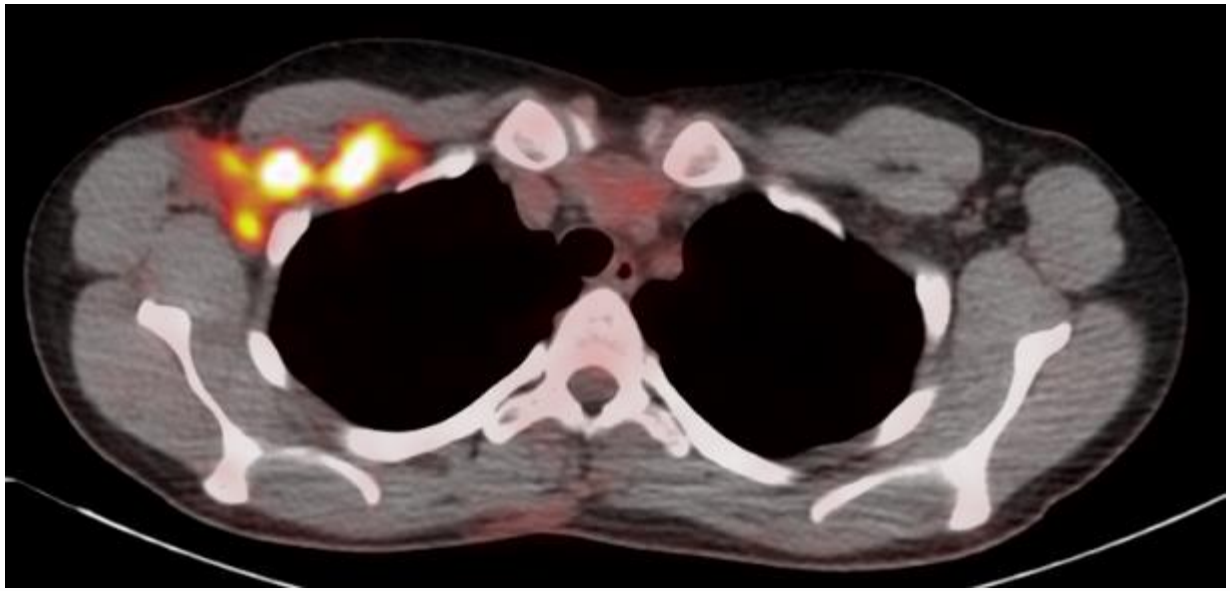
Case Continued

- PET-CT 2-3-2015: no mets
- PET-CT 4-5-2015: suspicion of new mets; axillary and subpectoral/infraclavicular



How would you proceed?

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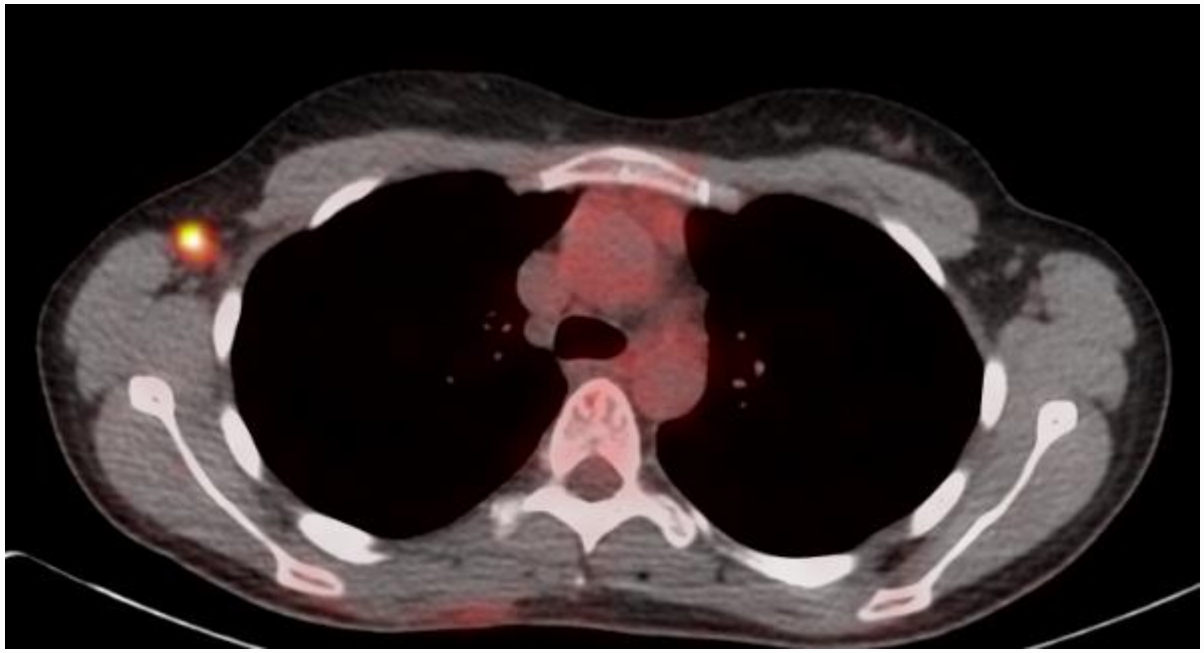

