Imaging in the immuno-oncology era: between immune response, pseudoprogression and hyperprogression:

what do we have to know?

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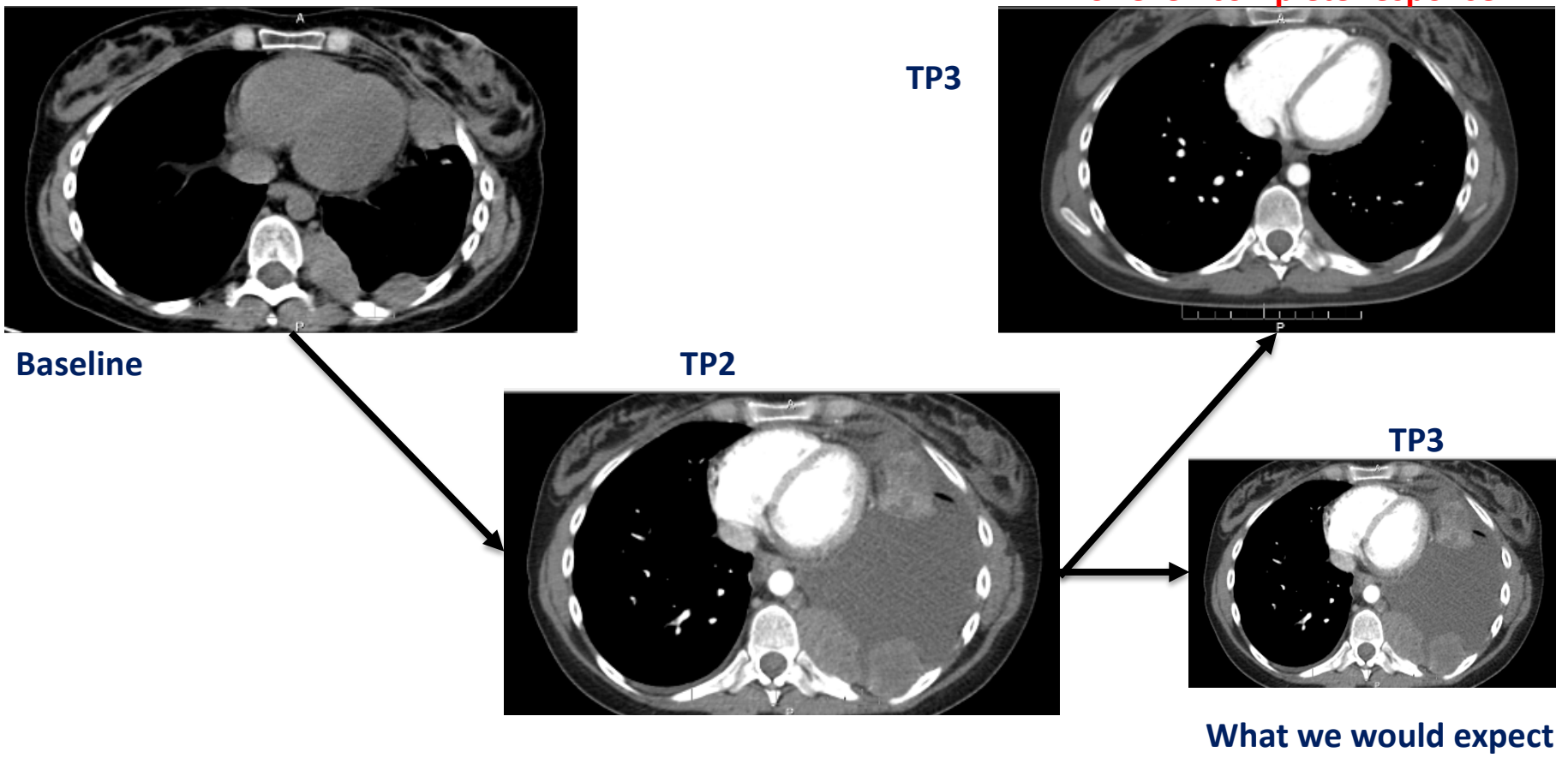
Unusual Response Patterns

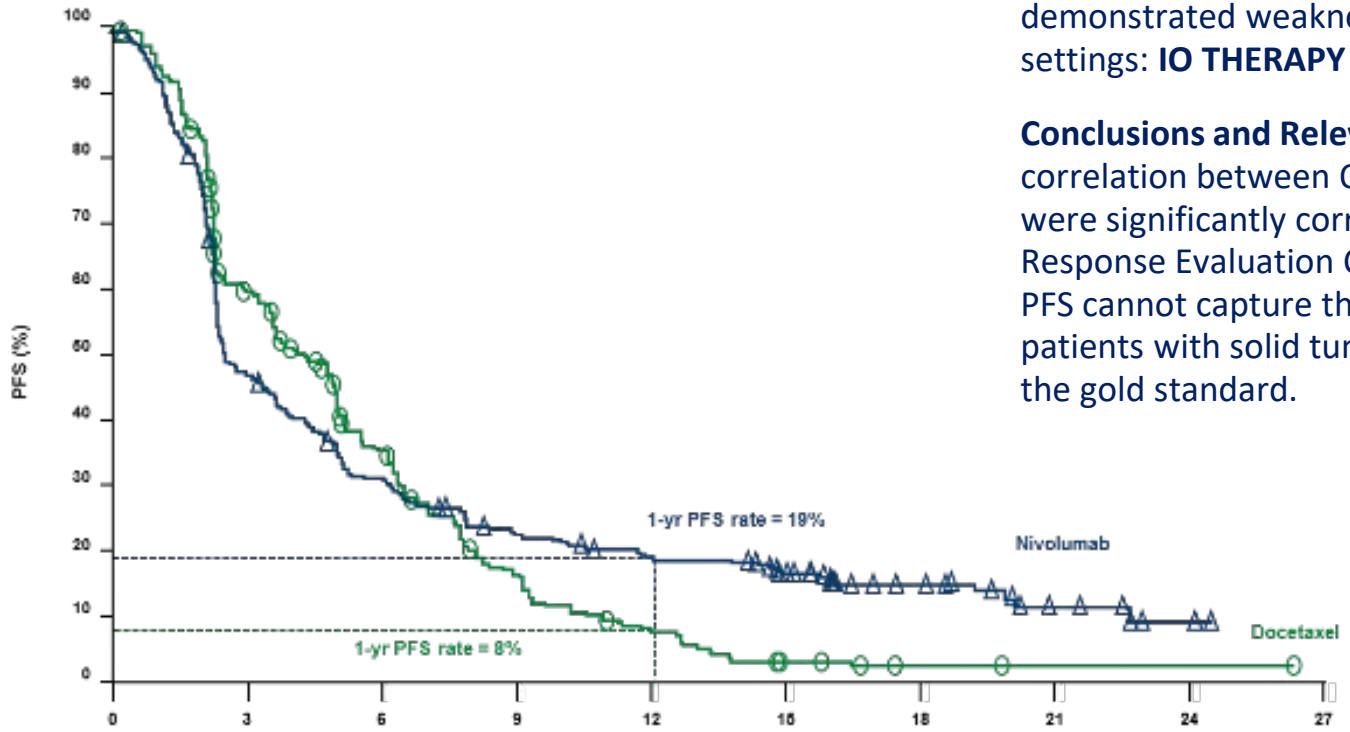


Response and Immunotherapy

- **We know**
  - Unusual response patterns well described *especially in melanoma*
  - Immune based therapies are a major advancement in patient care, as access to immunotherapies increases, OS will be increasingly confounded as a primary endpoint in randomized studies due to crossover, so reliance of PFS will be critical
  - Recent analyses of randomized studies indicate that immunotherapies may yield an improvement in OS with minimal or no improvement in PFS, as assessed by RECIST 1.1

Response and Immunotherapy

- **We don’t know**
  - True frequency of unusual response patterns
  - Optimal response criteria or how to implement them



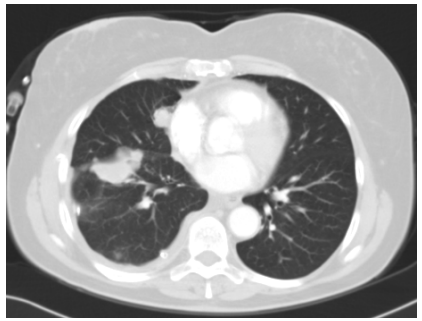
RECIST progression free survival (PFS) has demonstrated weaknesses across a number of settings: **IO THERAPY**

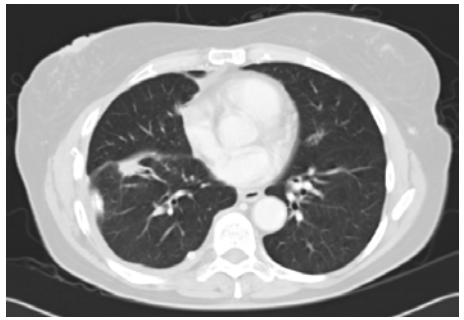
Conclusions and Relevance There was no significant correlation between OS and PFS … but their HRs were significantly correlated. …..Traditional Response Evaluation Criteria in Solid Tumors–based PFS cannot capture the benefit of PD-1 inhibitors in patients with solid tumors, and OS should remain the gold standard.

