ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

Workshop

Treatment management: measuring response

Kyoto, floor 2

Johan Vansteenkiste, *Univ. Hospital KU Leuven*

Moderated by

Stefan Rauh, *Centre Hospitalier Emile Mayrisch, Luxemburg*

Mercury number IOBE18NP04371-02
Date of preparation: December 2018

IMMUNOTHERAPY IS PRACTICE-CHANGING : MULTIDISCIPLINARY MEDICAL CHALLENGES IN CANCER PATIENT MANAGEMENT

Treatment management: Measuring response

Johan Vansteenkiste

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Job code: IOBE18NP04371-02
Date of preparation: December 2018

Disclosures [updated 12/2018, alphabetical order]

- **Research funding at University Hospitals KU Leuven**
  - **MSD**
- **Advisory functions**
  - **AstraZeneca, Boehringer Ingelheim, MSD, Novartis, Roche, Sanofi**
- **Lectures**
  - **AstraZeneca, BMS, Boehringer-ingelheim, MSD, Roche**
- **Others**
  - **None**

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Stage IV NSCLC therapy
> duration of treatment

- **What to do when it goes wrong ?**

Chemotherapy	Targeted therapy	Immunotherapy

- **What to do when it goes well ?**

Chemotherapy	Targeted therapy	Immunotherapy

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Stage IV NSCLC therapy
> duration of treatment

- **What to do when it goes wrong ?**

Chemotherapy	Targeted therapy	Immunotherapy
PD ≈ stop	PD • Slow PD ≈ continue • Oligo PD ≈ local R/ • Major PD ≈ stop	PD • Pseudo PD • Real PD • Hyper PD

- **What to do when it goes well ?**

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Immunotherapy response evaluation

- New needs for response evaluation in the IO era
- Response evaluation systems for the IO era
  - irRC
  - imRECIST
  - iRECIST
- Conclusion

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Response evaluation

> standard criteria (chemotherapy era)

WHO	RECIST
2D measurement	1D measurement
Imaging type not stipulated	Imaging type stipulated
Target lesions not well defined	Defines target lesions
Number of lesions not specified	Number of lesions specified
PR >50% decrease	PR > 30% decrease
PD > 25% increase	PD > 20% increase

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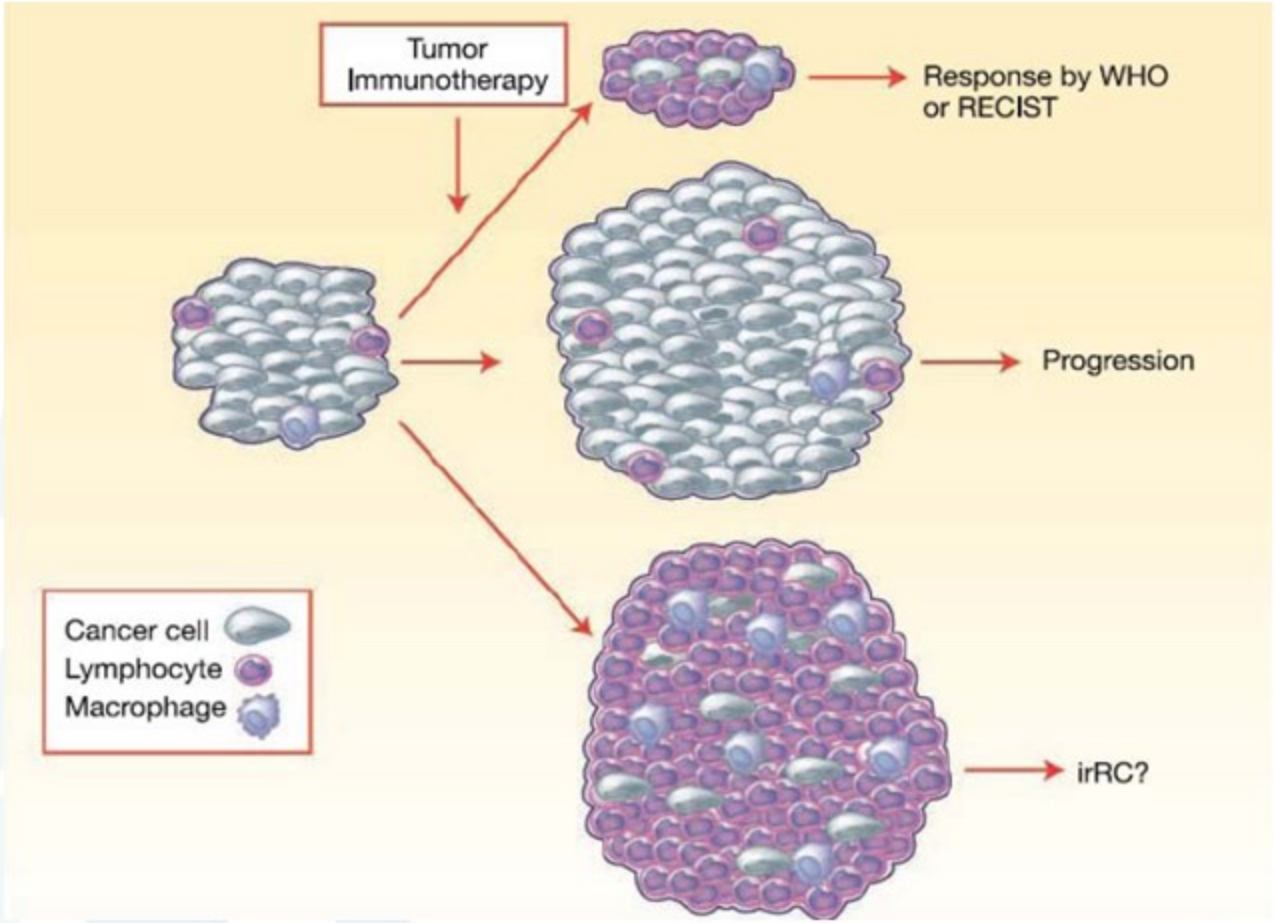
Immunotherapy response evaluation

> pseudoprogression *vs.* true progression



Avoid continuation of non-effective therapy and delay of salvage therapy

Avoid stop of effective therapy based on "pseudo-progression"

Ribas et al, Clin Cancer Res 15:7116-7118, 2009

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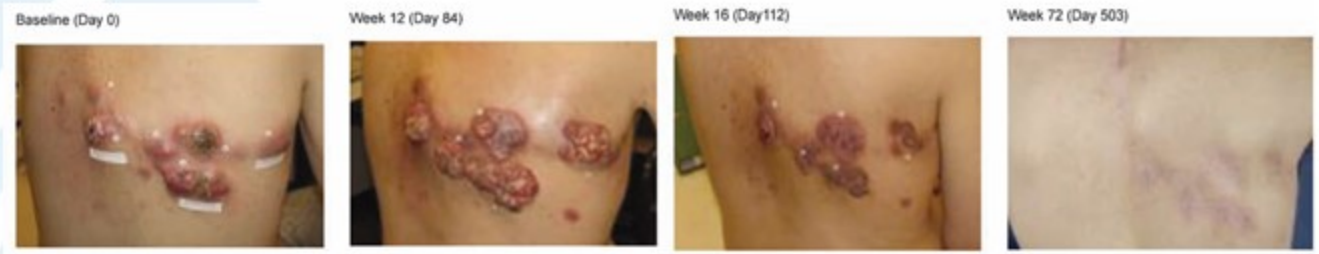
Immunotherapy response evaluation
> delayed responses

- **Cancer Immunotherapy may require significant lag-time before translating into a clinically detectable benefit**
  - **Activation and proliferation of tumor-reactive immune cells needed**
- **Once established, immune response leads to inflammation of tumor, which may appear clinically as false progression**
- **Tumor-progression endpoints based on RECIST criteria have been recognized as invalid surrogates of clinical benefit of several immunotherapeutics**



Ipilimumab in melanoma

Hoos et al, J Natl Cancer Inst 102:1388-1397, 2010
Kantoff et al, N Engl J Med 363:411-422, 2010

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Immunotherapy response evaluation
> pseudoprogression in NSCLC

