Treating Beyond Progression: why PSA is not everything

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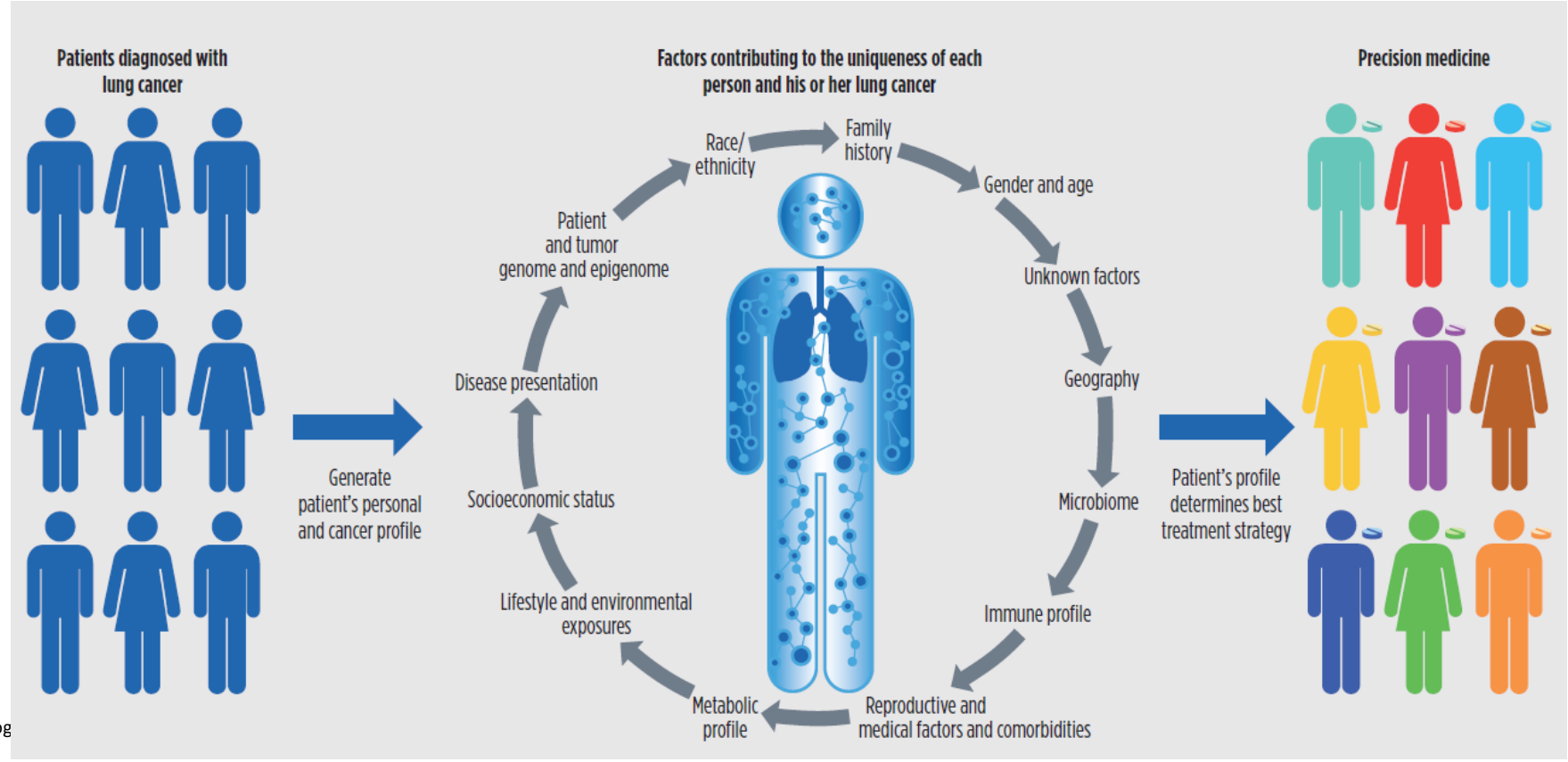
Knowing your Patient's Tumor Profile: Example – Lung Ca

Precision Medicine May be the Key to Improving Survival



cancerprog

Pathology Testing for Solid Tumors

What Is the Right Biomarker? What Is the Right Test?

Test	Colorectal Cancer	NSCLC	Prostate Cancer	SCLC
DNA sequence: (PCR-based, NGS panel)	BRAF, KRAS, NRAS, PIK3CA, PTEN, MSI •BRAF - codon 600 •KRAS - codons 12, 13, 61 •NRAS - codons 12, 13, 61 •PIK3CA - codons 542, 545, 1047	EGFR, BRAF, ERBB2 (HER2), PIK3CA, MAP2K1/MEK1 KRAS, NRAS MSI	BRCA2, PALB2, ATM MSI	MSI
Protein: IHC	MMR (MLH1, MSH2, MSH6, PMS2)	PD-L1, TTF1, p40, p63		TTF-1, Ki-67
Chromosomal rearrangement: FISH or NGS		ROS1, RET, MET		
Note: Formalin-fixed paraffin embedded (FFPE) material is suitable for most molecular analyses				

Rising PSAs: What does it really mean?