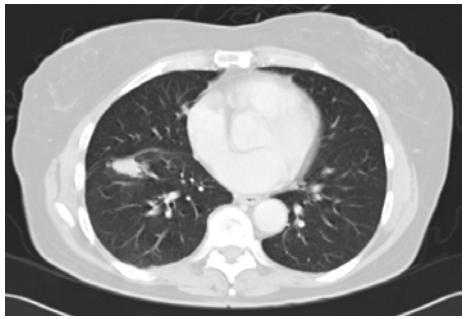
CheckMate 057 trial, Paz-Arez et al, ASCO, 2015 JAMA Network Open. 2018;1(2):e180416

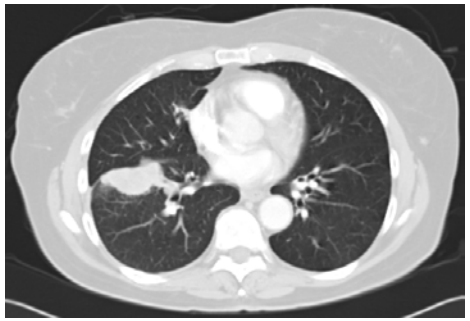
Variable Presentation of Progressive Disease Complicates Assessment

Example 1

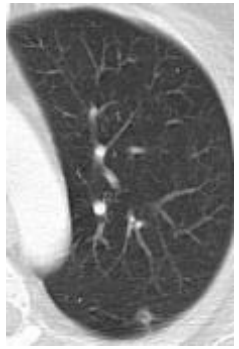

Baseline

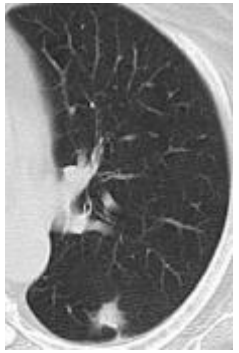
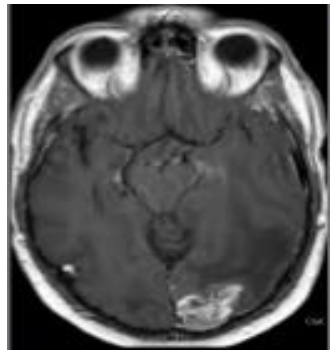

3m: Response


14m: RECIST PD


30m: Follow-up

Example 2


Baseline



Cycle 4

Are these two PD's the same ?

Oxnard et al, ASCO, 2012

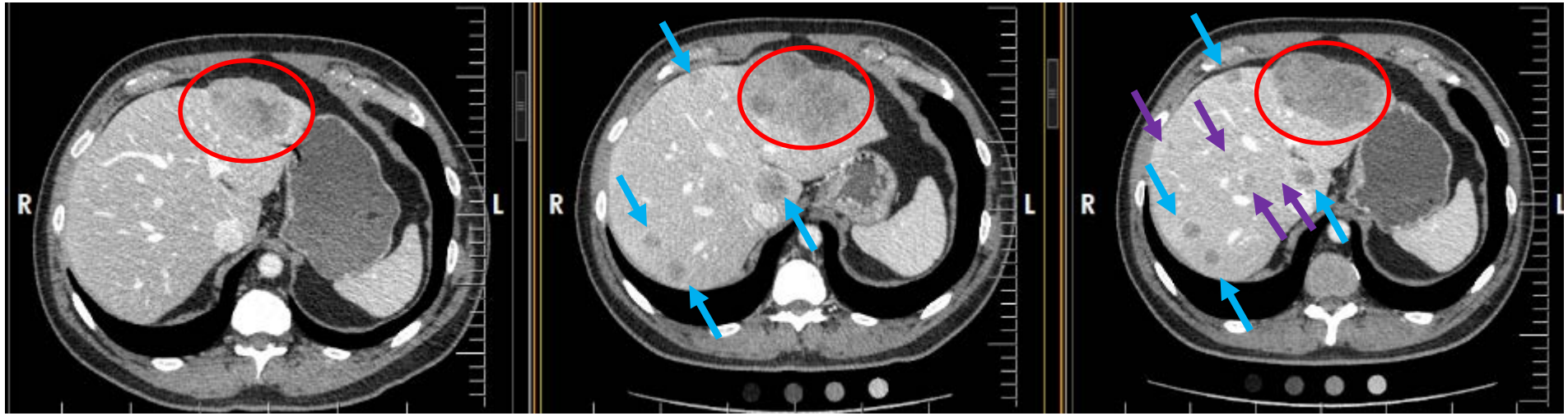
Background: Immune Response Criteria

- irRC - ***consensus*** based recommendations (2009)
  - Based on WHO, bi-dimensional measures
  - New lesion measures included in sum of measures of target lesions
- Subsequent modifications proposed
  - Based on RECIST/RECIST 1.1

Wolchok JD, et al. *Clin Cancer Res*. 2009;15:7412–20.

Variable Presentation of Progressive Disease Complicates Assessment

- The irRC are guidelines but are not definitive rules:



Baseline

Cycle 2 – SD or PD

Cycle 4
Confirming PD ?

- irRC / irRECIST are based more on instinct rather than outcomes correlations
- Analysis of existing imaging and outcomes can standardize and optimize irRECIST

Response Criteria Summarized

	RECIST 1.1	irRC (+ unidimensional variant)	"irRECIST /irRECIST1.1" variants
Bi/unidimen.?	Unidimensional	**Bidimensional**	Unidimensional
N Target	5	**15; (≥5 × 5mm)**	10 / 5 (≥10mm/ ≥10mm (15 for nodes))
New target lesions added to sum or measures (SOM)?	No	(≥5 × 5mm); **Yes** - does not automatically define PD	(RECIST or RECIST 1.1 rules) **Yes**
How many ?	NA	10 visceral, 5 cutaneous	10 / 5 (RECIST 1.1 rules)
Definition of progression (PD)	≥ 20% ↑ compared to nadir (≥ 5mm ↑)	≥ 25% ↑ compared to baseline (BL), nadir/**reset BL**	≥ 20% ↑ compared to nadir (≥ 5mm ↑)
Confirmation ?	No	Yes, required	Yes, recommended
How confirmed?	NA	**Not defined**	**Not defined;** not improved? Imager feels is worse?

The Tower of Babel !

iRECIST Addresses

- Standardise data management and collection - develop consensus guidelines (termed iRECIST)
- Recommendations on
  - Terminology (“i” prefix)
  - Data to be collected after RECIST 1.1 defined PD
  - Definition of “events”
  - Primary endpoints versus exploratory endpoints
- They are not treatment decision guidelines
- These are not (yet) validated response criteria
- They are internationally agreed data recommendations from academia, pharma and regulatory authorities

iRECIST vs RECIST 1.1: **Unchanged**

RECIST 1.1	iRECIST
Definitions of measurable, non-measurable disease	√
Definitions of target (T) and non target (NT) lesions	√
Measurement and management of nodal disease	√
Calculation of the sum of measurement (SOM)	√
Definitions of CR, PR, SD and their duration	√
Confirmation of CR and PR	√
Definition of progression in T and NT (iRECIST terms i-unconfirmed progression (iUPD))	√

iRECIST vs RECIST 1.1: **Changes**

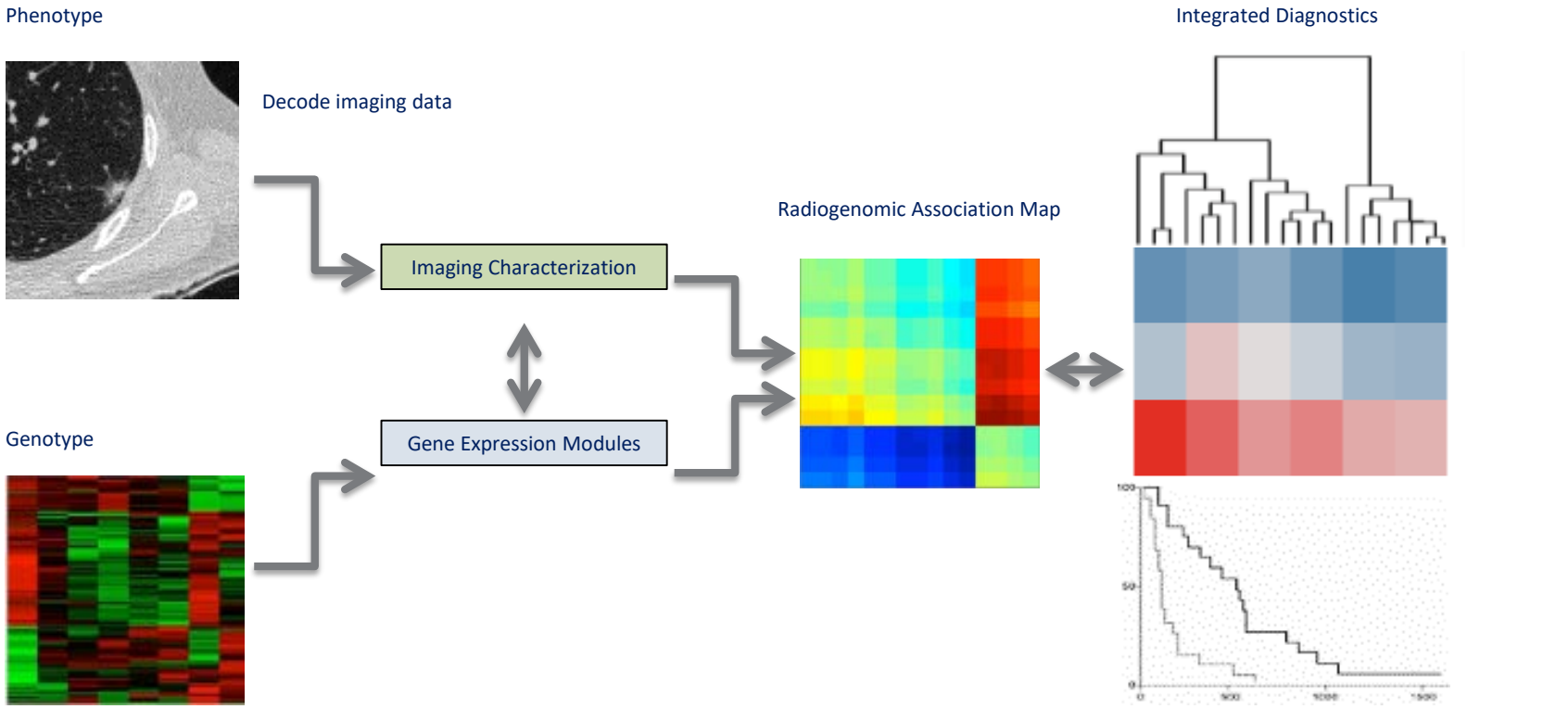
RECIST 1.1	iRECIST
Management of new lesions	**NEW**
Time point response after RECIST 1.1 progression	**NEW**
Confirmation of progression required	**NEW**
Collection of reason why progression cannot be confirmed	**NEW**
Inclusion and recording of clinical status	**NEW**