- Rare in NSCLC (<5%)
  - In contrast, true PD is frequent (e.g. KN024 study: 1/3 of pts had PFS <3 months)
- In contrast with the CT-scan, patients with pseudo PD are doing well
  - No decline in PS
  - No increase in tumor-related symptoms (pain, dyspnea, …)
  - No need for intensified therapy for disease-related symptoms
- Next scan should be after a brief delay
  - Don't wait for "delayed responses" in NSCLC (e.g. KN024 study: median time to response 2.2 months)
- Importance of clinical judgement
  - If patient is not doing well, switch to another treatment

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Immunotherapy response evaluation

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Immunotherapy response evaluation

> irRC [WHO based]

- **New paradigm in treatment**
  - Release the brakes of the immune system to fight the tumor
- **Novel responses to therapy**
  - Responses may be delayed
  - New lesions may not represent progressive disease
  - Stable persistent lesions may represent a satisfactory endpoint
- **Based on 487 advanced melanoma patients treated with ipilimumab:**

Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,[1] Axel Hoos,[2] Steven O'Day,[3] Jeffrey S. Weber,[4] Omid Hamid,[3] Celeste Lebbé,[5] Michele Maio,[6] Michael Binder,[7] Oliver Bohnsack,[8] Geoffrey Nichol,[9] Rachel Humphrey,[2] and F. Stephen Hodi[10]

Wolchok et al, Clin Canc Res 15:7412, 2009

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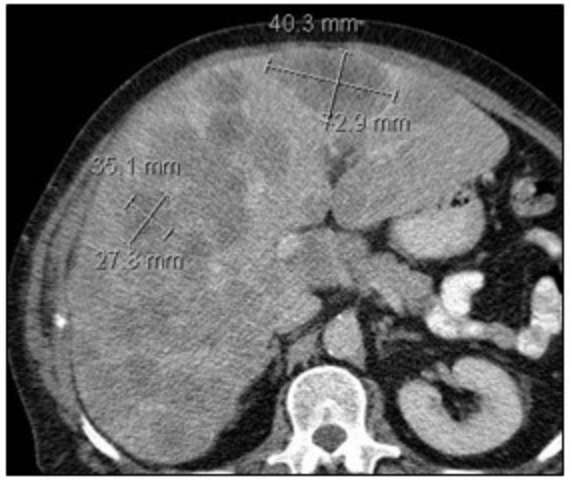
Immunotherapy response evaluation

> irRC principles

- **Back to 2D WHO measurements**
  - **Product of perpendicular diameters**
- **New target lesions (≥5x5 mm)**
  - **Up to 10 visceral (max. 5 per organ)**
  - **And up to 5 new cutaneous lesions**



- **Calculations**
  - **Tumor value = sum of the products of diameters (SPD)**
  - **Appearance of new lesions added to total tumor burden (*tumor burden = SPD index lesions + SPD new lesions*)**

Wolchok et al, Clin Canc Res 15:7412, 2009

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Immunotherapy response evaluation

> irRC: response criteria

- **irCR: complete response, confirmed with repeat imaging at 4 weeks**
- **irPR: >50% decrease in tumor burden from baseline**
- **irPD: increase in tumor burden >25% relative to nadir, confirmed by repeat imaging at 4 weeks**
- **irSD: does not meet criteria for irCR, irPR, or irPD**

Wolchok et al, Clin Canc Res 15:7412, 2009

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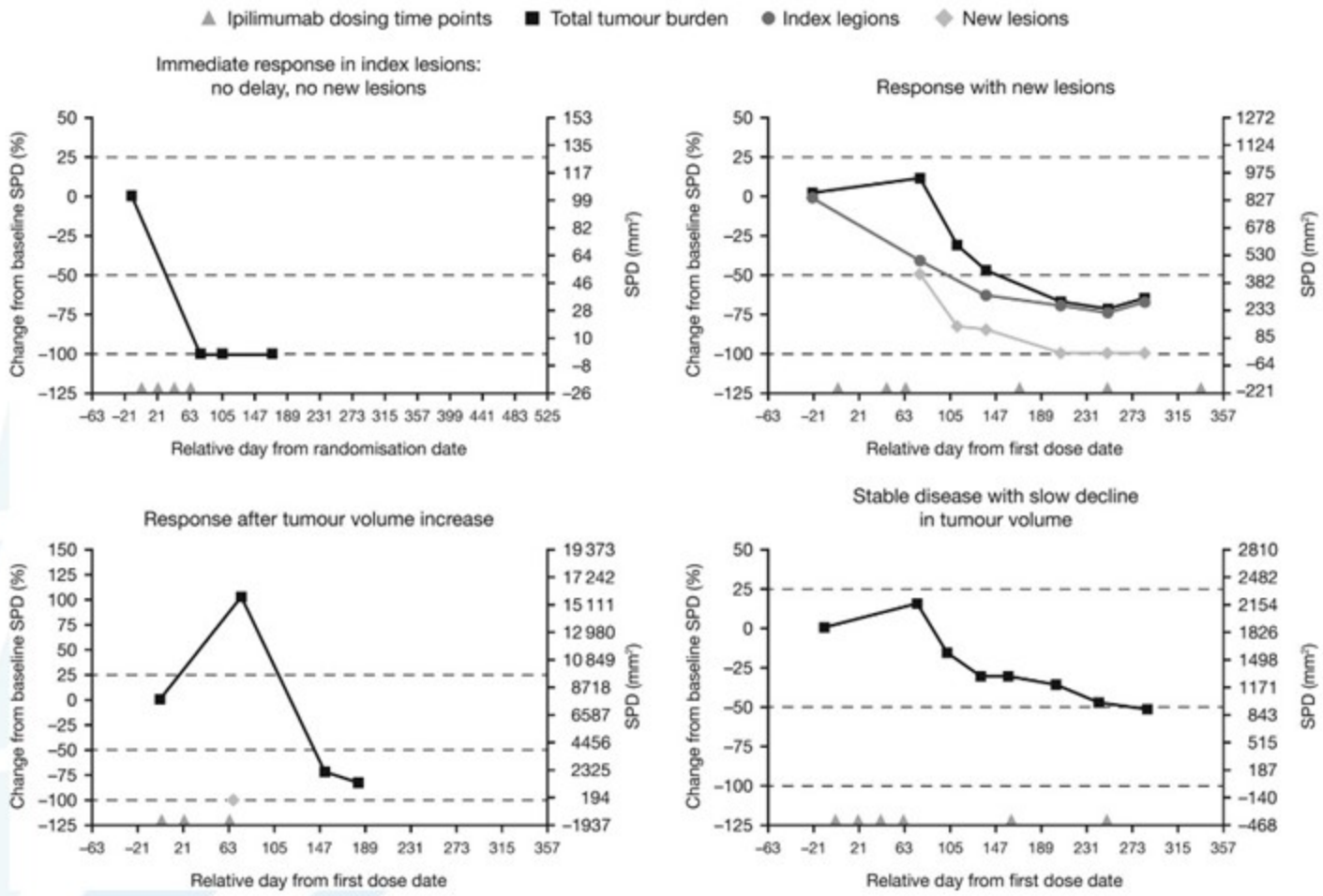
Immunotherapy response evaluation

> irRC: response patterns



Wolchok et al, Clin Canc Res 15:7412, 2009

Four response patterns

1. **Response in baseline lesions and no development of new lesions**
2. **Stable disease, sometimes followed by a gradual decline in tumor burden**
3. **Response after an initial increase in total tumor burden**
4. **Response in index and appearance of new lesions**

➢ **All patterns have been associated with improved overall survival**

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Immunotherapy response evaluation

> irRC: limitations

- irResponse criteria
  - From ipilimimab in melanoma experience. May be different in other tumors
  - Very cumbersome compared to RECIST v1.1

- Most anti-PD-1 and anti-PD-L1 trials use RECIST v1.1 criteria
  - But allow treatment beyond progression with CT control 4 weeks later

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Immunotherapy response evaluation

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Immunotherapy response evaluation