1. My disease is getting worse!
2. There is "**x**" times the amount of disease compared with previously
3. I'm dying!
4. I must be treated immediately or else!
5. The disease is active!

What is treating beyond progression and why is this important?

- Novel therapies with unique mechanisms of action (PARPs, ICI, ARSIs)
- Drugs have led to dramatic responses in several advanced cancers, including metastatic melanoma, lung cancer, kidney cancer, bladder cancer, and head and neck cancers.
- However, in some patients, these drugs do not shrink the tumors or reduce tumor growth, and these patients may need to undergo alternative treatments.
- Some oncologists continue to treat patients even when imaging data indicates that the tumor has progressed. This is called **“treatment beyond progression.”**
- The clinical benefit of treatment beyond progression is unknown, and the approach carries some risks

Concept of Treating Beyond Progression…

- Applicable to multiple solid tumors, lung, GI, ovarian
- Potential benefit of a drug would be unrealized
- Drug would be deemed ineffective and discarded only if evaluated by a single parameter
- Benefit could be determined by: pain control, stable disease, improved QOL, normalization of laboratory parameters, ie CBC
- Therefore, a drug could be approved if it improved some aspect of patient response based on independent review

Patterns of Response

- Tumor resolves completely (CR) – *goes away*
- Tumor partially responds (pCR) – *partially goes away*
- Tumor progresses (POD) - *more disease*
- Tumor "pseudoprogression" – tumor gets larger before shrinking
- Pseudoprogression may be due to:

  a) immune cell infiltrate if using ICI

  b) early healing processes in bone lesions (bone turnover) – scan looks worse before it gets better (increase in alkaline phosphatase)

Prognostic Factors for Response

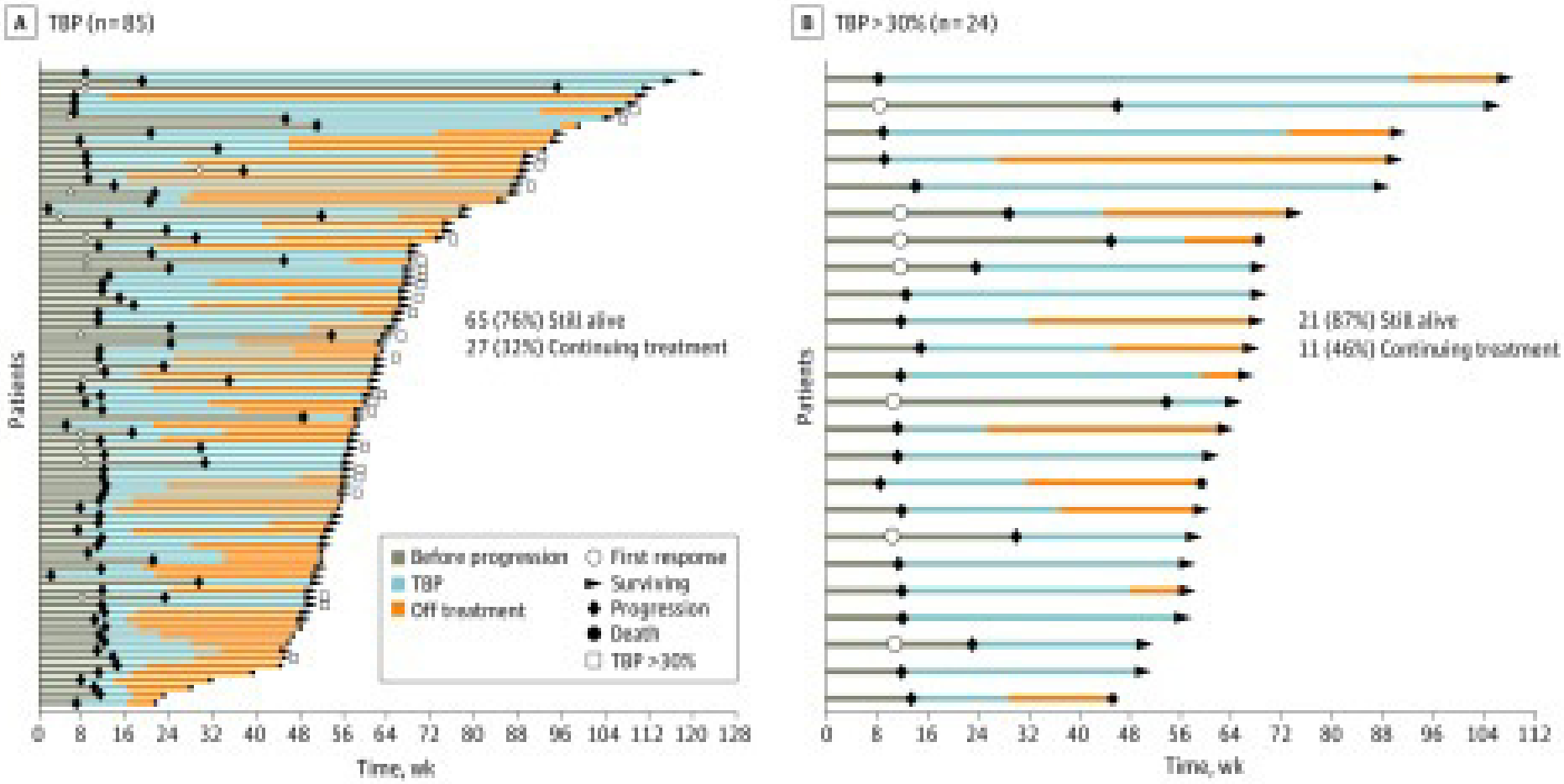
- A **prognostic factor** - something that affects a patient's overall outcome for a disease regardless of an intervention.
- Beaver et al. hypothesized that pts treated beyond progression in the trials included in the FDA pooled analysis may have been selected by the physicians because of positive prognostic factors, such as:

  a) Absence of signs and symptoms

  b) Laboratory values

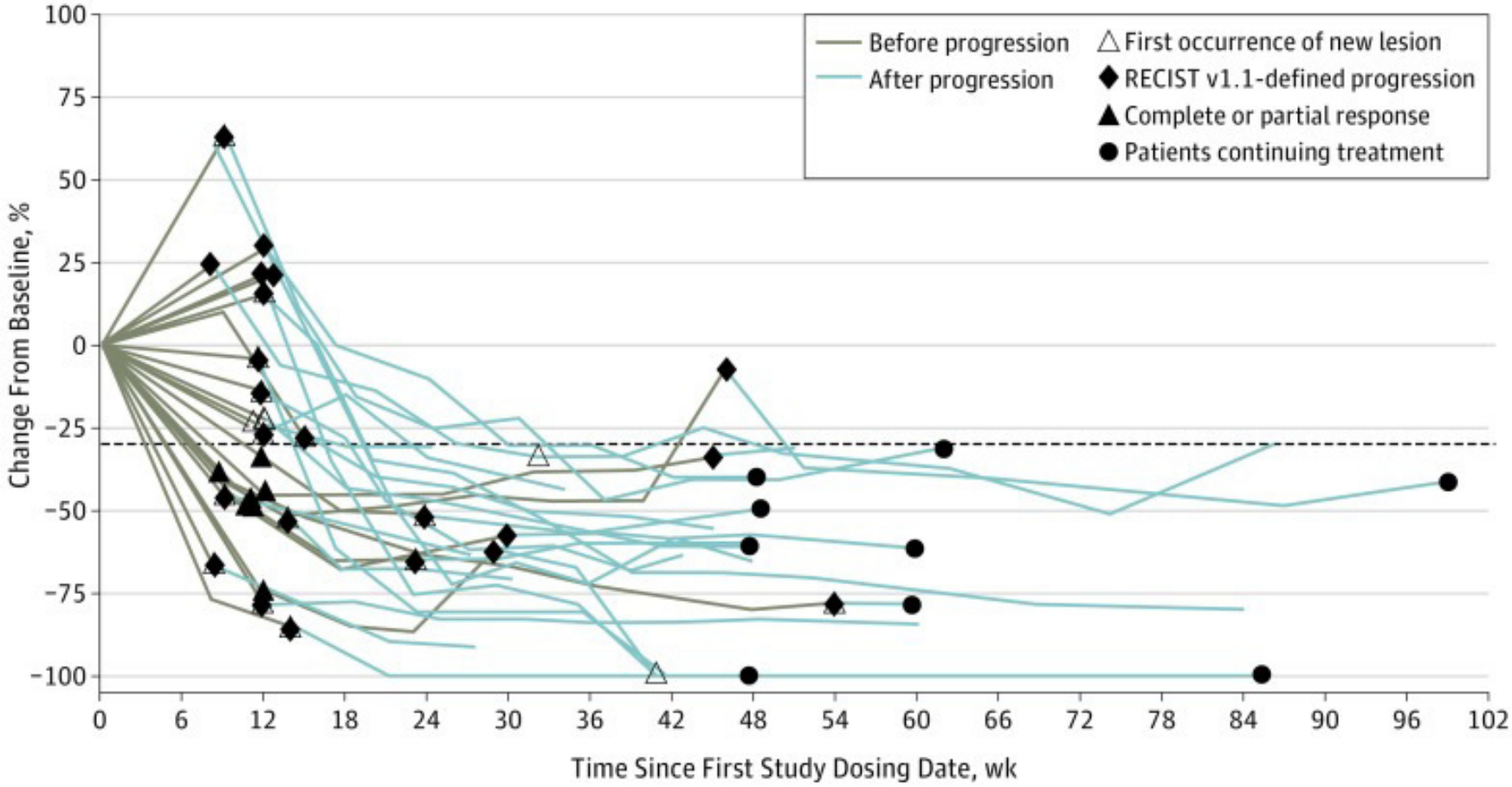
  c) Stable or improved ECOG performance score

  d)Absence of rapid disease progression that requires urgent attention
- The possibility that different groups of pts have different prognostic factors confounds attempts of the analysis to conclude whether treatment beyond progression led to a better outcome for these patients.