iRECIST vs RECIST 1.1: Changes

- Treatment past PD should only be considered if patient clinically stable*
  - No worsening of performance status.
  - No clinically relevant ↑in disease related symptoms
  - No requirement for intensified management of disease related symptoms (analgesics, radiation, palliative care)
- Record the reason iUPD not confirmed
  - Not stable
  - Treatment stopped but patient not reassessed/imaging not performed
  - iCPD never occurs
  - Patient has died

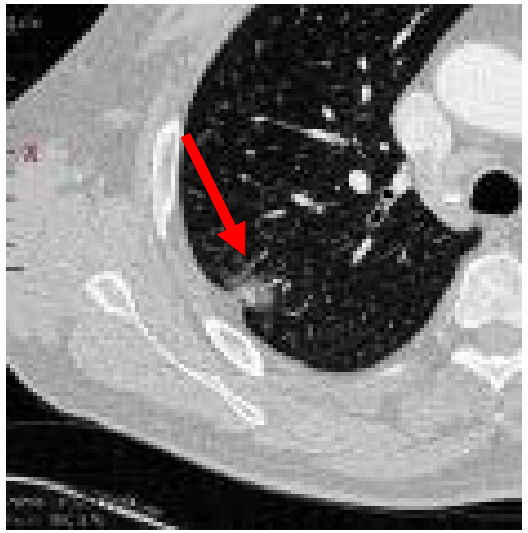
* recommendation – may be protocol specific

Radiomics and immune-related patterns of response

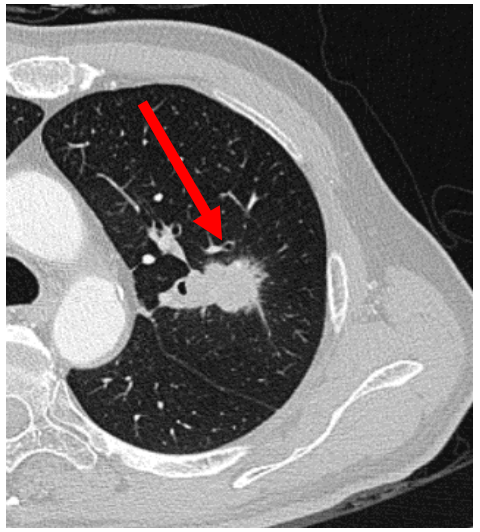


- Quantitative molecular imaging provides a potential platform for linking specific imaging traits with specific gene expression patterns that inform the underlying cellular pathophysiology
- Imaging features may serve as molecular surrogates that contribute to the diagnosis, prognosis, and likely gene-expression-associated treatment response of various forms of human cancer

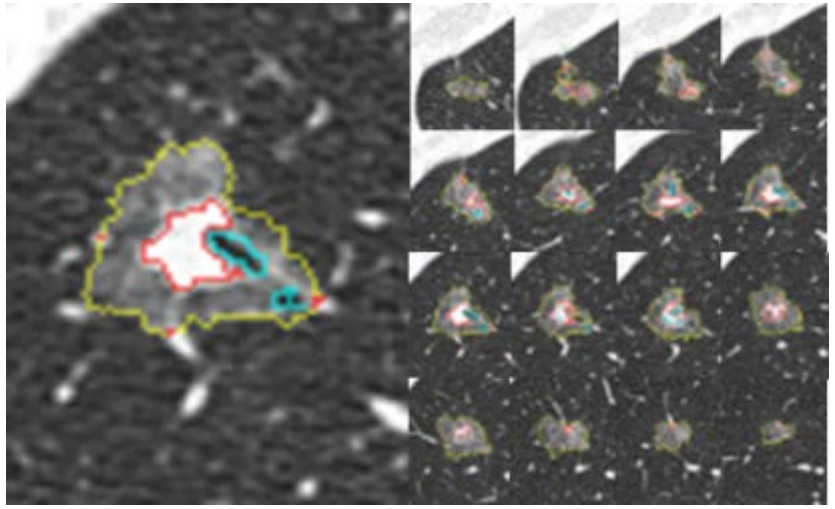
Radiomics
Creating a link between molecular diagnostics and diagnostic imaging