> imRECIST: principles

Immune-Modified Response Evaluation Criteria In Solid Tumors (imRECIST): Refining Guidelines to Assess the Clinical Benefit of Cancer Immunotherapy

F. Stephen Hodi, Marcus Ballinger, Benjamin Lyons, Jean-Charles Soria, Mizuki Nishino, Josep Tabernero, Thomas Powles, David Smith, Axel Hoos, Chris McKenna, Ulrich Beyer, Ina Rhee, Gregg Fine, Nathan Winslow, Daniel S. Chen, and Jedd D. Wolchok

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

- **Trying to capture effect on OS of unconventional responses with immunotherapy**
  - **Principles of irRC transferred to unidimensional measurement of RECIST v1.1**
  - **Based on Atezolizumab studies only (BIRCH, POPLAR, IMvigor210 -> rather small numbers)**

- **Changes**
  - **New lesions and increase in non-target lesions do not contribute to PD definition**
  - **Best overall response may be registered after PD**

Hodi et al, J Clin Oncol 36:850-858, 2018

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Immunotherapy response evaluation
> imRECIST: findings

- **When using imRECIST in stead of RECIST v1.1**
  - **Best ORR increase of 1 to 2%**
  - **DCR increase of 8 to 13%**
  - **PFS increase of 0.5 to 1.5 months**

- **Observations**
  - **Extension of PFS in imRECIST was associated with longer or similar OS**
  - **PD based on new lesions without target lesion increase -> poor sign for OS**
  - **PD based on target lesion increase without new lesions -> good sign for OS**

Hodi et al, J Clin Oncol 36:850-858, 2018

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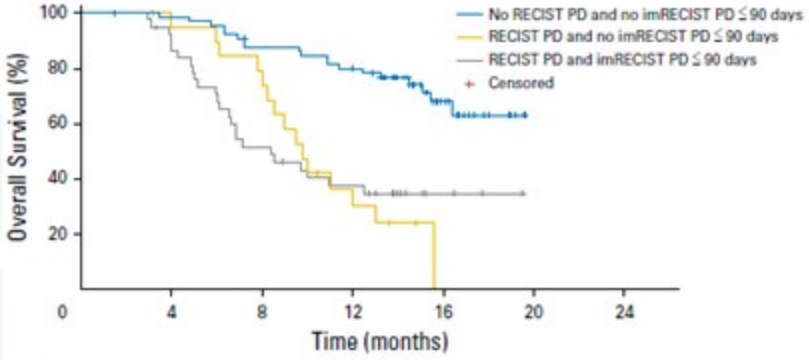
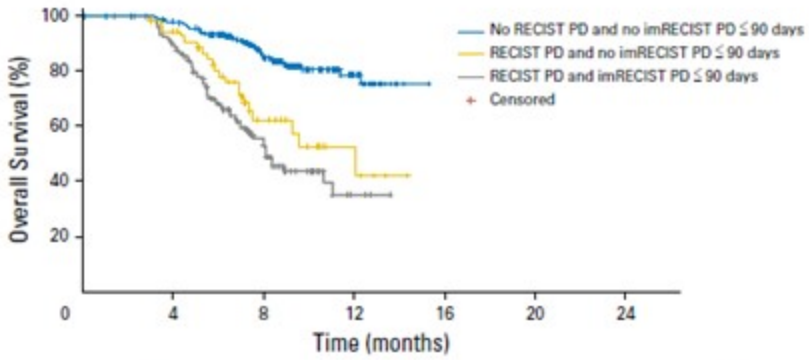
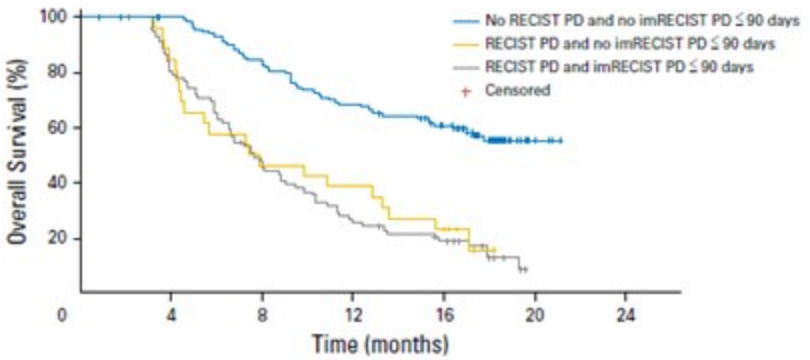
Immunotherapy response evaluation
> imRECIST: findings



BIRCH NSCLC ≥2nd line



POPLAR NSCLC ≥2nd line



IMvigor210 mUC ≥2nd line

Hodi et al, J Clin Oncol 36:850-858, 2018

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Immunotherapy response evaluation

- New needs for response evaluation in the IO era
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Immunotherapy response evaluation

> iRECIST: principles

iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics

Lesley Seymour, Jan Bogaerts, Andrea Perrone, Robert Ford, Lawrence H Schwartz, Sumithra Mandrekar, Nancy U Lin, Saskia Litière, Janet Dancey, Alice Chen, F Stephen Hodi, Patrick Therasse, Otto S Hoekstra, Lalitha K Shankar, Jedd D Wolchok, Marcus Ballinger, Caroline Caramella, Elisabeth G E de Vries, on behalf of the RECIST working group

- **Most principles of RECIST v1.1 are maintained**
  - **Definition of target and non-target lesions (e.g. exclusion of bone, cystic, irradiated, …)**
  - **Max. of 5 target lesions (2 per organ)**
  - **Methods of measurement (e.g. >10mm on spiral CT, >15mm for LNs, …)**
- **Major change: handling of lesion increases**
  - **If RECIST v1.1 is used -> no confirmation of PD needed, no further scans** (… no further therapy?)
  - **In iRECIST: term iUPD ("unconfirmed PD") with further scan 4-8 weeks later** (… continuation of therapy?)
  - **iUPD can be assigned several times, as long as there is no iCPD ("confirmed PD")**
  - **New lesions are recorded (NOT added to the sum)**

Seymour et al, Lancet Oncol 18:e143-e152, 2017

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Immunotherapy response evaluation