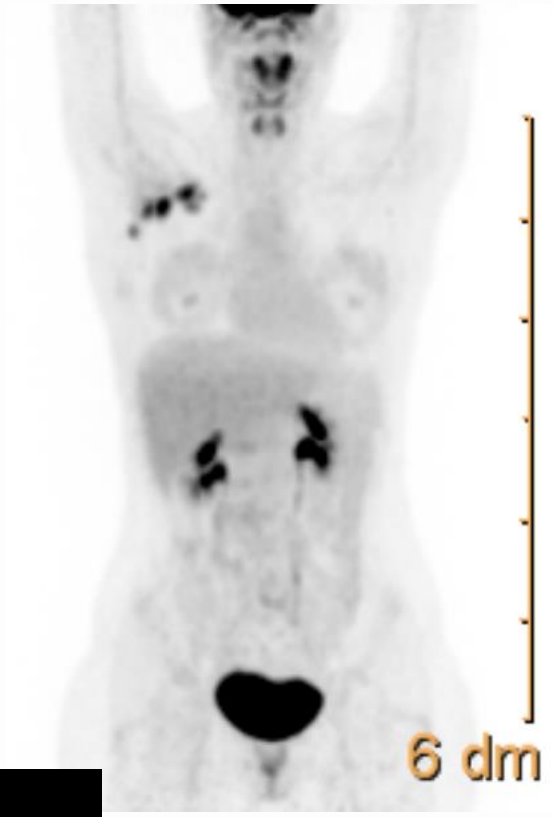

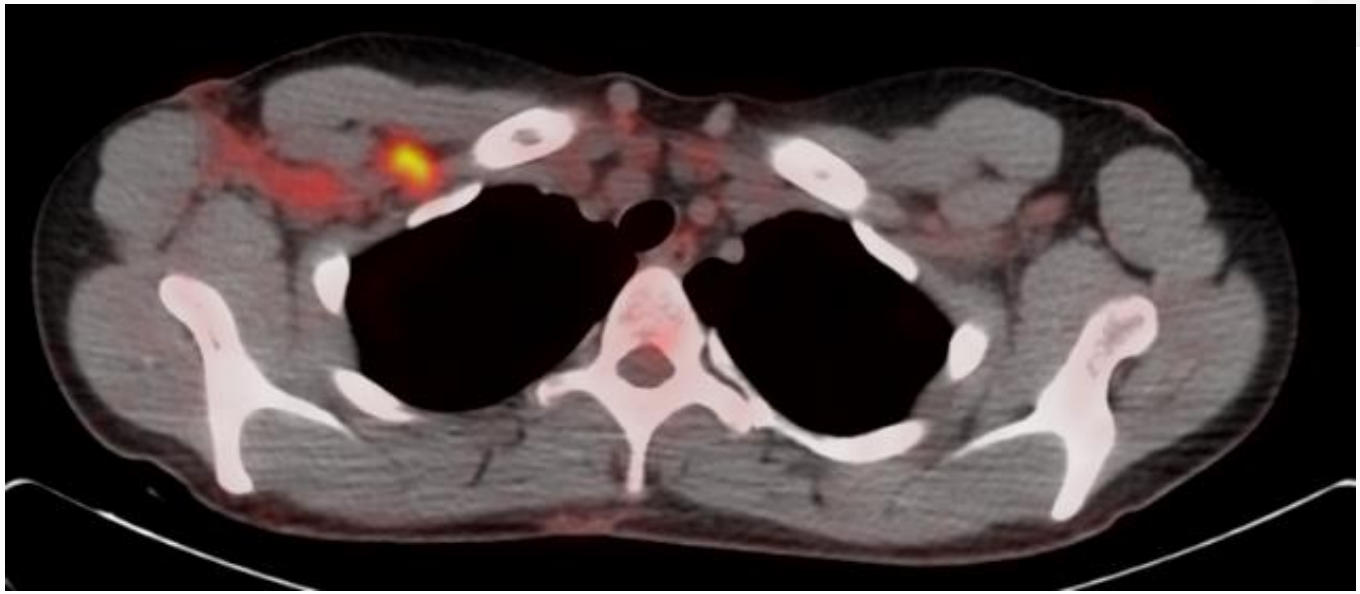

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What to do?

- Upfront Surgery?
- (Palliative) Radiotherapy?
- Systemic Therapy?
  - Immunotherapy?
  - BRAFi/MEKi?
- Neo-adjuvant approach?
- Other ideas?

- **Reductor study**

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Reductor Study

- Irresectable stage III melanoma patients
  - or when R+ resection (R1/R2) risk is high
  - ≤ 3 solitary (resectable) metastases (M+) allowed
- 8 weeks induction BRAFi/MEKi
- Needs to be able to become resectable after induction treatment
- Evaluation with PET-CT after 2 and 8 weeks