E21mis; EX-S



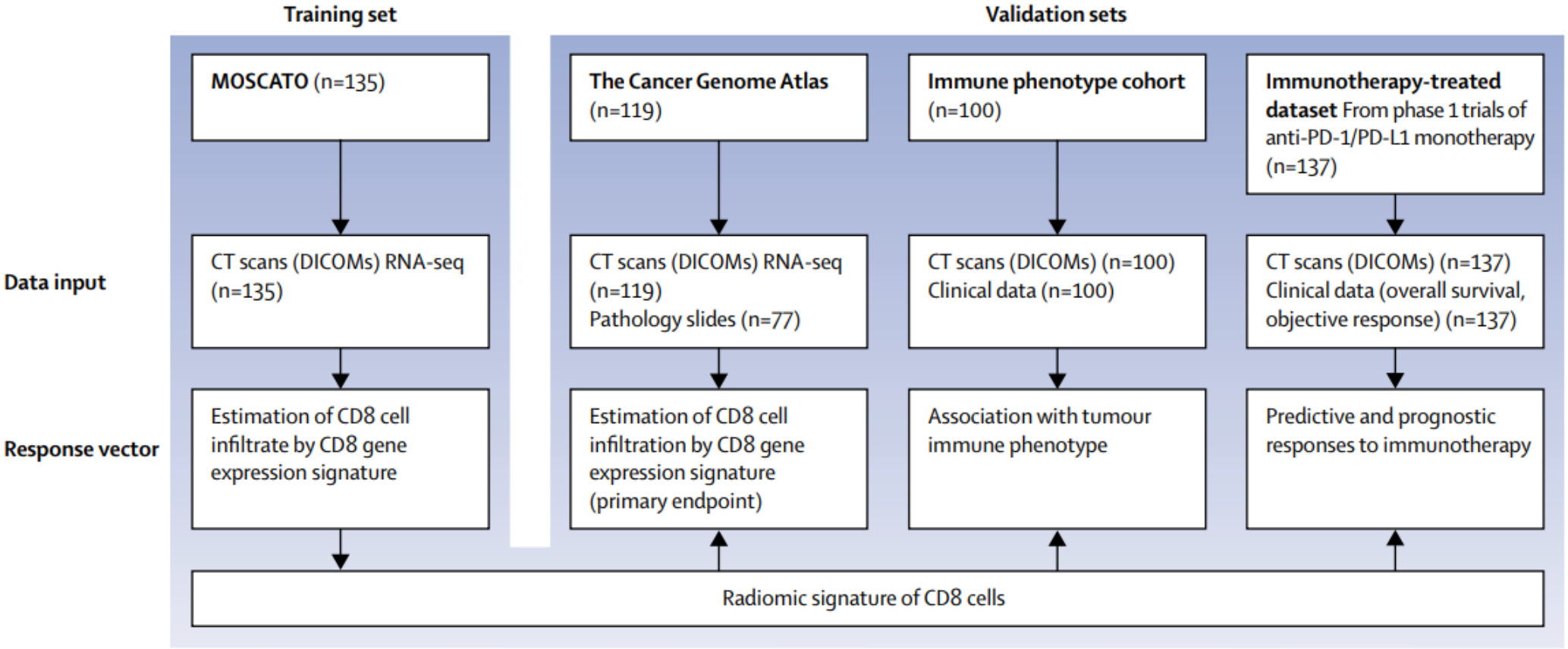
WT; EX-S



Lee HJ, Radiology. Jul 2013

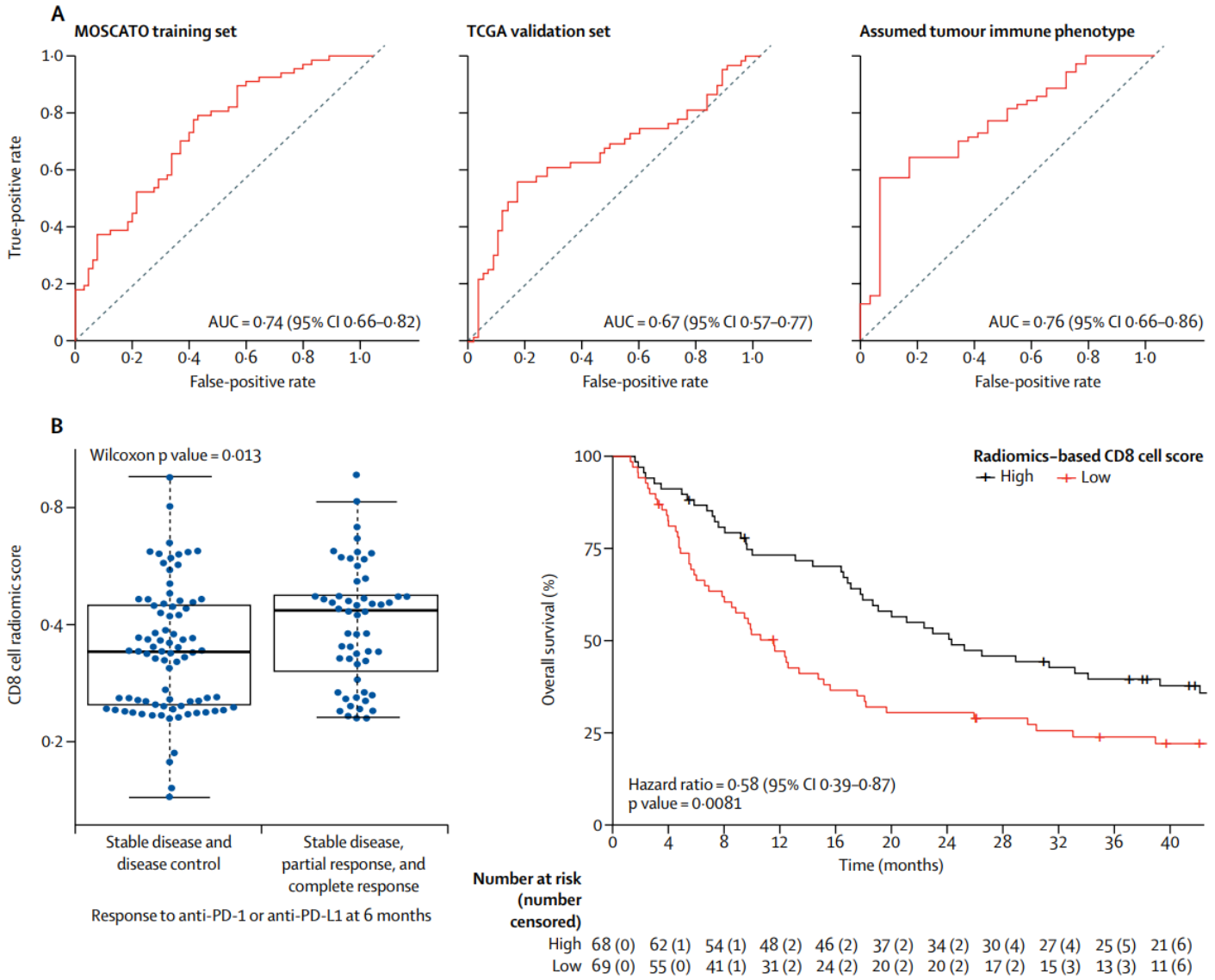
Radiomics
Creating a link between molecular diagnostics and diagnostic imaging

A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study



Lancet Oncol 2018; 19: 1180–91

A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study



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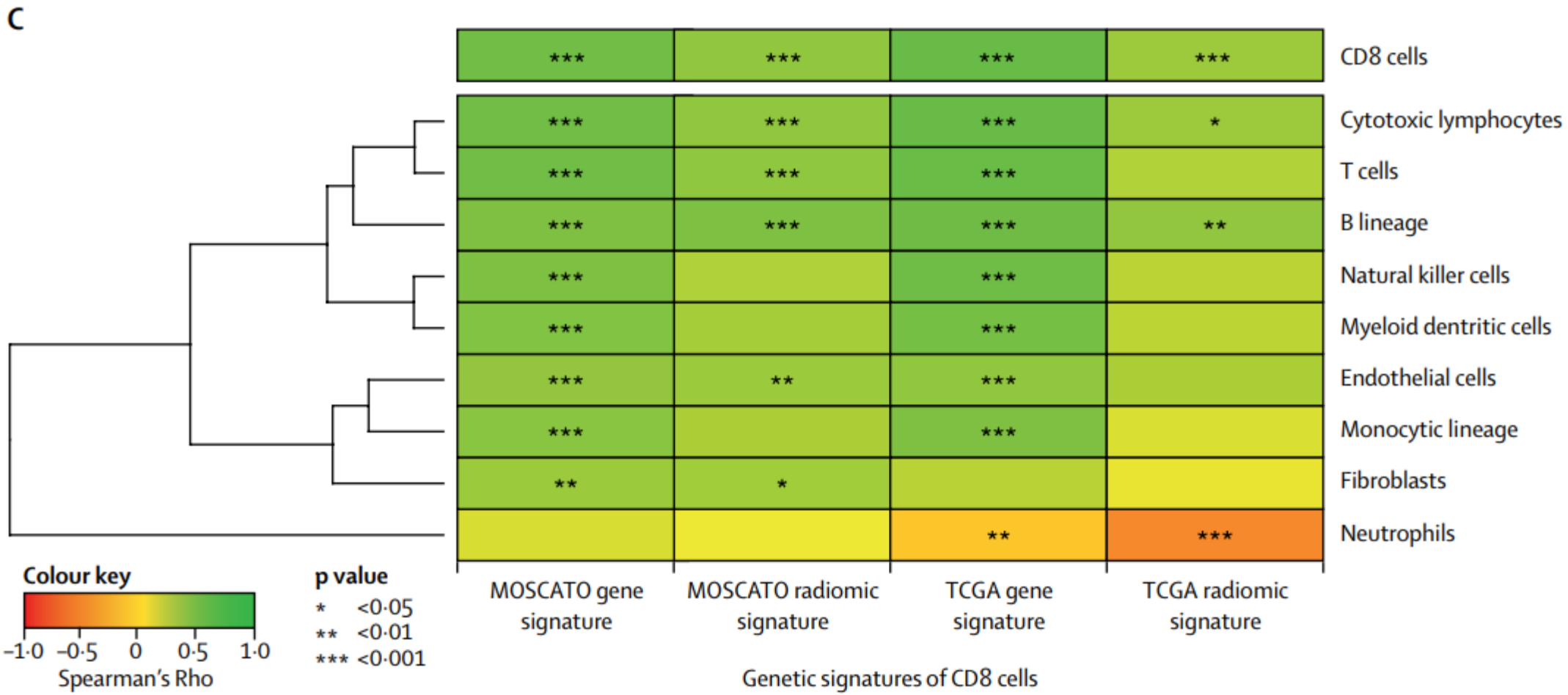