> RECIST 1.1 and iRECIST

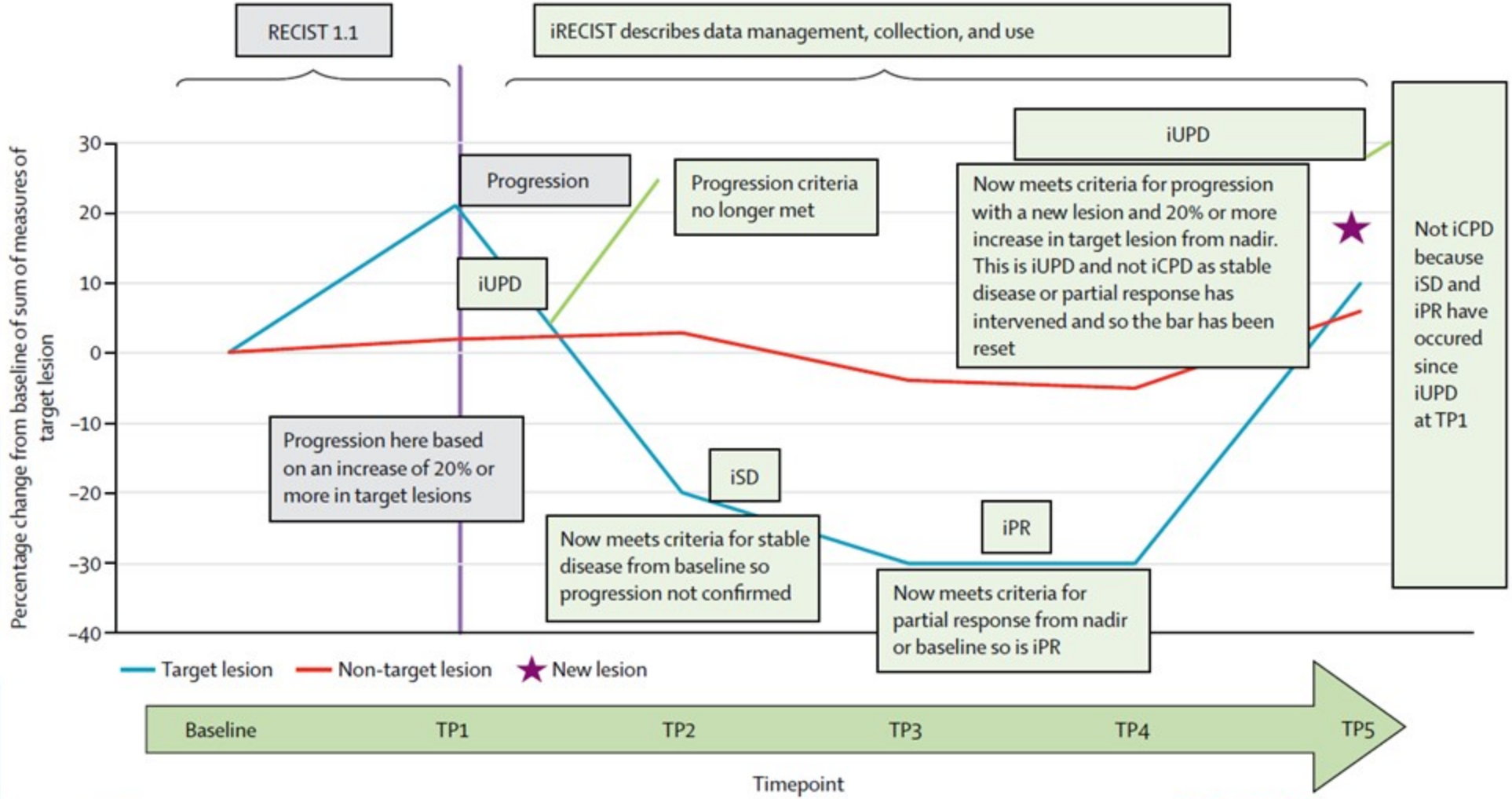
Target	Non-target	New	Overall
CR	CR	No	CR
CR	non-CR/PD	No	PR
PR	non-CR/PD	No	PR
SD	non-CR/PD	No	SD
PD	Any	No	PD
Any	PD	No	PD
Any	Any	Yes	PD

Target	Non-target	New	Overall	Clarifications
iCR	iCR	No	iCR	
iCR	non-iCR/iPD	No	iPR	
iPR	non-iCR/iPD	No	iPR	
iSD	non-iCR/iPD	No	iSD	
iUPD	iCR *or* non-iCR/iPD	No	iUPD	iCPD only if ▪ further increase in sum of measures ≥5 mm
iCR *or* iPR *or* iSD	iUPD	No	iUPD	iCPD only if • further increase in non-target disease
iUPD	iUPD	No	iUPD	iCPD only if • further increase in sum of measures ≥5 mm, *or* • further increase in non-target disease
iUPD	iUPD	Yes	iUPD	iCPD only if • further increase in sum of measures ≥5 mm, *or* • further increase in non-target diasease, *or* • further increase in size/number of new lesions
Non-iUPD	Non-iUPD	Yes	iUPD	iCPD only if • further increase in size/number of new lesions

Seymour et al,
Lancet Oncol 18:e143-e152, 2017

Immunotherapy response evaluation

> example



Seymour et al, Lancet Oncol 18:e143-e152, 2017

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Immunotherapy response evaluation
> iRECIST: individual treatment decisions

- **Avoid stop of effective (IO)therapy based on pseudo-progression**
  - **Use of iRECIST and principles of iUPD -> treatment continuation until iCPD**
  - **Availability of effective salvage therapy important in case of doubt**
  - **Continue same therapy only in *clinically stable* patients**
    - **No decline in PS**
    - **No increase in tumor-related symptoms (pain, dyspnea, …)**
    - **No need for intensified therapy for disease-related symptoms**
- **Avoid continuation of non-effective therapy and delay of salvage therapy**
  - **When iUPD occurs, next imaging 4 to max. 8 weeks later** (ipilimumab in melanoma?) **to assess iCPD**

➢**Aim is standardized assessment (e.g. clinical trials), NOT guide individual treatment decisions**

Seymour et al, Lancet Oncol 18:e143-e152, 2017

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Immunotherapy response evaluation

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Response evaluation
> different systems

Criterion	RECIST v1.1	irRC	imRECIST	iRECIST
Tumor burden	1D measurement	2D (previous WHO)	1D measurement	1D measurement
Target lesions	Measure up to 5 (2 per organ)	Measure up to 10 (5 per organ)	Measure up to 5 (2 per organ)	Measure up to 5 (2 per organ)
New lesions	Always PD	Do not define PD (incorporated in sum of lesions)		i-uPD
Non-target lesions	Can contribute to CR or PD	Can contribute to CR Do not define PD		i-uPD
Progression	≥20% increase / Increase in non-target / New lesion(s)	≥25% increase / Negated by subsequent non-PD	≥20% increase / Increase in non-target New lesion(s)	≥20% increase / Increase in non-target / New lesion(s)
PD confirmation	Not required	Required	Required	If further increase: i-cPD

Eisenhauer et al, Eur J Cancer 45:228-217, 2009
Wolchok et al, Clin Cancer Res 15:7412, 2009
Hodi et al, J Clin Oncol 36:850-858, 2018
Seymour et al, Lancet Oncol 18:e143-e152, 2017

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Thank you for your kind attention

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Progression or pseudoprogression? Continue treatment or not?

Stefan Rauh

Job code: IOBE18NP04371-06
Date of preparation: December 2018

Case #1: 67 year-old male patient

- PS 1
- Past medical history
  - Over 10 years of COPD, GOLD 2
  - Diabetes with polyneuropathy
  - Renal insufficiency; glomerular filtration rate = 29cc/min
  - Stented stable ischemic heart disease (ejection fraction = 55%)
- 65kg, 165cm

- Admitted due to respiratory distress
- Diagnosis of malignant pleural effusion (cytology: adenocarcinoma TTF positive)
- Trans-thoracic biopsy:
  - Adenocarcinoma grade 3
  - PD-L1 40%
  - No oncogene addiction (EGFR / *ALK* / *BRAF*, *Ros1* negative)
- No extra thoracic tumor manifestation
- Stays 4 weeks in ICU due to chest drain complications

COPD, chronic obstructive pulmonary disease; EGFR, epidermal growth factor receptor; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICU, intensive care unit; TTF, thyroid transcription factor.
S. Rauh, personal communication 2018.

Treatment choice and evolution

- Not considered fit for chemotherapy (renal insufficiency, multiple morbidities)
- No place for targeting agents (anti-EGFR, anti-*BRAF*, anti-*ALK*/*Ros1*)
- Pembrolizumab started…(well tolerated) starting August 5th 2018
- Patient re-admitted in October 8th for respiratory distress (according to him, due to a cigarette ..)
- A CT scan is performed

EGFR, epidermal growth factor receptor.
S. Rauh, personal communication 2018.