A, All patients treated beyond progression. B, Patients treated beyond progression with greater than 30% tumor reduction in target lesion after progression when compared with baseline. TBP indicates treatment beyond progression.

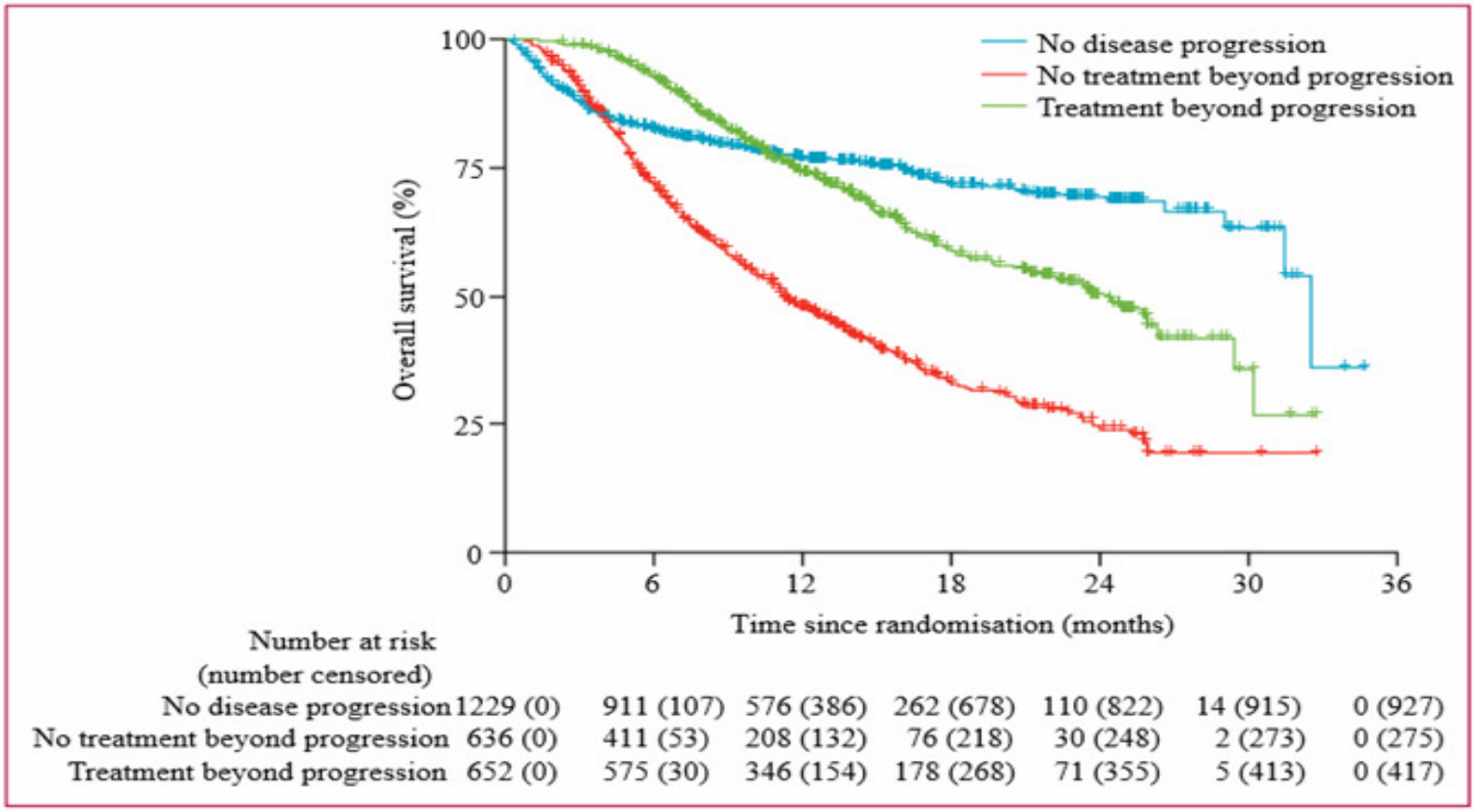
Long, et al, JAMA Onc 2017



Tumor Burden Change Over Time in 24 Patients Treated Beyond Progression With Greater Than 30% Tumor Reduction in Target Lesion After Progression Compared With Baseline. Horizontal dashed reference line indicates the 30% reduction consistent with a Response Evaluation Criteria in Solid Tumors v1.1 response. Long, et al, JAMA Onc, 2017