Endpoint = % of R0 resections

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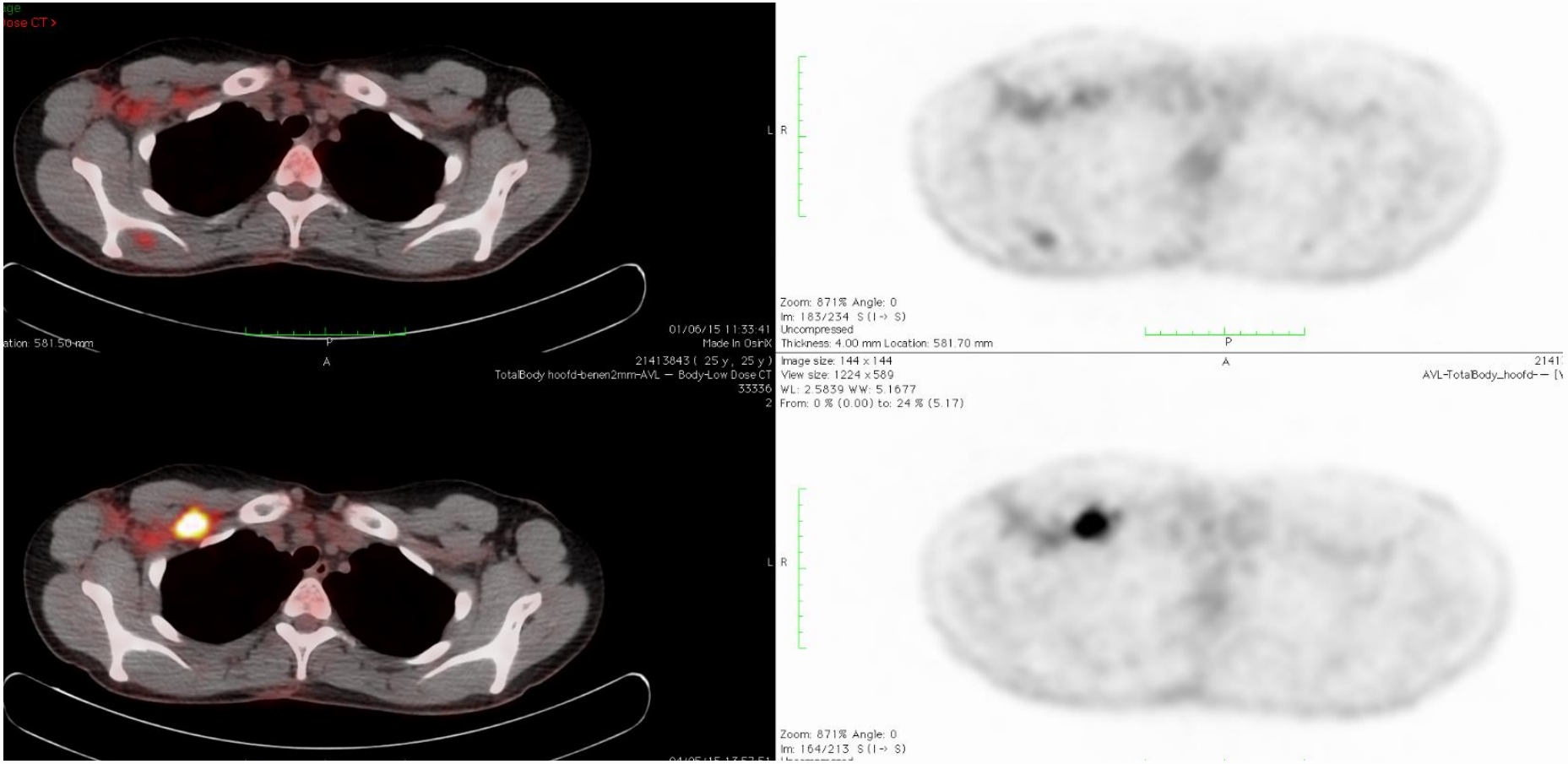