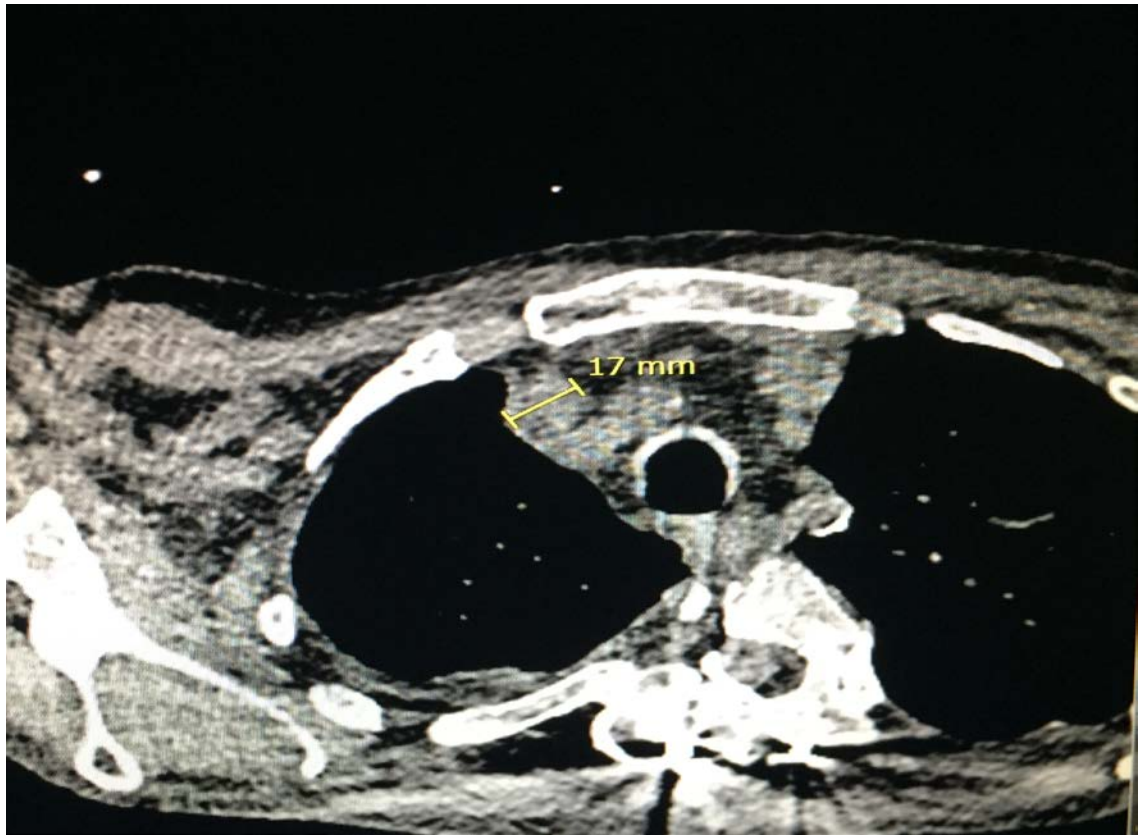
Laboratory work

- GB 12400/mm^3 with neutrophilia
- CRP 76 mg/l, procalcitonine 3 x nl
- cea: rise from 24 mg/l baseline to 33 mg/l at admission (October)

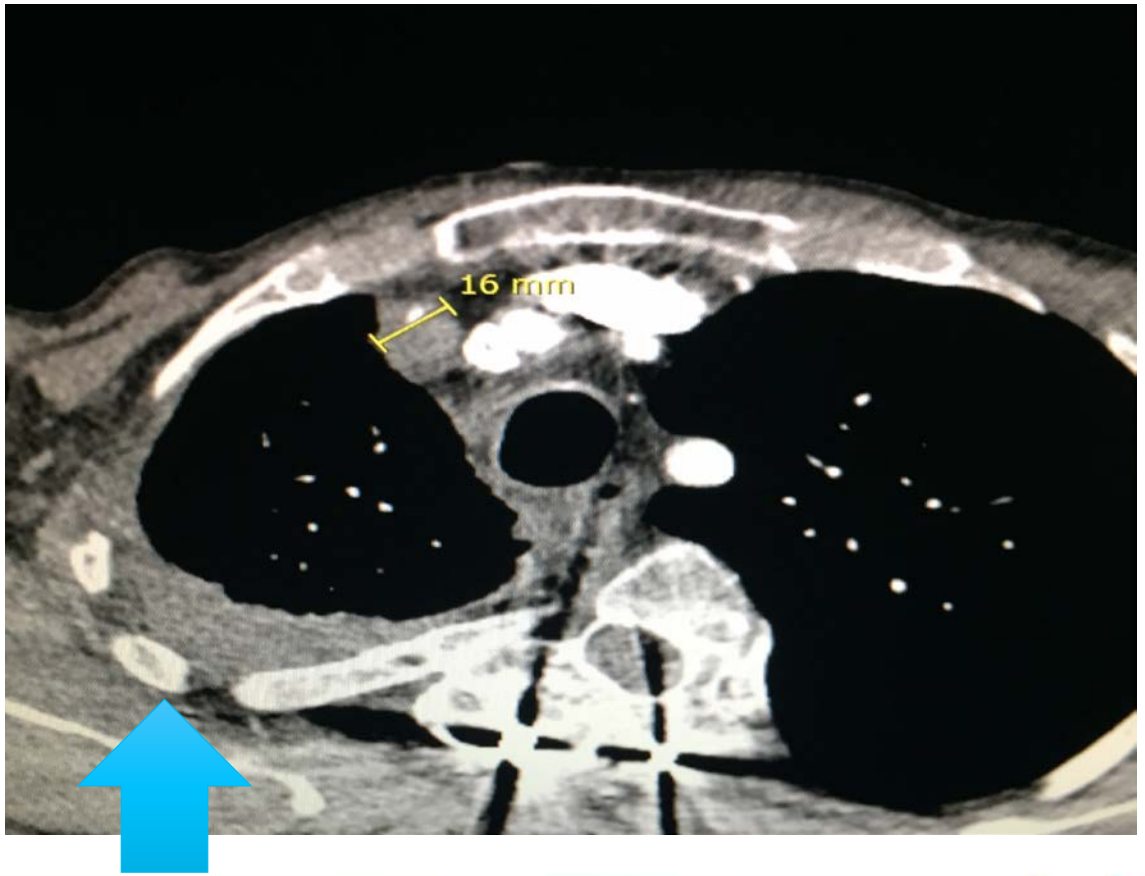
CRP, C-reactive protein.
S. Rauh, personal communication 2018.