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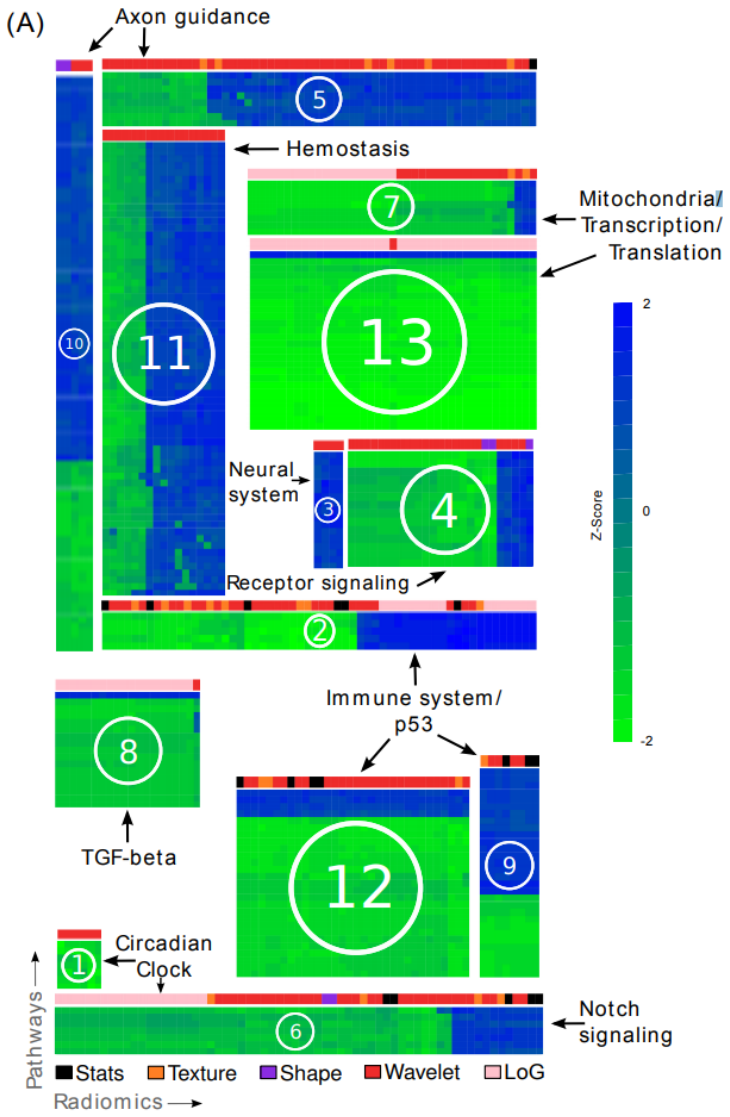
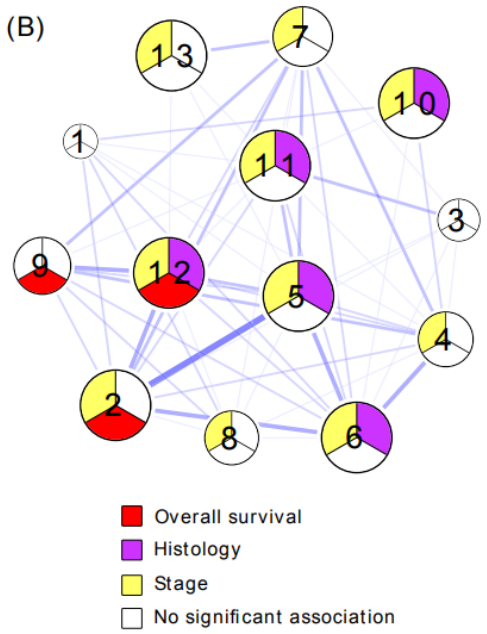
Defining the biological basis of radiomic phenotypes in lung cancer



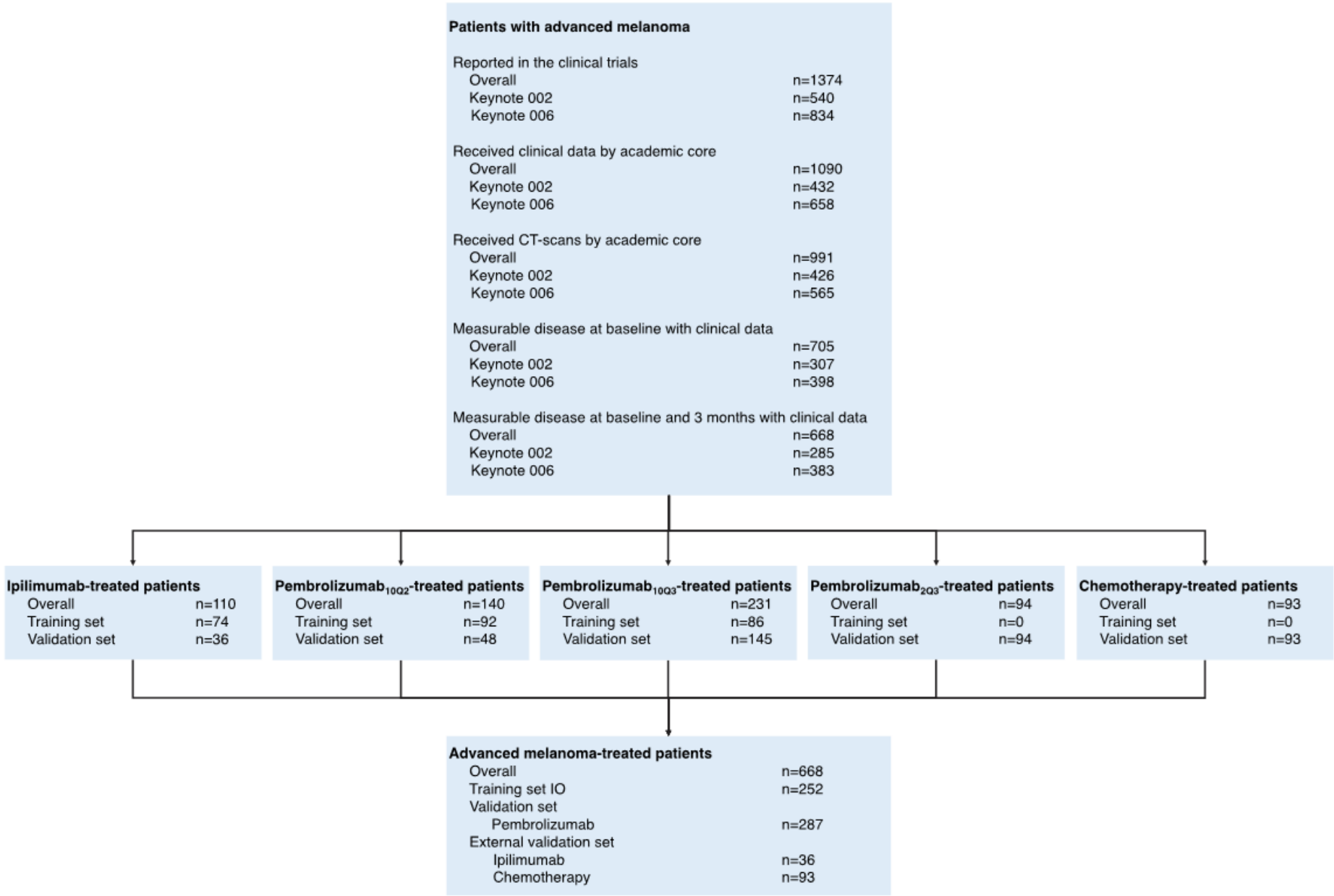


Module	nr	np	Radiomic	Pathway
M1	6	7	Wavelet texture gray-level runs	Lipid and lipoprotein metabolism, Notch signaling, circadian clock
M2	58	5	Wavelet intensity entropy; Laplace of Gaussian intensity standard deviation	Immune system, p53
M3	4	17	Wavelet minimum intensity	Neural system, axon guidance
M4	25	14	Intensity variance and mean; wavelet minimum intensity min	Biological oxidations, signaling by insulin receptor, signaling by GPCR, neuronal system
M5	58	8	Wavelet texture gray-level runs; wavelet intensity range and median; (wavelet) texture information correlation and cluster tendency	Axon guidance and synaptic transmission, lipoprotein metabolism, cell type determination
M6	64	7	Laplace of Gaussian standard deviation; wavelet texture gray-level runs; wavelet texture cluster tendency	Circadian clock, signaling by Notch
M7	39	8	Laplace of Gaussian intensity entropy; wavelet intensity variance; Laplace of Gaussian texture information correlation	Mitochondria, Pol III transcription
M8	20	17	Laplace of Gaussian standard deviation	TCA cycle and electron transport, TGF-beta receptor signaling, response to stress, transcription regulation, protein synthesis,
M9	8	30	Intensity variance; wavelet intensity variance	Immune system, p53, cell cycle regulation checkpoints, cell-cell interaction, circadian clock
M10	5	83	Shape surface (SH); wavelet texture gray-level runs	Axon guidance, neuronal system, (innate) immune system, hemostasis, FGFR signaling, TGF-beta receptor signaling, Notch signaling, circadian clock
M11	17	66	Wavelet intensity range; wavelet texture information correlation	Hemostasis, neural system
M12	32	27	Wavelet texture entropy; intensity variance; wavelet texture cluster tendency	P53, immune system
M13	39	26	Intensity entropy	Gene expression regulation, Pol II/III transcription

DOI: 10.7554/eLife.23421.012

Grossmann et al. eLife 2017;6:e23421.