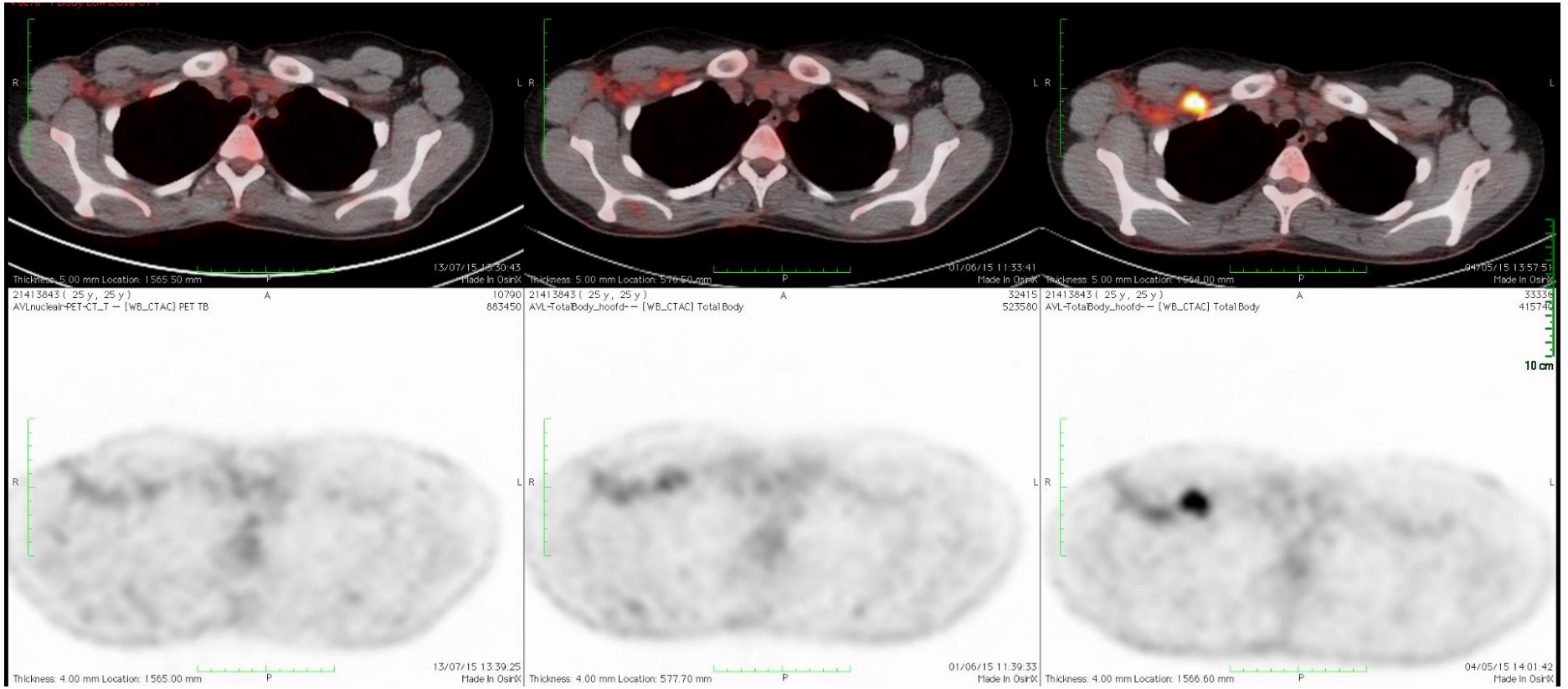
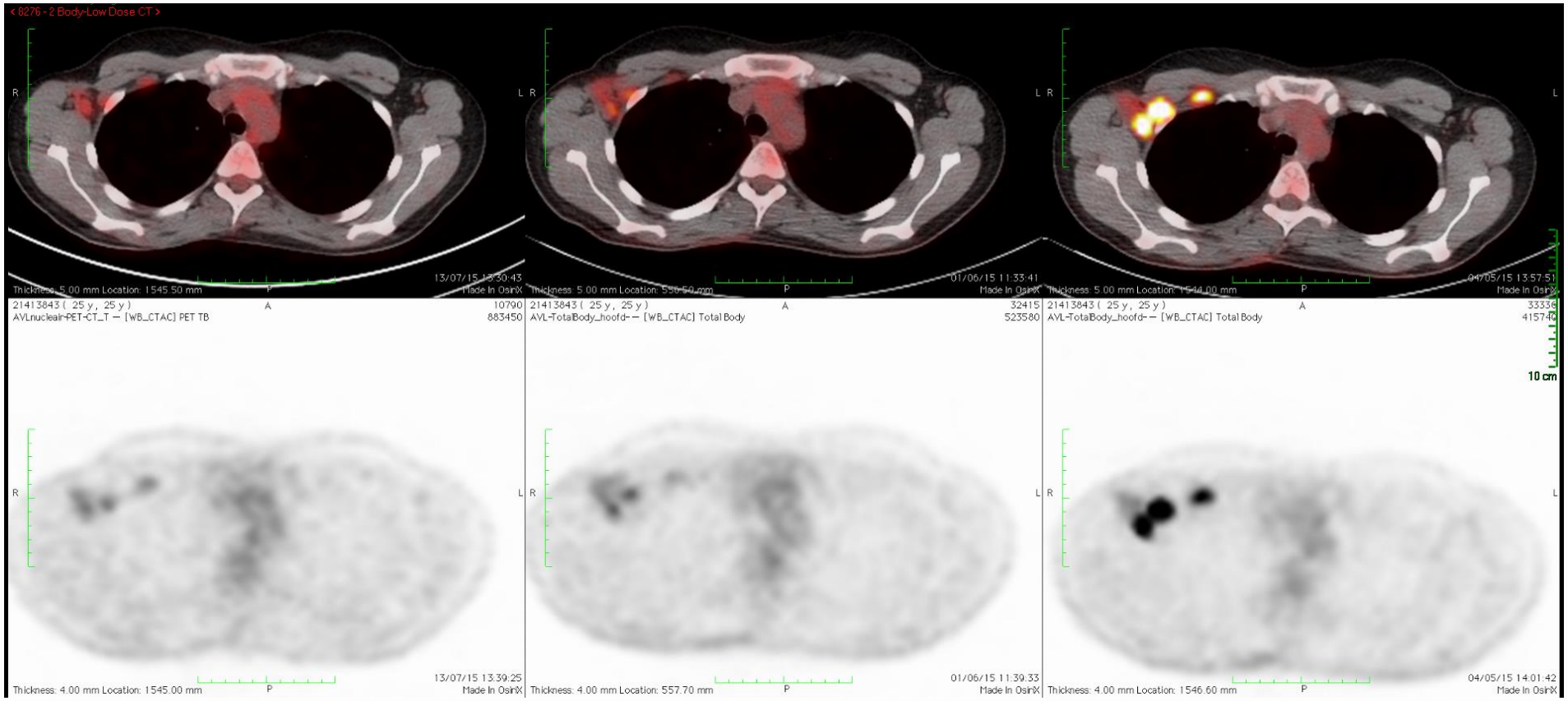
Response Evaluation 2 Weeks