CT scans

June 2018



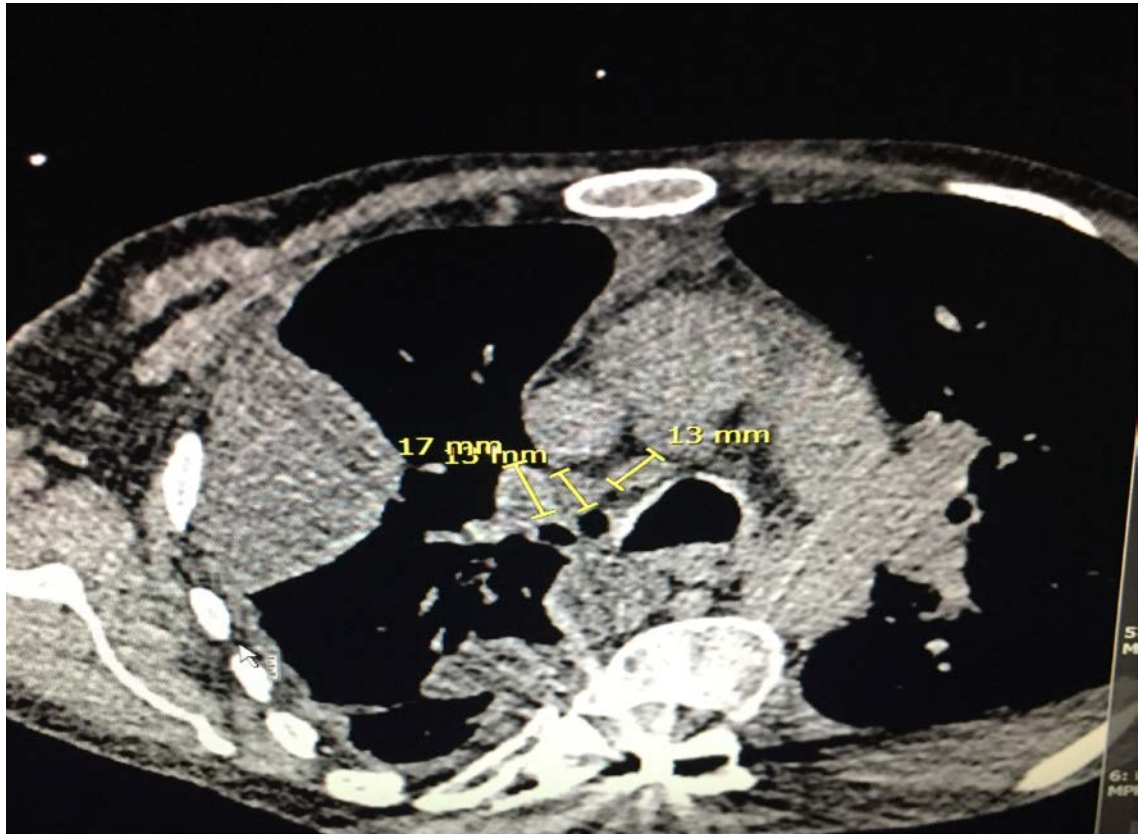
October 2018



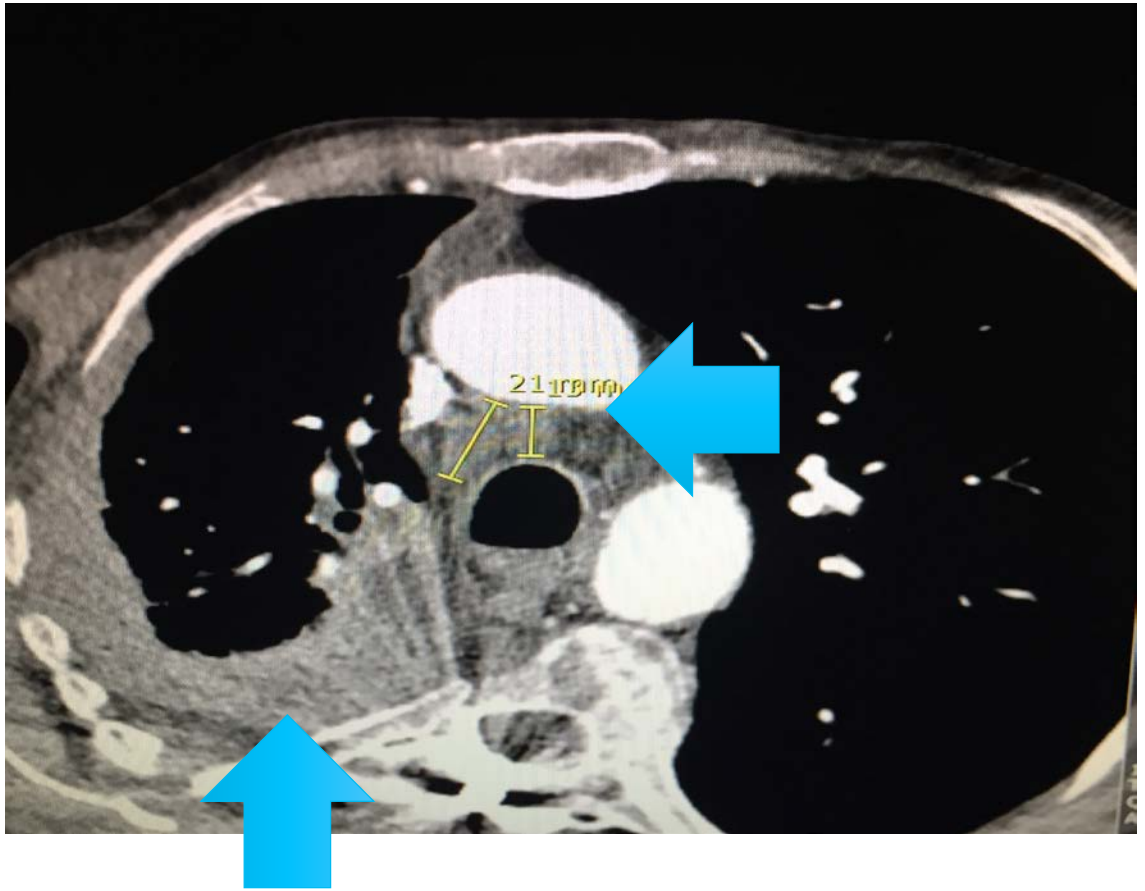
S. Rauh, personal communication 2018.

CT scans

June 2018



October 2018



S. Rauh, personal communication 2018.

Outcome

- Patient recovers quickly with supportive care (physiotherapy, aerosols) and “probabilistic antibiotherapy”
- Discharged in the same physical state as at the start of treatment

S. Rauh, personal communication 2018.

Patient declares feeling well,
at least not worst than before,
and wants to continue

Is this progressive disease?

2 months after start from IT: continue treatment?

S. Rauh, personal communication 2018.

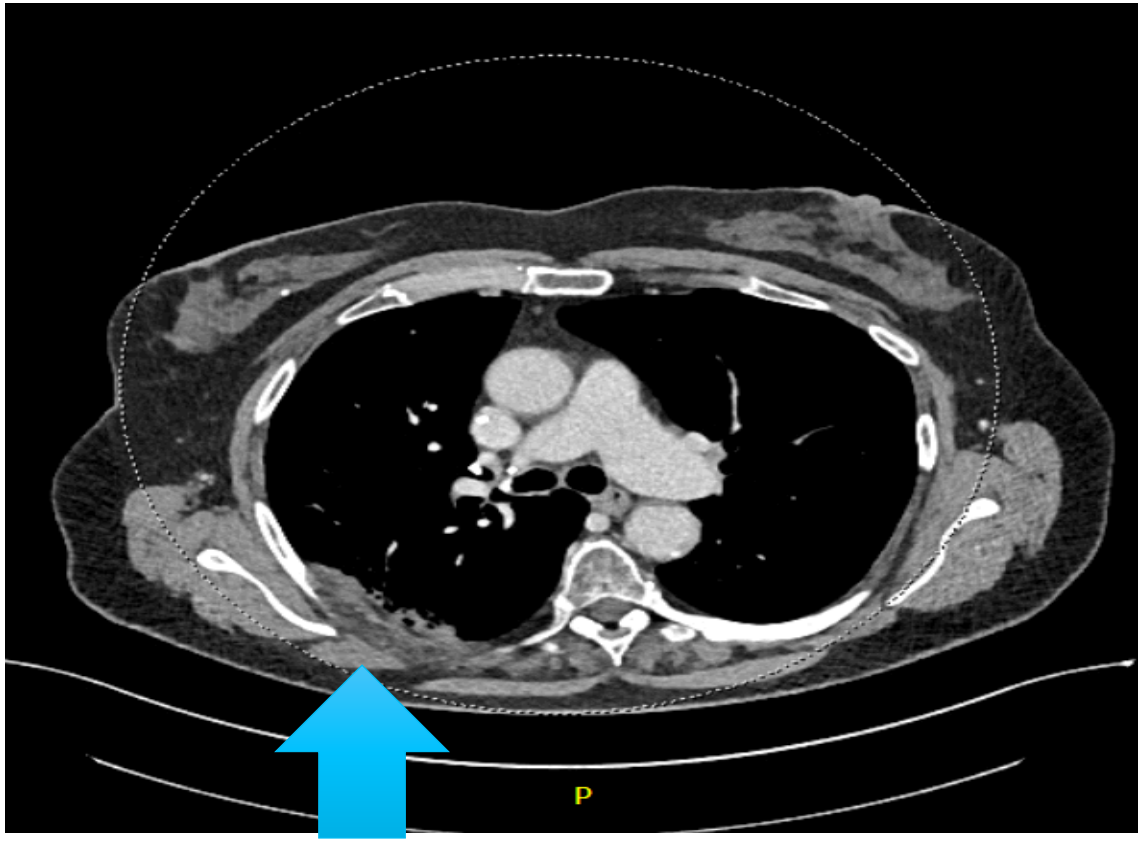
Case #2: 74 year-old patient

- Squamous NSCLC 2015
  - left upper lobe 2 cm : surgery pT2N0 G3 R0 2015
- Apr 2017: local relapse RCT, 4 cycles of carboplatin/gemcitabine
- May 2018: Progression to metastatic disease: lesion D6,D7, left adrenal gland
  - Immunotherapy (nivolumab) started
- Scans: May 2018 and Nov 2018