Treating Beyond Progression…

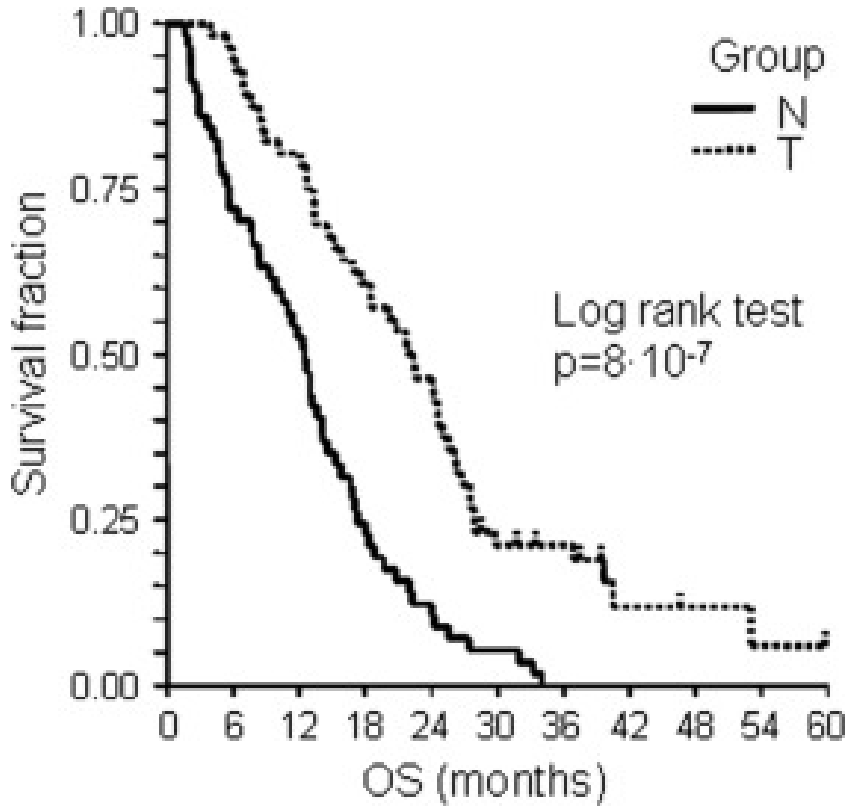
- Risks exist
- If using ICI, the safety risks of the anti-PD-1 antibody increase
- Risk of continuing an inefficacious agent with delay of alternative therapy
- Needs to be balanced with the modest potential of a subsequent reduction in tumor burden or prolonged stability
- In order words, is it ok to ride out the wave?



Summary of Pooled Overall Survival Analysis

This figure summarizes the results of a study from Beaver et. al., where the group of patients who received treatment beyond progression demonstrated a longer median overall survival than the group who did not. Source: Beaver et al. 2018.

Overall survival (OS) of metastatic CRPC treated with abiraterone acetate + prednisolone until PSA and radiographic progression (PRP) (group NT, solid line) or beyond PRP until clinical progression (group T, dashed line).



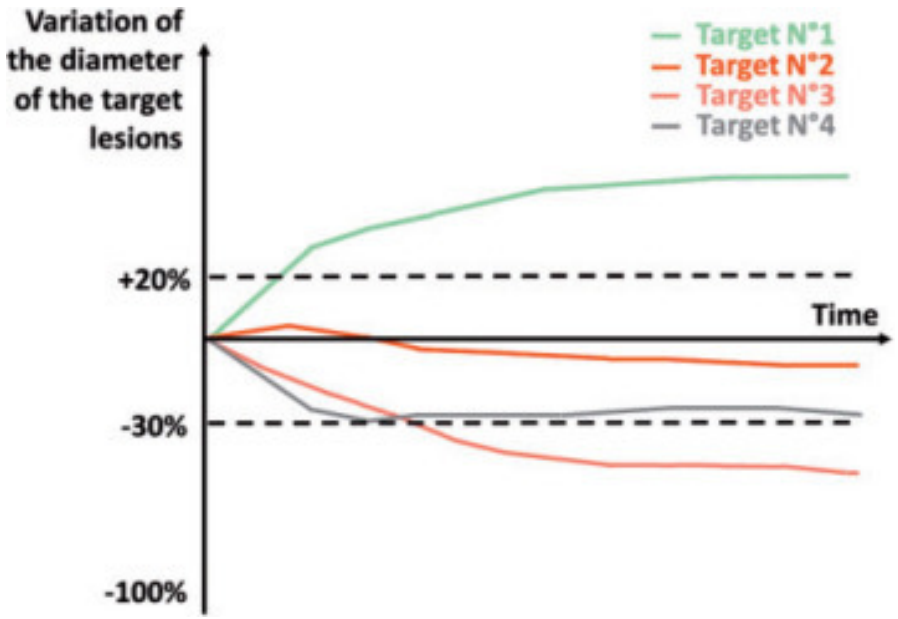
Biro, et al, Urol Onc, 2018

Can we use the same criteria in assessing prostate cancer responses as we do in other solid tumors?