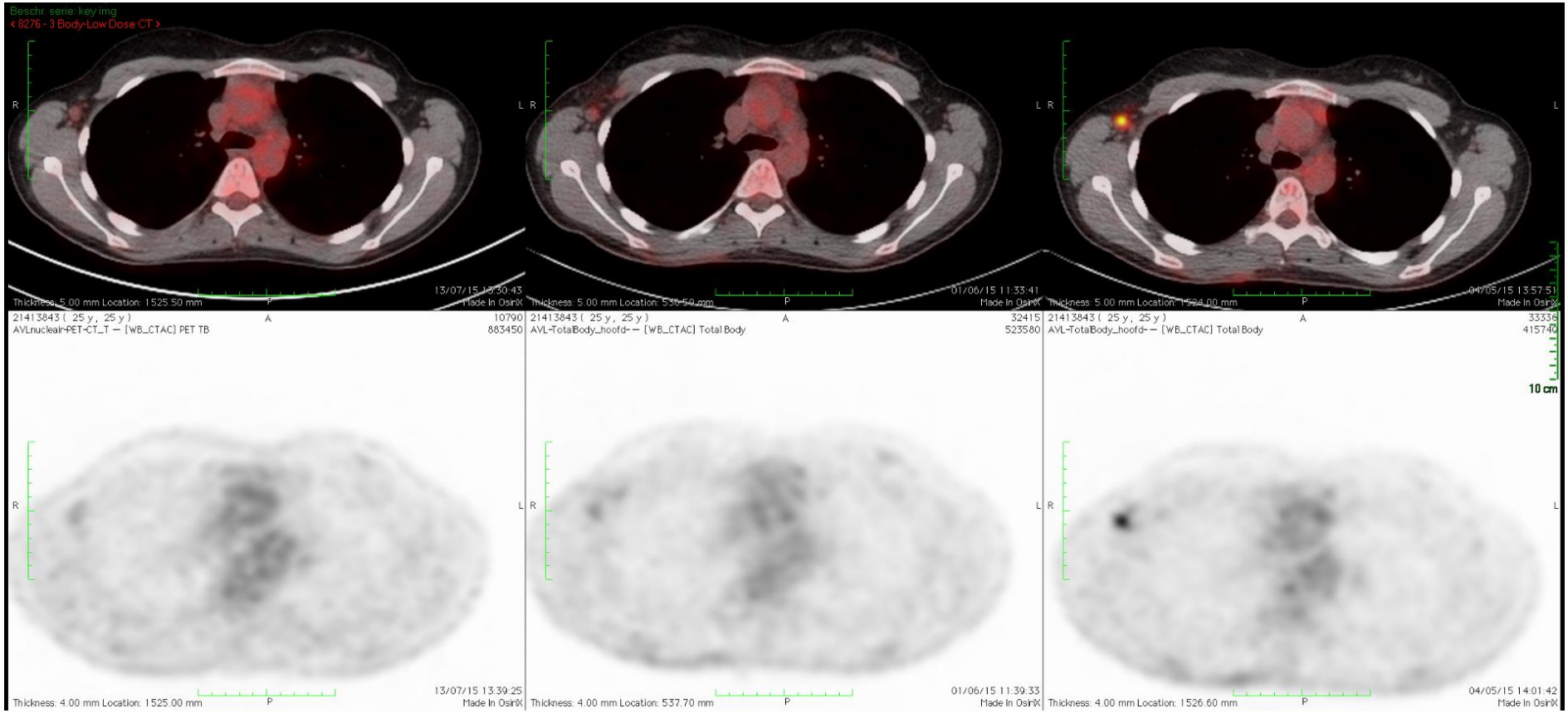
Response Evaluation 8 Weeks



Response Evaluation 8 Weeks



Response Evaluation 8 Weeks



Results

16-7-2015 Resection of axillary and subpectoral / infraclavicular lymph node metastases

Axilla: 5/5 lymph nodes +

Subpectoral/infraclavicular: 9/10 lymph nodes +

R0: free resection margins

How would you proceed?

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Case Summary

11-2014: pT4b Melanoma (Breslow 5mm, ulc+)

01-2015: Axillary dissection (21/34 LN+) BRAFV600E+

05-2015: Recurrence, start Reductor study

07-2015: Resection of axillary and subpectoral / infraclavicular recurrence, R0

09-2015: Radiotherapy 48Gy in 20 fractions

No recurrence or distant metastases yet

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Reductor Study

- 8 patients until this date (powered for 45% R0 resections; <20% = failure, total 26 patients)
- 2 on treatment (just started study)
- 1 PD on PET-CT → Nivo
- 5 Operated → 1 still irresectable (iliac recurrence after previous resection elsewhere)
- 4 Resected (80% R0): 1 CR, 3 PR, 0 Recurrences

- Only 8 / 26 cases in Phase 2 study
- Follow-up not mature yet

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Another Case

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Case 2: 70 year old male

1954 fracture right leg

2008 tibia plateau fracture right leg

2014-04: Acral Melanoma right foot sole (Breslow 1.8 mm, ulcerated) pT2b

2014-05: WLE + FTG + SN → 0.5 mm metastasis, subcapsular and parenchymal location

How to proceed?

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SN Tumor Burden

- Maximal Diameter
  - 1, 2, 3 mm cut-off
  - ≤0.1 mm cut-off (sub-micrometastasis)
- Microanatomic Location
  - –Subcapsular vs. parenchymal
- Infiltrations from capsule (Starz)
- Surface Area in mm^2
- % involved by tumor
- Extracapsular extension

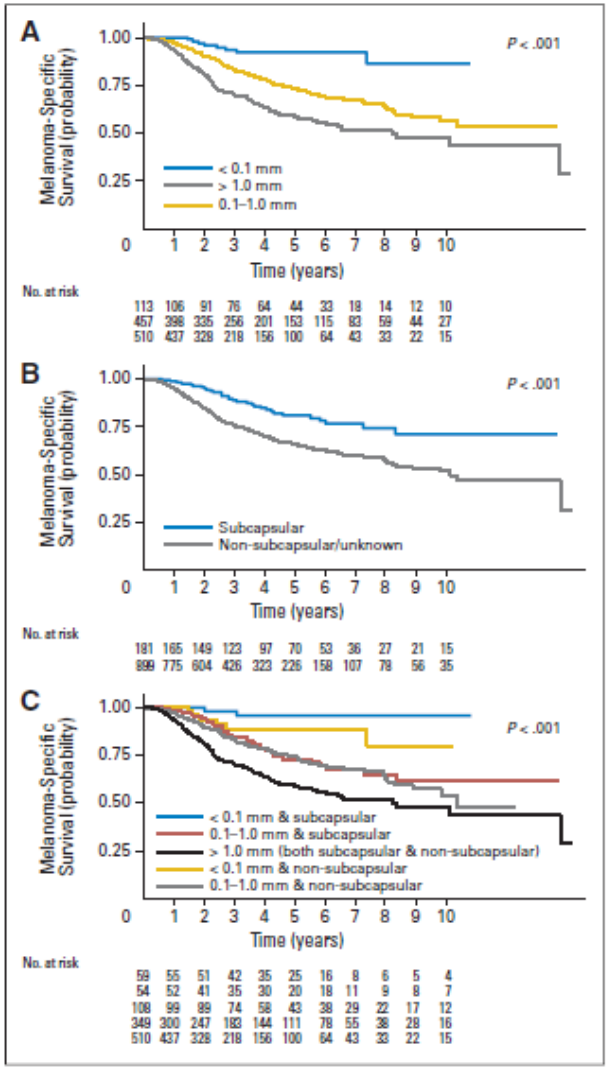

Fig 1. Melanoma-specific survival for sentinel-node tumor burden according to (A) Rotterdam criteria, (B) subcapsular location, and (C) Rotterdam-Dewar Combination criteria.