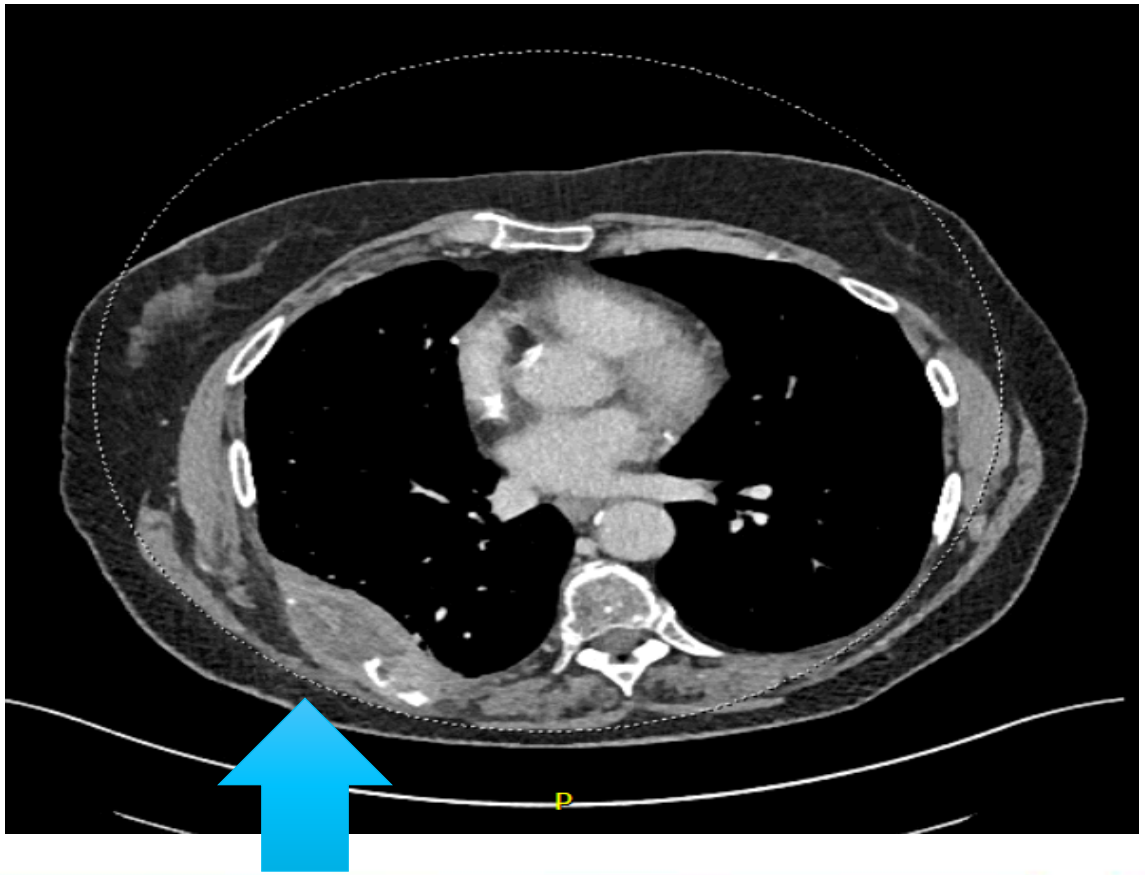
NSCLC, non-small-cell lung cancer
S. Rauh, personal communication 2018.

CT scans

May 2018



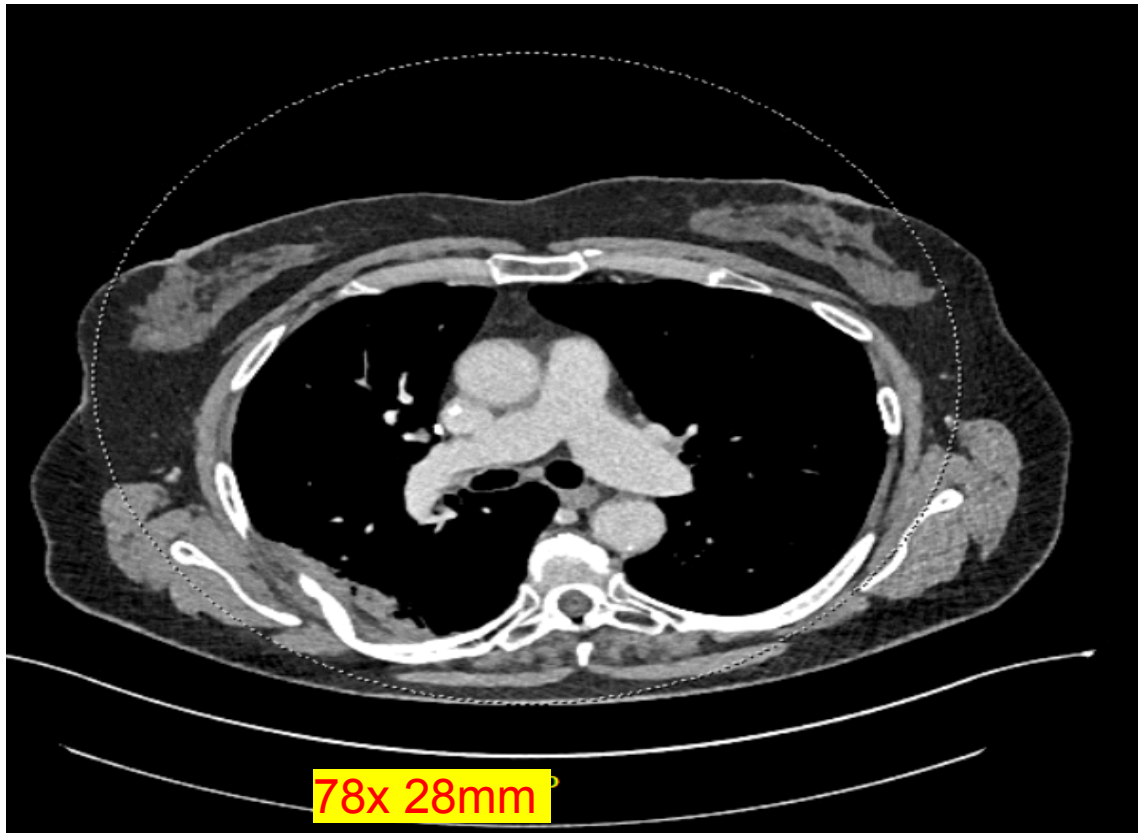
November 2018



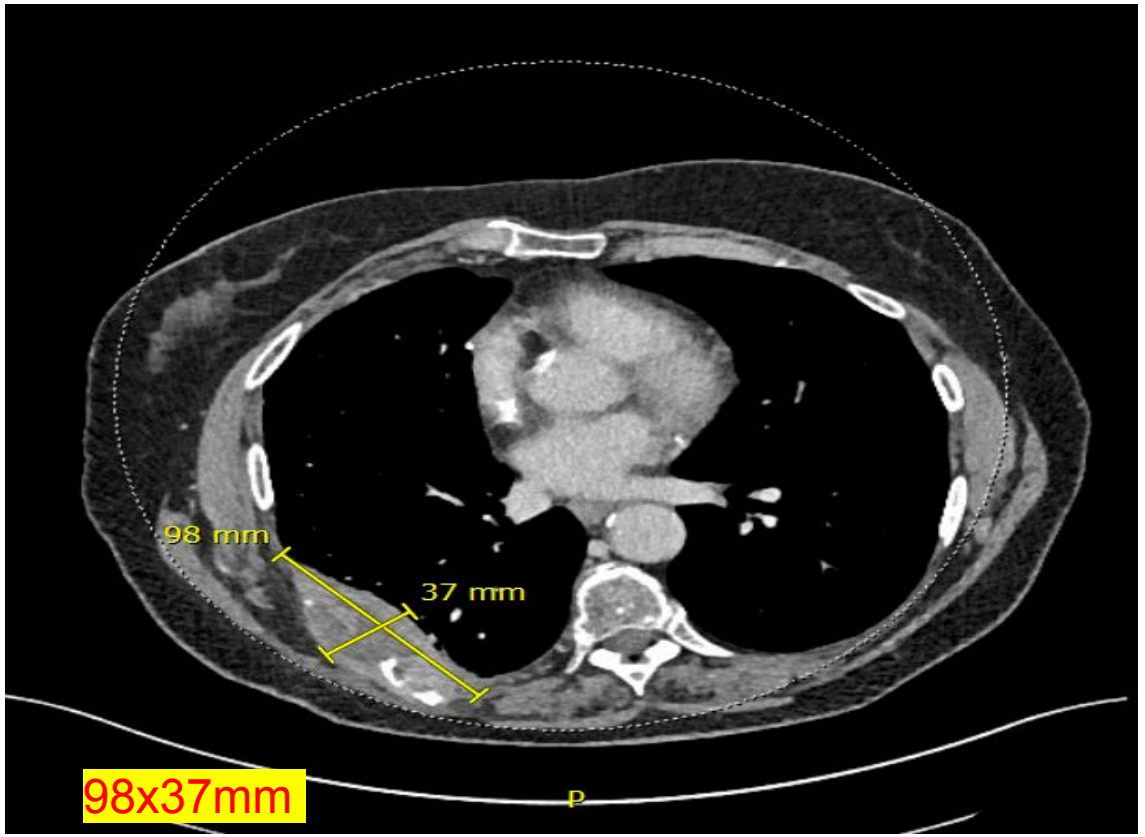
S. Rauh, personal communication 2018.