Radiomic Change Analysis – IO - Melanoma



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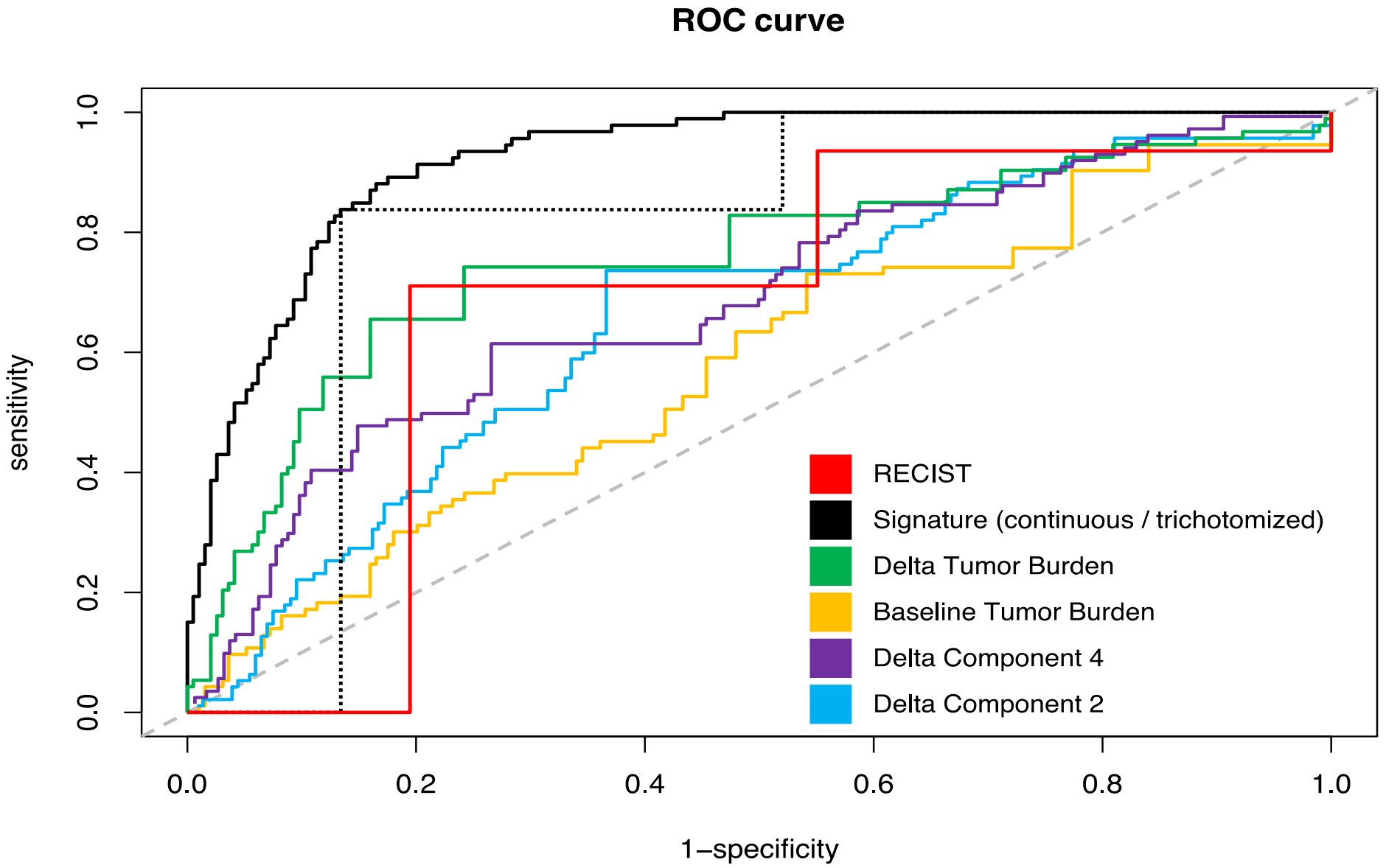

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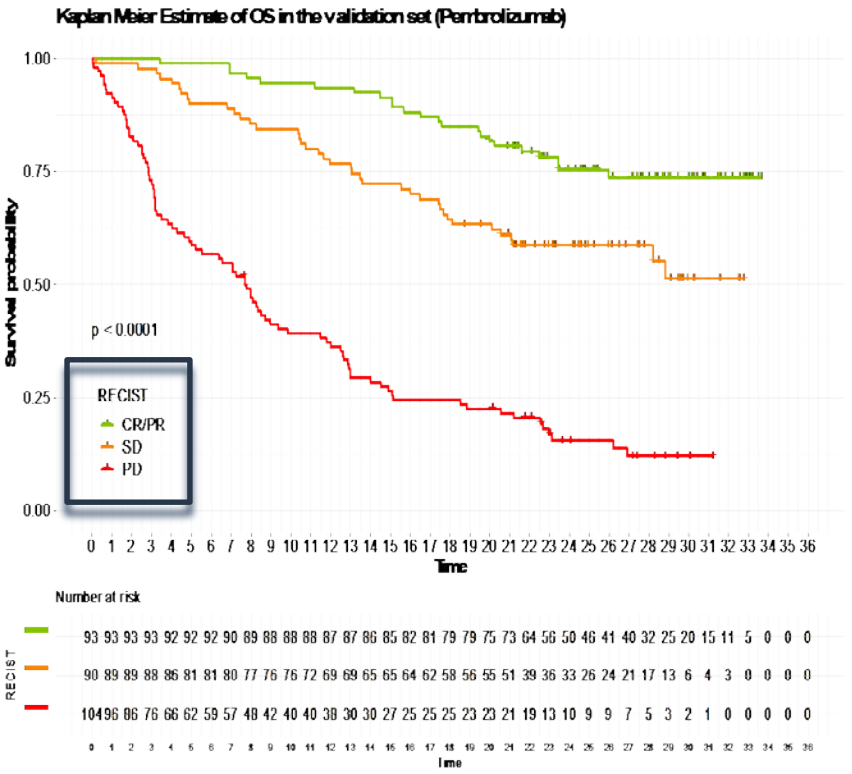
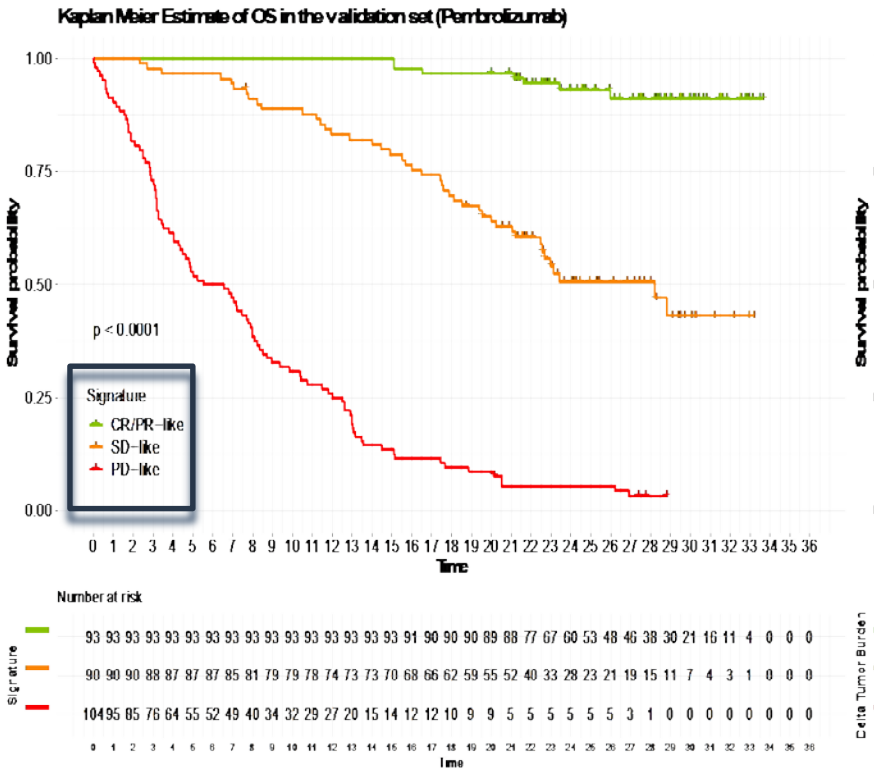
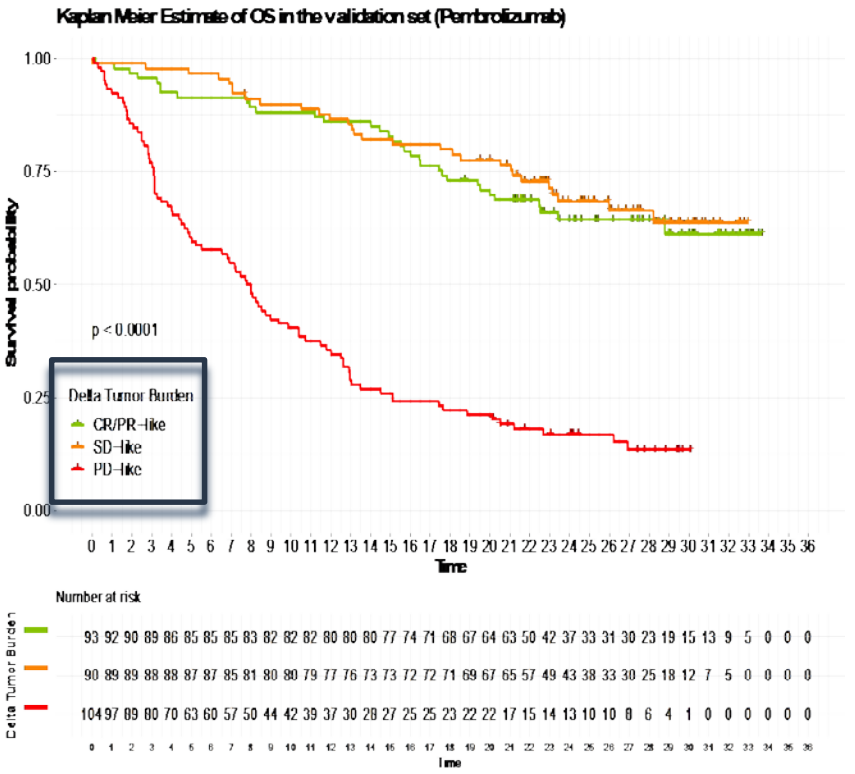






Pseudoprogression – Is there a signature?