van der Ploeg et al. JCO 2011

Back-to-case: Ultrasound

2014-05: WLE + FTG + SN → 0.5 mm metastasis, subcapsular and parenchymal location → discuss CLND

- 10-20% risk of additional mets
- 5-year survival 70-80%
- MSLT-2 pending

Patient declines CLND →

Follow-up with ultrasound and S100B

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August 2015

After 15 months of NED during FU

Ultrasound: suspicious node → FNAC +

S100B = 0.06 µg/l, LDH = 160 (U/l)

PET-CT & MRI Brain → no visceral metastases

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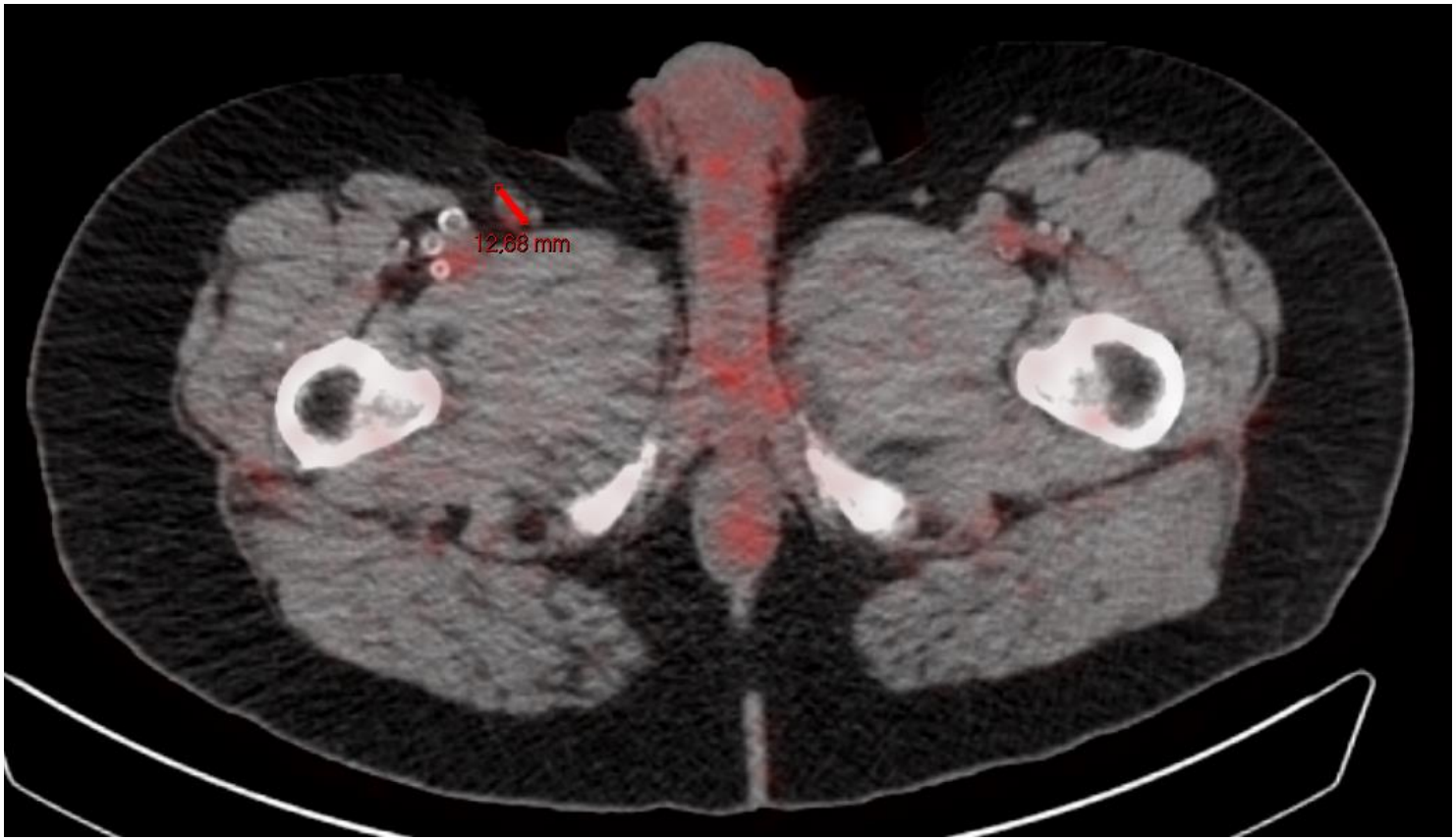

Planned for lymph node dissection

Agreed? Other suggestions?