CT scans

May 2018



December 2018



S. Rauh, personal communication 2018.

May to November 2018

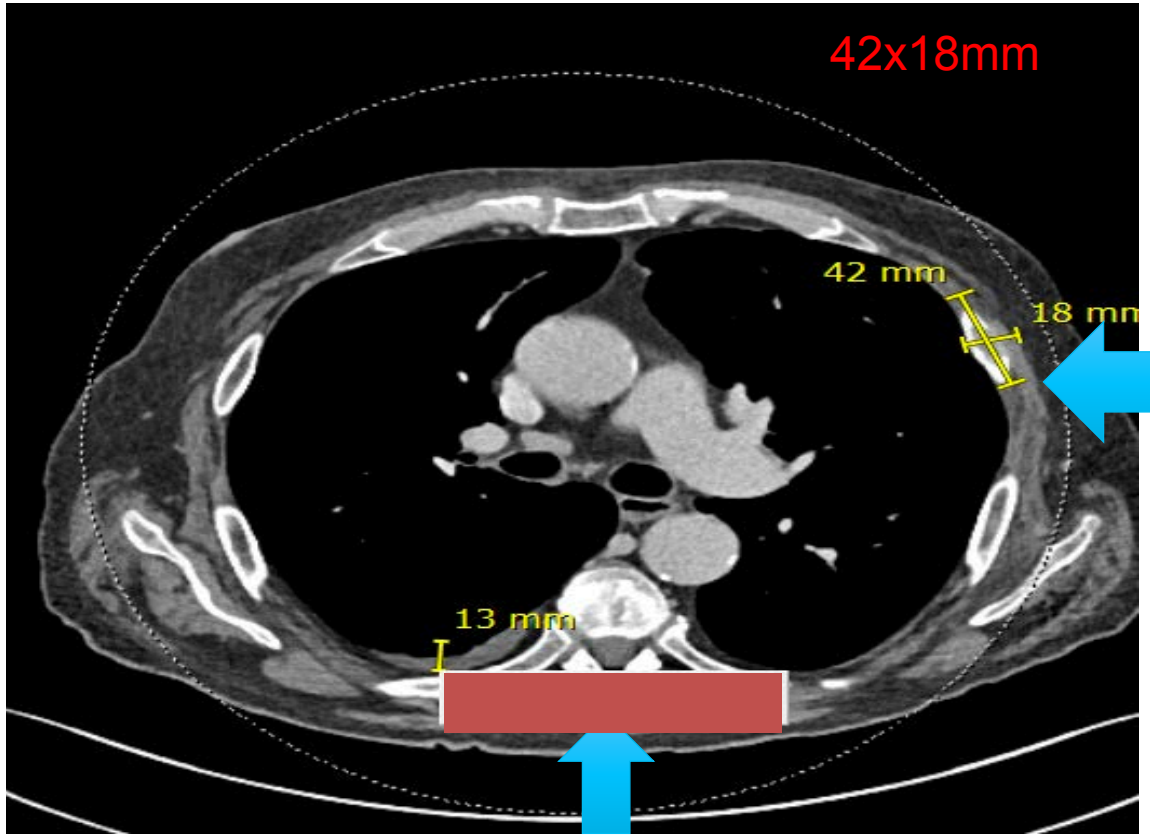
Patient declares feeling better!

Continue treatment?

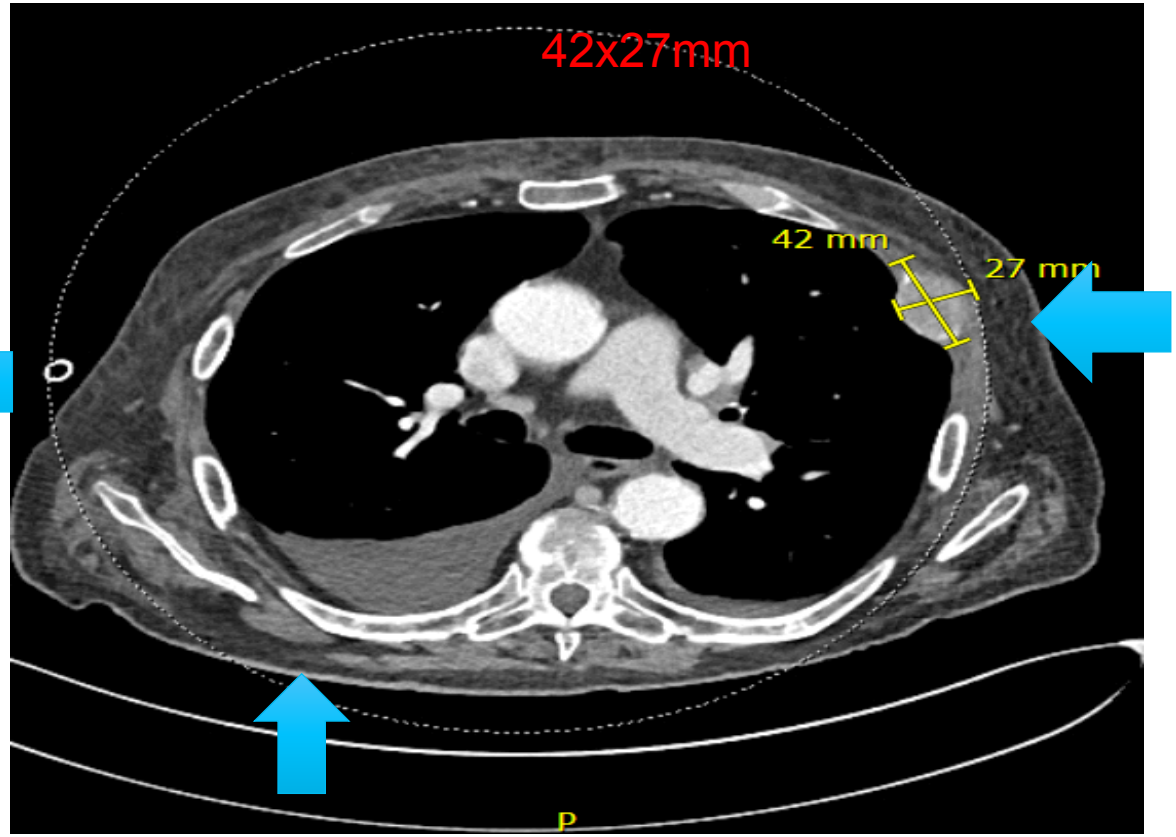
S. Rauh, personal communication 2018.

Case #3: CT scans

March 2017



May 2017



S. Rauh, personal communication 2018.

Is this pseudoprogression?

- If pleural effusion quantity augments?
- With a non-significant but painful growing lesion
- If the patients general shape diminishes?
- In any of these?
- Only their combination?
- Or other criteria?

S. Rauh, personal communication 2018.

www.immunoscienceacademy.be

Thank you

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