- The antitumor activity of Pembrolizumab is difficult to evaluate due to atypical patterns of response and progression

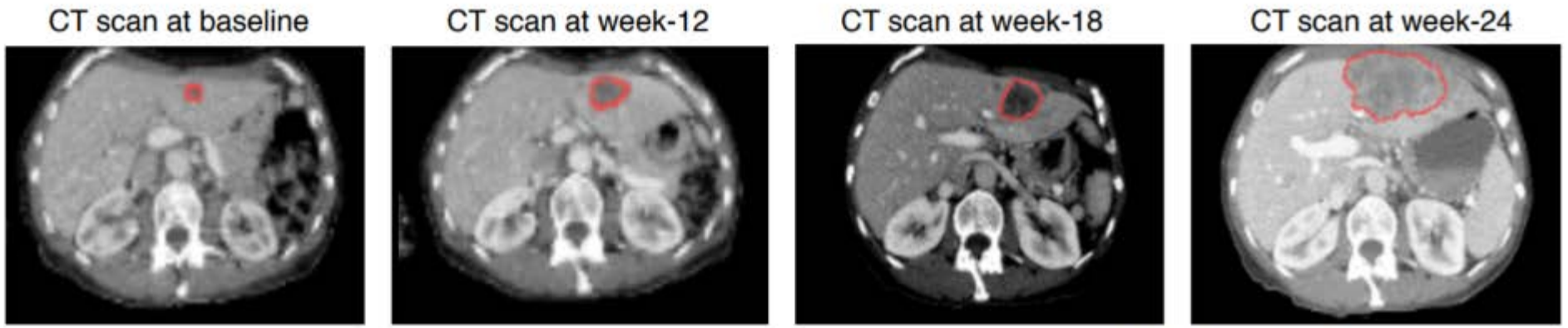
- Patterns seen:
  - Late Pseudoprogression
  - Early Pseudoprogression
  - Heterogeneous progression
  - Long term partial responders