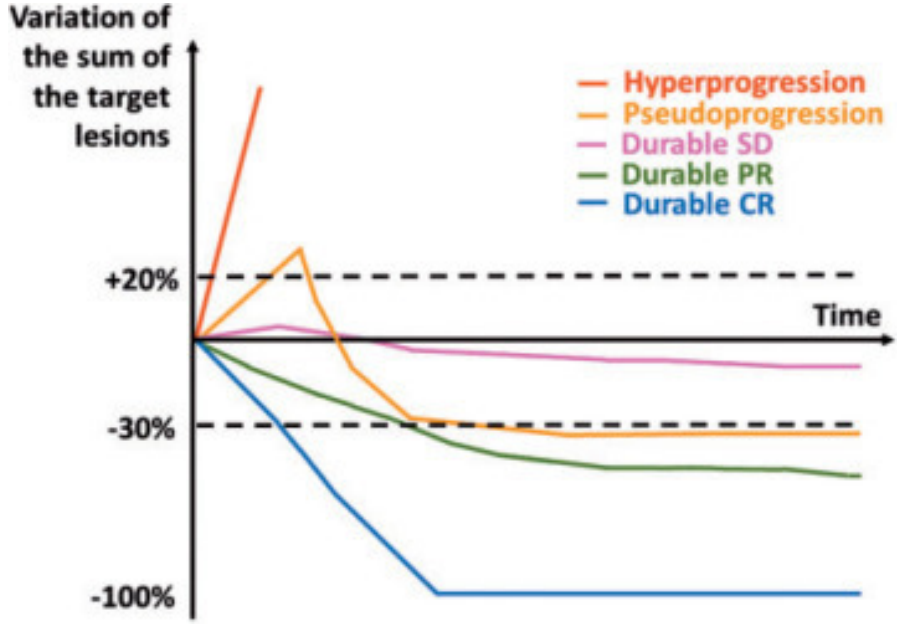
- NO!
- Criteria for response may depend on the type of drug used and its effect on the tumor
- ICIs cause immune infiltrates, hence swelling of the lesions such that they appear transiently larger suggesting disease progression
- Over time, an anti-tumor effect takes place and the lesion shrinks
- Immune effects take time but so do other drugs
- Since responses can be slow, PSA does not always correspond to stable or less disease

Prostate Cancer Working Groups 1-3

- Definitive guidelines to determine what is disease progression on imaging
- If bone scan, is the development of 1 lesion c/w POD?
- NO, would need to repeat imaging 6 weeks later to determine if additional lesion is still there
- Criteria is 2 or more lesions confirmed 6 weeks apart on a second scan
- Remember bone lesions may come and go and not all are cancer!
- Specific criteria “RECIST” exist to measure and record LNs and other sites of disease on CT scans