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OPACIN Study

Study to Identify the Optimal Adjuvant Combination Scheme of Ipilimumab and Nivolumab in Melanoma Patients (OpACIN) (NCT02437279)

- Neo-adjuvant IPI + NIVO vs. Adjuvant IPI + NIVO
- Stage IIIB Resectable Melanoma to Groin / Axilla
- No previous systemic therapy
- No radiotherapy (pre or post surgery)

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OPACIN Study

Primary Endpoints

- The alteration in magnitude of the neo-antigen specific T cell response in the time interval pre- to post-adjuvant therapy in peripheral blood
- Safety & Feasibility

Secondary Endpoint

- RFS

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Flow-chart

Figure 1

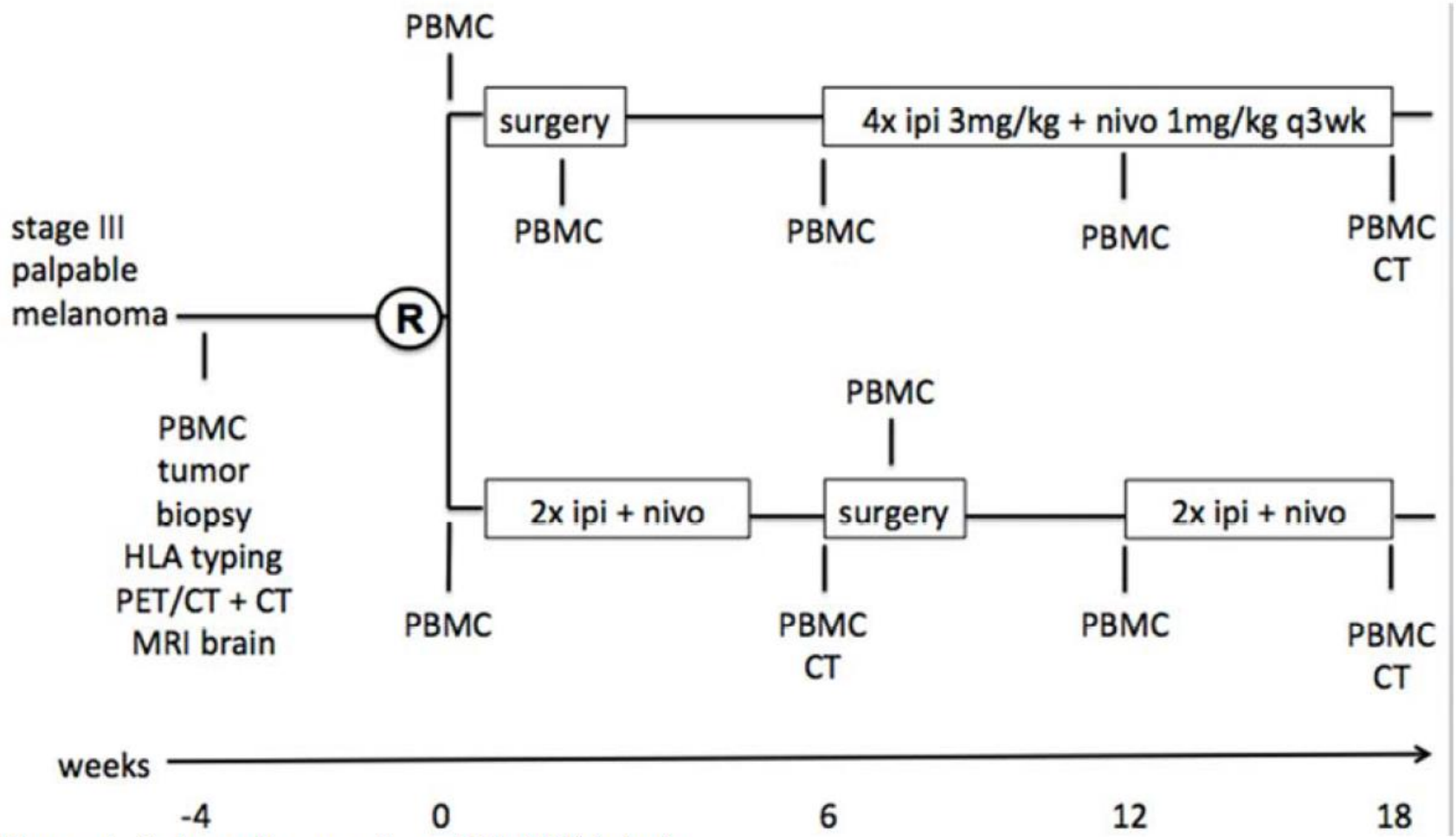

Figure 1: Schematic overview of OpACIN study.

Case Continued

- Participated in OPACIN study
- Developed diarrhea after 2nd course
  - High dose prednisolone & infliximab
- Surgery 2 weeks after 2nd course (no delay)

Results:

Inguinal dissection: 1/6 lymph nodes+

Metastasis diameter 0.5 mm!

(Initially 1.2 cm !!)

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OPACIN Study

- 10 patients screened
- 2 screening failures (1 x low grade astrocytoma, 1 x bone met)
- 6 randomized, 2 waiting for randomization
- 2 neo-adjuvant & operated
- 2 neo-adjuvant & operation planned Dec/Jan
- 2 adjuvant

- 20 patients required

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Neo-Adjuvant Studies

- **EORTC 18081** = Adjuvant PEG-IFN vs. OBS in pT2-4bN0
- **EORTC 18071** = Adjuvant Ipilimumab in stage III disease after lymph node dissection (N1a > 1 mm or palpable)
- **EORTC 1208 (Minitub)** = Prospective registry of SN minimal tumor burden patients.
- **EORTC 1325** = Adjuvant Pembrolizumab in stage III disease after lymph node dissection (N1a > 1 mm or palpable)
- **Reductor** = neo-adjuvant BRAFi & MEKi combination for irresectable stage IIIB disease (or potential R1)
- **OpACIN =** neo-adj vs. adj combination Ipilumumab + Nivolumab in palpable stage IIIB axilla/groin
- *ILP + Ipi/Nivo or Pembro Combination?*
- *TVEC + Pembro*