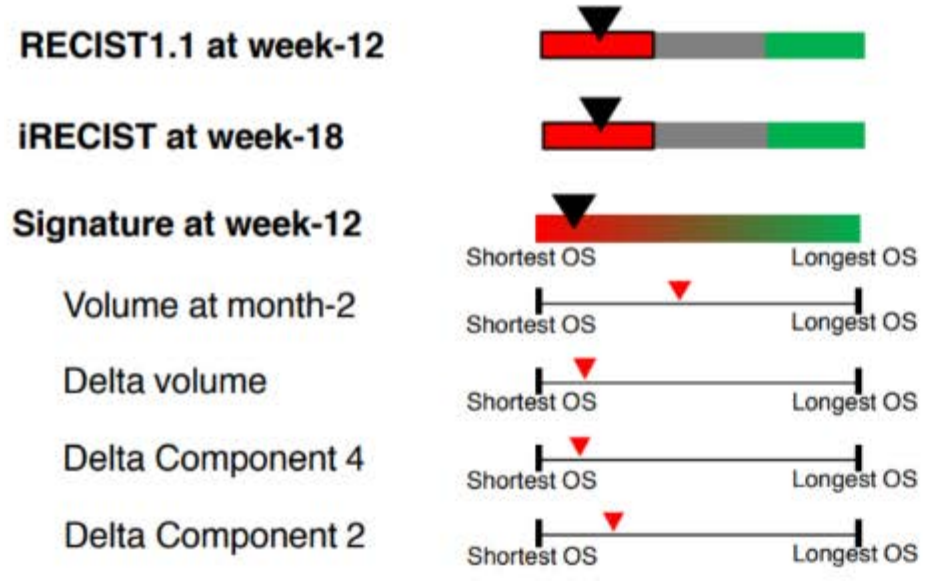
Key Features – Biologic Relevance

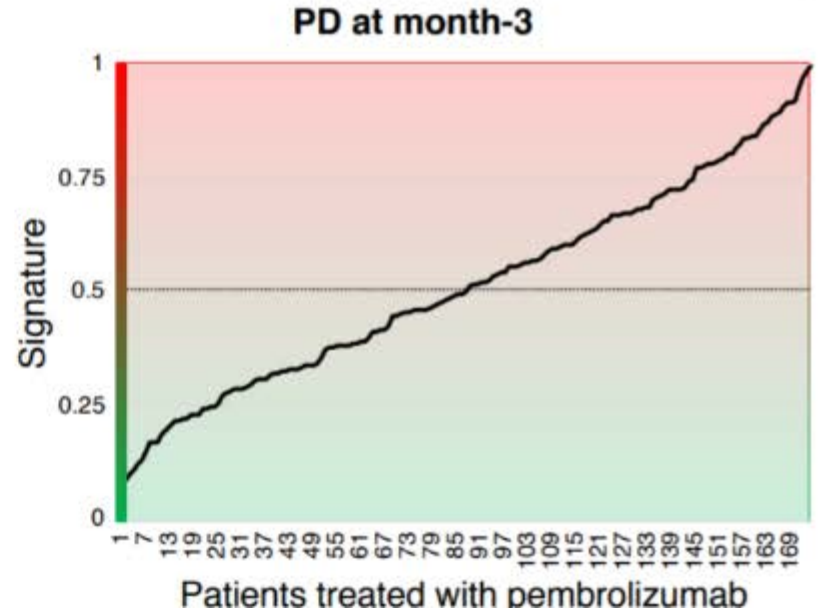
Immunotherapy

Key Features – Biologic Relevance

Progression per RECIST 1.1 at week-12 confirmed by iRECIST at week-18

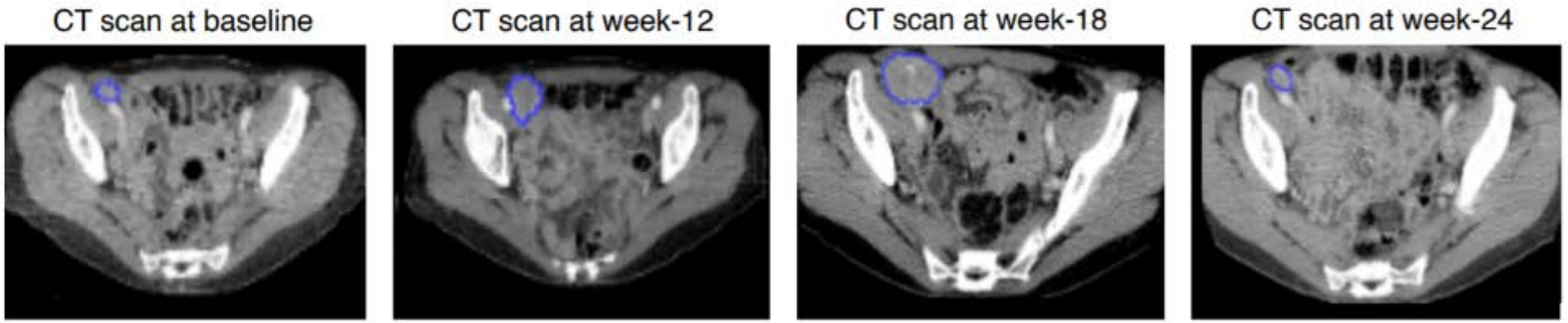


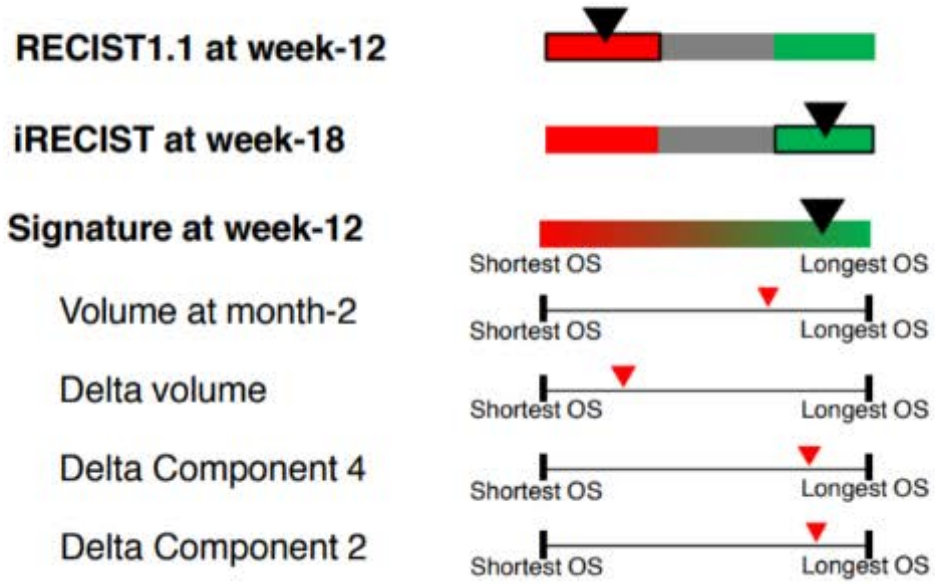


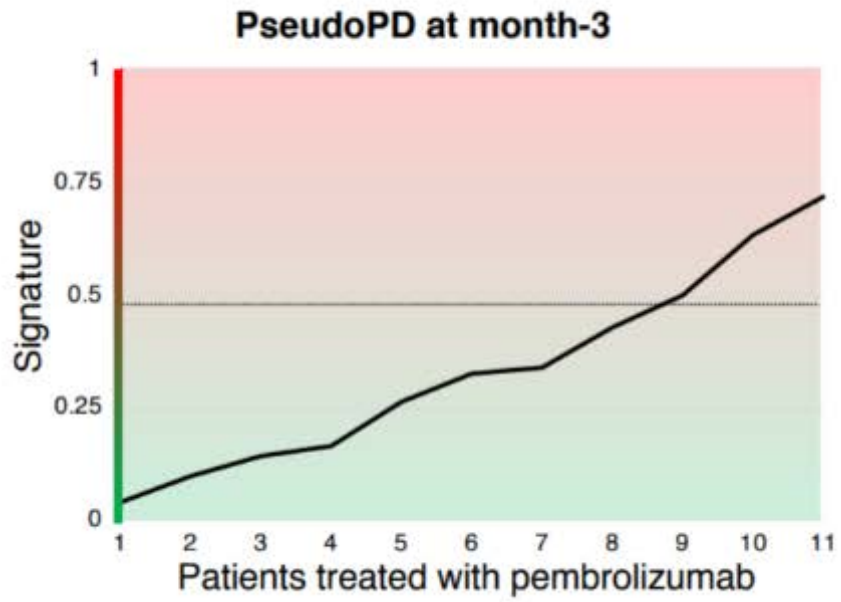


Key Features – Biologic Relevance

Progression per RECIST 1.1 at week-12 reclassified as pseudoprogression by iRECIST at week-18







Assessing Agreement between Radiomic Features Computed for Multiple CT Imaging Settings

Settings / QIF groups	1.25S vs 2.5S	1.25L vs 2.5L	2.5S vs 5S	2.5L vs 5L	1.25S vs 5S	2.5S vs 5L	1.25S vs 5L	1.25L vs 5L	5L vs 5S	1.25S vs 2.5L	2.5L vs 2.5S	1.25L vs 1.25S	1.25L vs 2.5S	2.5L vs 5S	1.25L vs 5S	Average CCC of QIF groups
1	0.980	0.994	0.973	0.963	0.945	0.848	0.808	0.969	0.827	0.905	0.927	0.883	0.910	0.894	0.881	0.914
2	0.980	0.980	0.981	0.912	0.954	0.970	0.964	0.839	0.966	0.942	0.895	0.884	0.825	0.843	0.764	0.913
3	0.989	0.986	0.949	0.938	0.910	0.909	0.900	0.899	0.882	0.907	0.888	0.902	0.878	0.787	0.758	0.899
4	0.984	0.939	0.942	0.898	0.931	0.967	0.948	0.815	0.963	0.910	0.923	0.823	0.844	0.819	0.713	0.895
5	0.954	0.945	0.949	0.909	0.943	0.820	0.825	0.867	0.876	0.817	0.865	0.855	0.903	0.875	0.864	0.884
6	0.939	0.946	0.916	0.896	0.919	0.877	0.894	0.902	0.824	0.892	0.858	0.883	0.853	0.806	0.822	0.882
7	0.978	0.974	0.936	0.946	0.928	0.842	0.851	0.941	0.790	0.837	0.822	0.833	0.825	0.757	0.756	0.868
8	0.887	0.763	0.827	0.758	0.855	0.888	0.888	0.825	0.883	0.809	0.781	0.851	0.911	0.739	0.844	0.834
9	0.898	0.953	0.900	0.892	0.800	0.691	0.656	0.893	0.637	0.707	0.731	0.647	0.694	0.704	0.636	0.763
10	0.804	0.783	0.671	0.729	0.673	0.750	0.723	0.812	0.775	0.730	0.750	0.830	0.771	0.624	0.664	0.739
11	0.915	0.761	0.840	0.706	0.691	0.788	0.639	0.699	0.847	0.665	0.713	0.546	0.618	0.636	0.575	0.709
12	0.913	0.925	0.922	0.944	0.791	0.609	0.635	0.803	0.602	0.636	0.582	0.562	0.512	0.538	0.433	0.694
13	0.635	0.735	0.675	0.755	0.301	0.848	0.438	0.415	0.867	0.748	0.893	0.901	0.576	0.560	0.285	0.642
14	0.913	0.832	0.813	0.741	0.850	0.761	0.754	0.557	0.673	0.488	0.491	0.374	0.371	0.409	0.289	0.621
15	0.906	0.772	0.824	0.658	0.807	0.772	0.692	0.426	0.654	0.385	0.478	0.279	0.324	0.339	0.195	0.567
16	0.941	0.790	0.929	0.781	0.852	0.496	0.553	0.527	0.495	0.426	0.388	0.281	0.259	0.373	0.246	0.556
17	0.857	0.835	0.826	0.766	0.696	0.464	0.577	0.566	0.410	0.428	0.321	0.341	0.264	0.275	0.209	0.522
18	0.965	0.631	0.976	0.660	0.922	0.560	0.578	0.355	0.568	0.278	0.252	0.101	0.073	0.264	0.063	0.483
19	0.892	0.674	0.933	0.709	0.787	0.264	0.372	0.350	0.226	0.215	0.161	0.110	0.084	0.135	0.068	0.399
20	0.637	0.856	0.471	0.761	0.277	0.373	0.598	0.574	0.127	0.405	0.239	0.256	0.159	0.077	0.046	0.390
21	0.777	0.560	0.525	0.460	0.289	0.634	0.672	0.182	0.322	0.354	0.245	0.164	0.116	0.112	0.055	0.364
22	0.611	0.534	0.292	0.339	0.116	0.523	0.466	0.155	0.181	0.369	0.184	0.180	0.088	0.044	0.016	0.273
23	0.801	0.711	0.712	0.563	0.489	0.059	0.097	0.297	0.034	0.039	0.025	0.021	0.014	0.015	0.008	0.259
Average CCC of setting pairs	0.875	0.820	0.815	0.768	0.725	0.684	0.674	0.636	0.627	0.604	0.583	0.543	0.515	0.504	0.441	

#Group	Non-redundant QIF group
1	Shape_SI9
2	Sigmoid-Offset-Mean
3	LoG_Entropy-s2.5
4	Sigmoid-Amplitude-Mean,Intensity_Mean_2D,Density_Mean,GLCM_Sum-Average,GLCM_Sum-Variance
5	LoG_Mean-s0,LoG_Mean-s2.5
6	Shape_SI6,Shape_SI7
7	Shape_SI2,Run_PLU,Shape_SI5,Shape_SI3,Shape_SI4,LoG_Uniformity-s2.5,Run_GLU,Uni,Bi,Vol
8	Eccentricity_2D
9	Shape_SI8
10	Solidity_2D,Compact-Factor,Round-Factor_2D
11	Density_Kurtorsis,Intensity_Kurtorsis_2D
12	EdgeFreq_Contrast,GTDM_Contrast
13	GTDM_Strength,EdgeFreq_Coarseness,GTDM_Coarseness
14	Wavelet_LH,Wavelet_H,Gabor_Energy-dir90
15	Gabor_Energy-dir0,Wavelet_V,Wavelet_LV,Wavelet_LD,Gabor_Energy-dir45,Wavelet_D,Gabor_Energy-sum,Gabor_Energy-dir135
16	Density_Skewness,Intensity_Skewness_2D,GLCM_Entropy-2,GLCM_Entropy-1,Run_SPE,Run_PP,GLCM_Diff-Entropy,EdgeFreq_Mean,LoG_Entropy-s0
17	Intensity_SD_2D,Density_SD,Laws_Energy-1,GLCM_Contrast,GLCM_Squares,GLCM_Cluster-Tendency,Laws_Energy-2,Laws_Energy-11,Laws_Energy-8,Laws_Energy-5,Laws_Energy-3,Laws_Energy-6,Laws_Energy-12
18	Spatial_Corr
19	Run_LPE,LoG_Uniformity-s0,GLCM_ASM,GLCM_Max-Prob,GLCM_Diff-Variance,GLCM_Homogeneity,GLCM_IDM
20	Fractal_Dimension-Mean,GLCM_IMC1
21	Sigmoid-Slope-Mean
22	GLCM_IMC2,GLCM_Corr,GLCM_MCC
23	Laws_Energy-10,Laws_Energy-14,GTDM_Complexity,Laws_Energy-4,Laws_Energy-13,Laws_Energy-7,Laws_Energy-9

Group (a) Fixing reconstruction algorithm while changing slice thickness

Group (b) Fixing slice thickness while changing reconstruction algorithm

Group (c) Smooth reconstruction algorithm (S) plus thin slice thickness versus sharp reconstruction algorithm (L) plus thick slice thickness

Group (d) Sharp reconstruction algorithm (L) plus thin slice thickness versus smooth reconstruction algorithm (S) plus thick slice thickness

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SPECIAL ARTICLE

Starting the fight in the tumor: expert recommendations for the development of human intratumoral immunotherapy (HIT-IT)

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Response Criteria for Intratumoral Immunotherapy in Solid Tumors: itRECIST

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“Measure what is measurable, and make measurable what is not so”

- Galileo Galilei

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