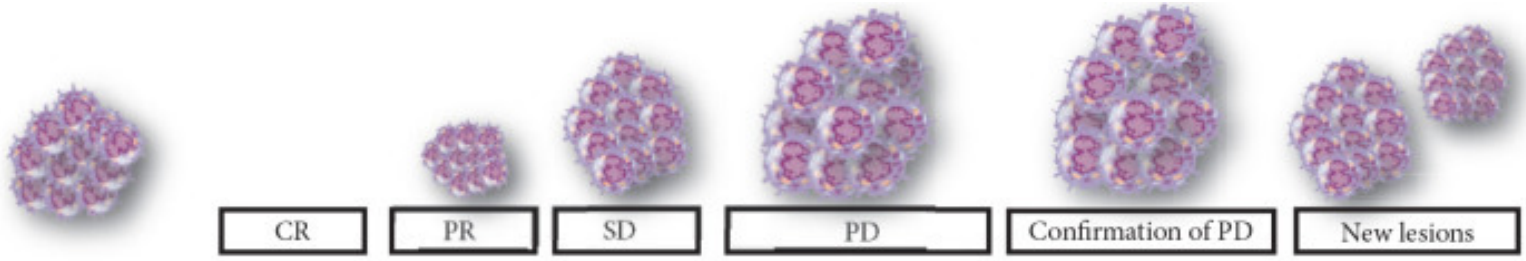


Patterns of Response



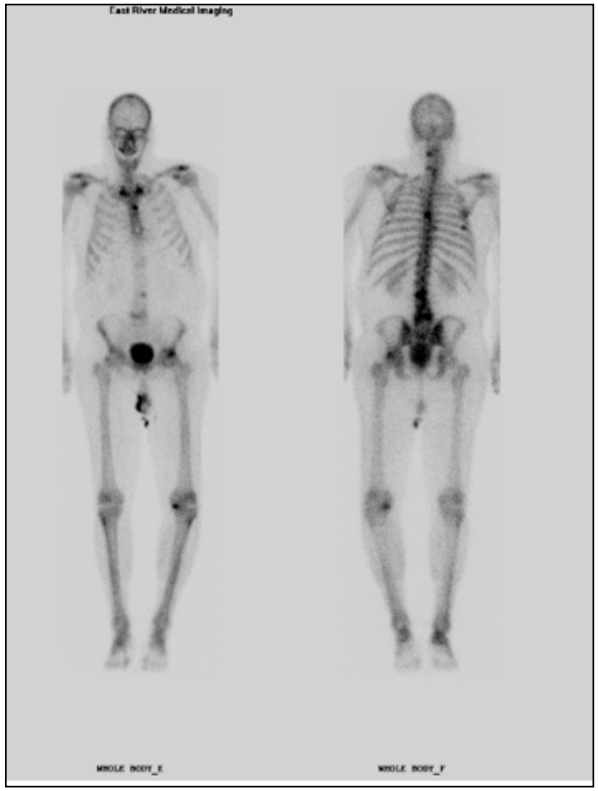
Dissociated Response to ICI

Borcoman,Ann Onc 2019



	CR	PR	SD	PD	Confirmation of PD	New lesions
RECIST1.1 [34] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	Not applicable	PD
irRC [74] Bi-dimensional 5mm x 5mm 15 lesions in total, 5 per organ	Disappearance of all lesions	≥ 50% decrease from baseline	Neither CR nor PD	≥ 25% increase in the nadir of the sum of target lesions	At least 4 weeks later	Incorporated in the sum of measurements
irRECIST [75] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks after and up to 12 weeks	Incorporated in the sum of measurements
iRECIST [76] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks after and up to 8 weeks	iUPD; not incorporated in the sum becomes iCPD if confirmed
imRECIST [77] Uni-dimensional ≥10mm 5 lesions in total, 2 per organ	Disappearance of all lesions	≥ 30% decrease from baseline	Neither CR nor PD	≥ 20% increase in the nadir of the sum of target lesions (with a minimum a of 5mm)	At least 4 weeks later	Incorporated in the sum of measurements

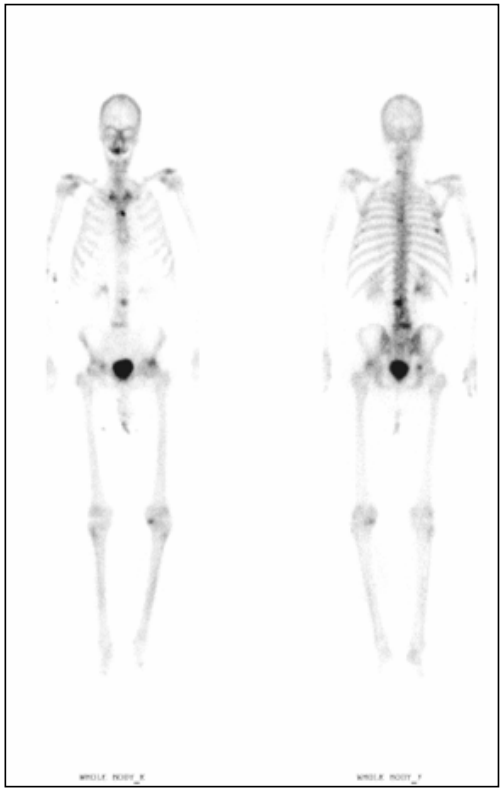
Borcoman,Ann Onc 2019



A.

12-23-2019

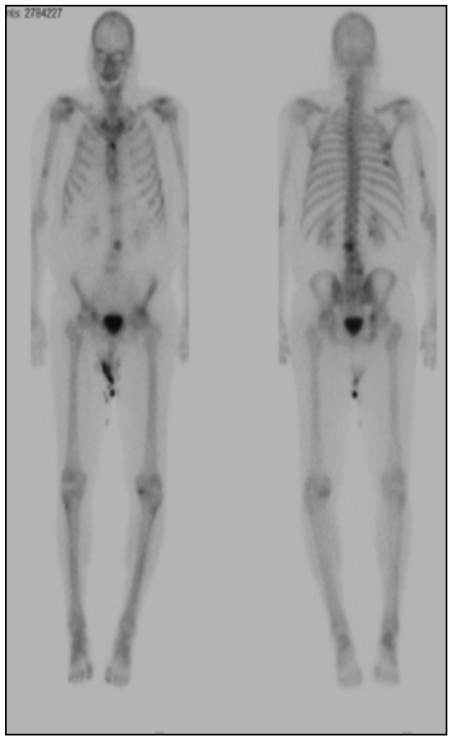
PSA 3.59



B.

2-24-2020

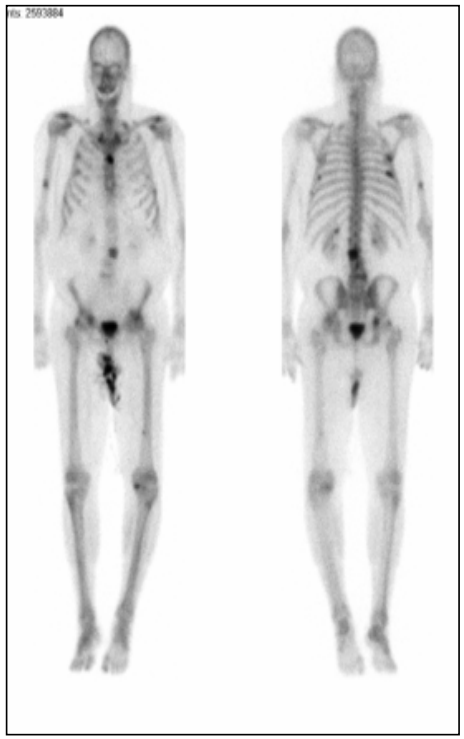
PSA 7.8



C.