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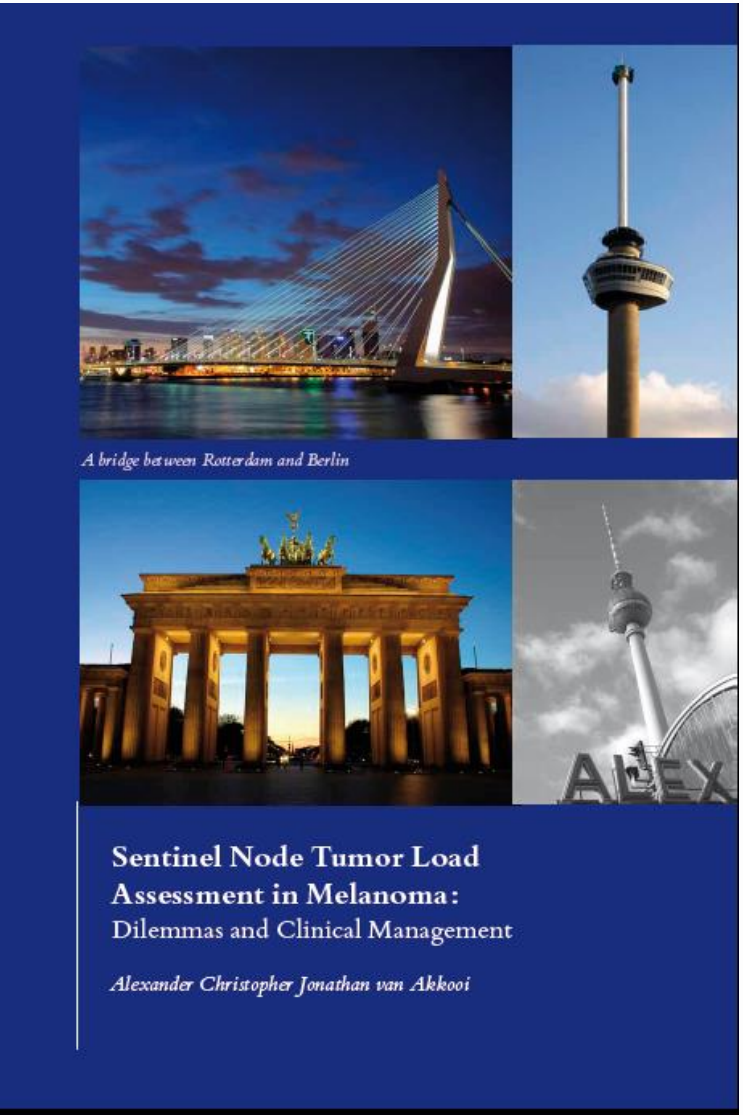
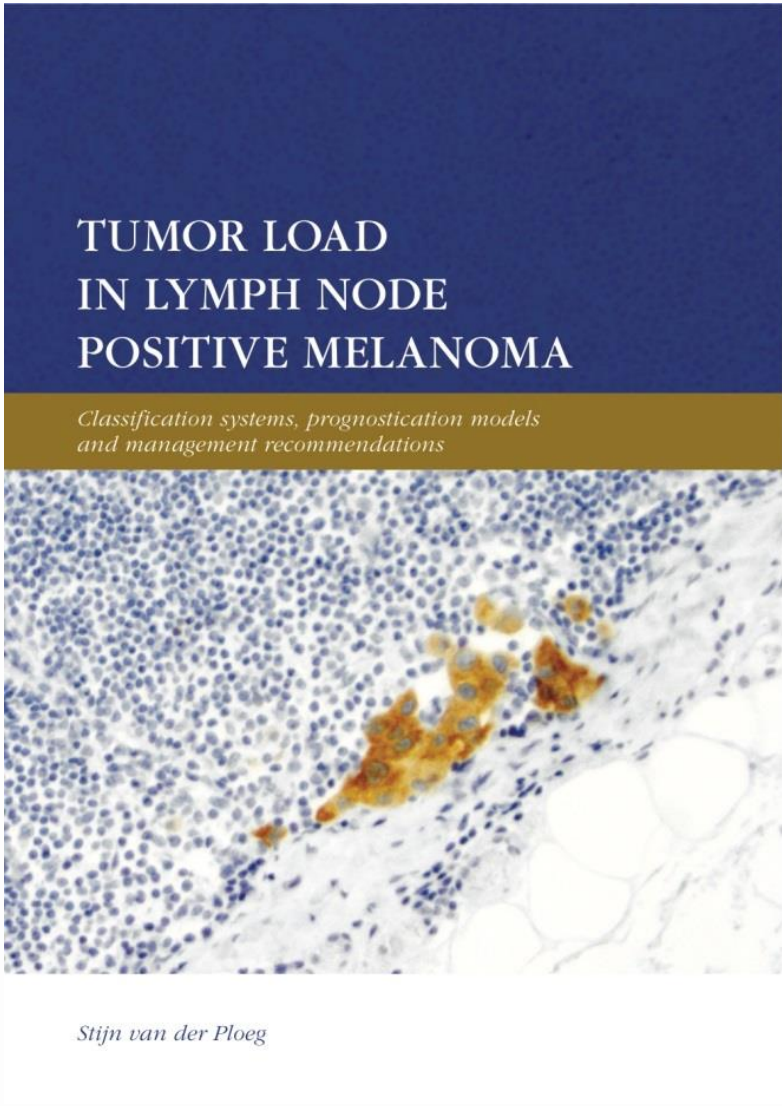
Questions?


A bridge between Rotterdam and Berlin
Sentinel Node Tumor Load
Assessment in Melanoma:
Dilemmas and Clinical Management
Alexander Christopher Jonathan van Akkooi


TUMOR LOAD
IN LYMPH NODE
POSITIVE MELANOMA
Classification systems, prognostication models
and management recommendations
Stijn van der Ploeg