4-29-2020

PSA 11.53

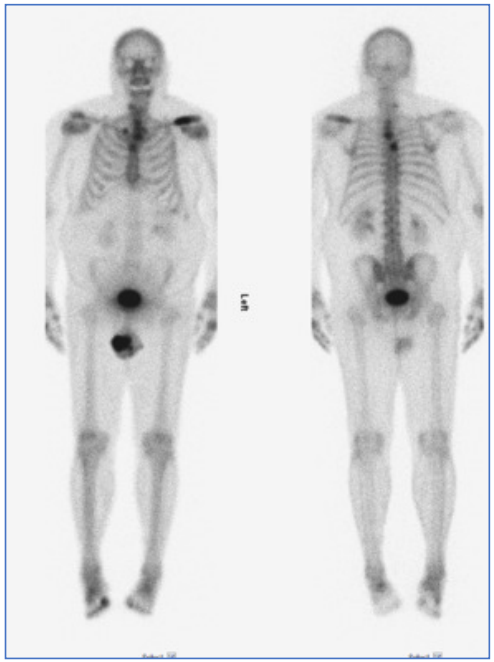


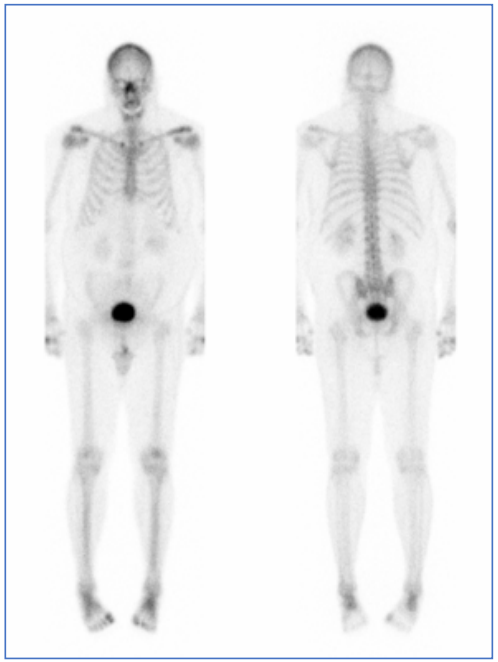
D.

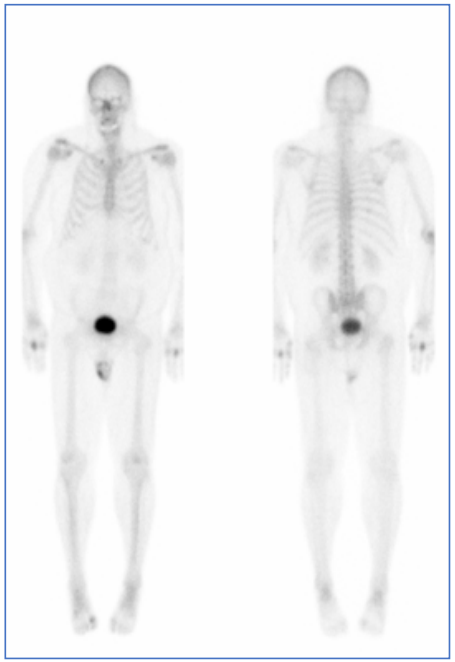
7-01-2020

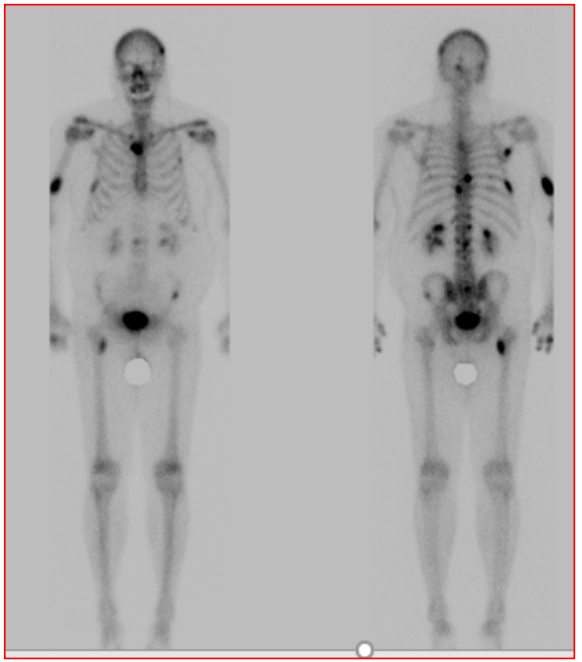
16.88

Stable Disease









A.

1-26-2017

PSA <0.05

B.

3-16-2018

PSA <0.05

C.

2-20-2019

PSA 0.41

D.

1-22-2020

PSA 21.09

Treating Beyond Progression

Conclusions

- “Benefit” from a therapy can be determined based on many factors
- Clinical benefit – improves quality of life, pain control
- Radiographic benefit – imaging with stabilization of disease
- Improvement in biomarkers: PSA, etc
- ***But,*** benefit can still occur despite discordance in clinical, radiographic and biomarker differences
- ***PSA does not*** tell everything about what is going on with the disease, hence it is important to discuss how a patient feels and is performing in all ADLs in addition to clinical factors

In other words…

A PSA is Not everything!!!!!

Thank you and stay safe!!!