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Cancer Immunotherapy:

Criteria of Assessment with Imaging iRECIST, irRECIST, irRC, RECIST1.1

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What is Immunotherapy?

Traditional Chemotherapies

Direct killing of tumor cells

Interferes with cell division

- DNA damaging alkylating agents
- DNA intercalating agents, anthracyclines
- DNA synthesis-blocking antimetabolites

Immunotherapies

Immune-mediated cell killing

Activates patient's immune system to detect and eliminate tumor cells

- Vaccines
- Recombinant cytokines
- Preformed monoclonal antibodies
- **Immunomodulatory antibodies**

Anti-tumor immune response

1. Cancer-cell antigen presented on APC
2. T cell recognition, activation, response
3. T cell proliferation
4. T cell migration to tumor site
5. Immune-mediated tumor cell death
   - CD8+ cytolytic T cells kill tumor cells
   - CD4+ helper T cells secrete cytokines

T cell activation and response are regulated by a balance of stimulatory and inhibitory signals called **immune checkpoints**, which control the magnitude of response

Immunotherapy Treatment Takes Time

Immunotherapy treatment is a 3-step process

1 → 2 → 3

Administration of drug activates immune system = **cellular response**

Cellular response begins to attack tumor cells = **anti-tumor response**

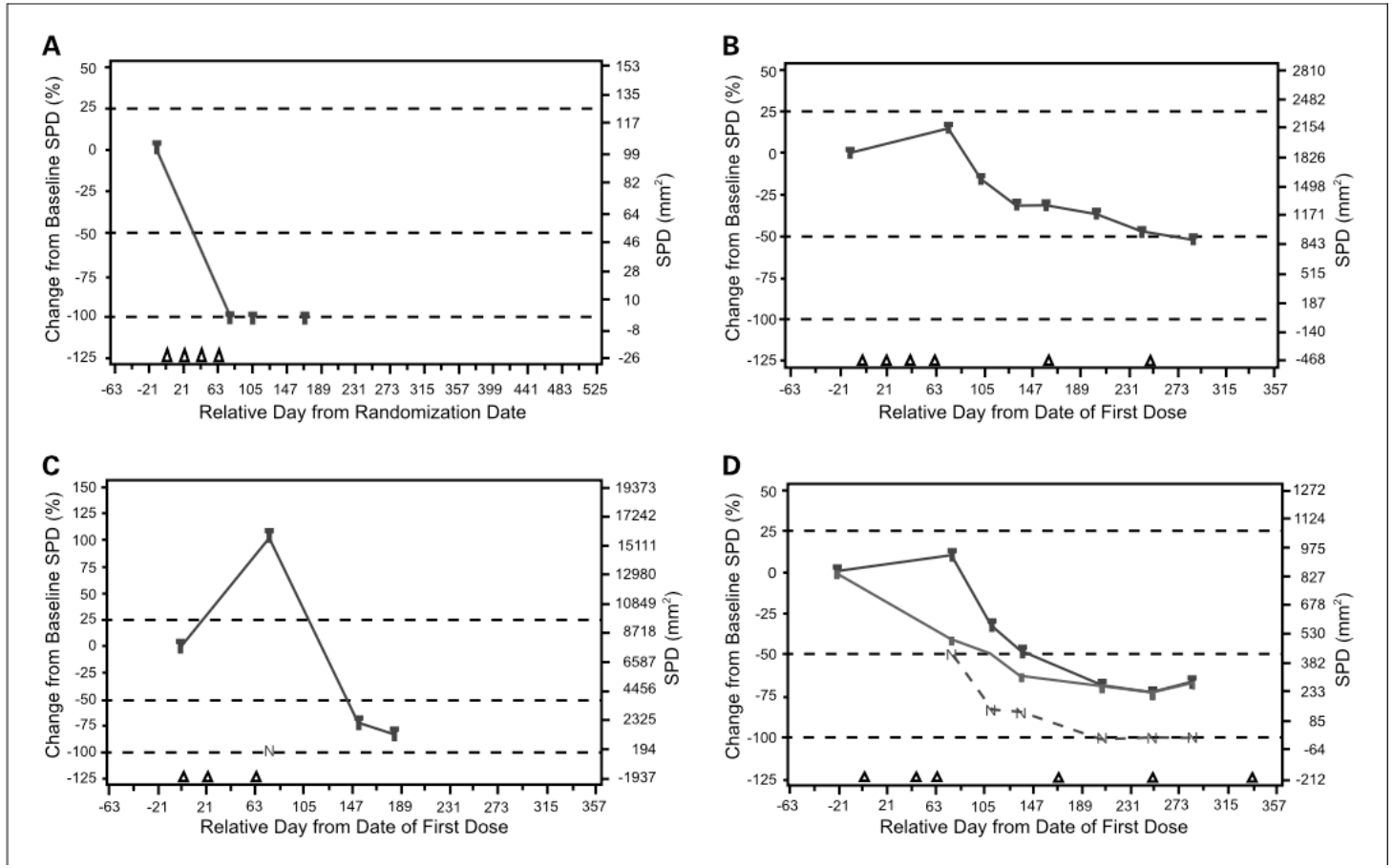
Anti-tumor response reduces tumor burden and impacts a patient's survival = **treatment response**

This process takes time!

- For treatment of melanoma patients with ipilimumab, it took 30 months to see a complete response
- This is very unlike chemotherapy treatment, where cell killing/tumor shrinkage is almost immediate

Novel Patterns of Response

Novel response patterns for immunotherapies were mapped out using Ipilimumab data



A. Immediate response, no new lesions

B. Durable stable disease

C. Response after initial tumor burden increases **Flare effect**

D. Response with new lesions

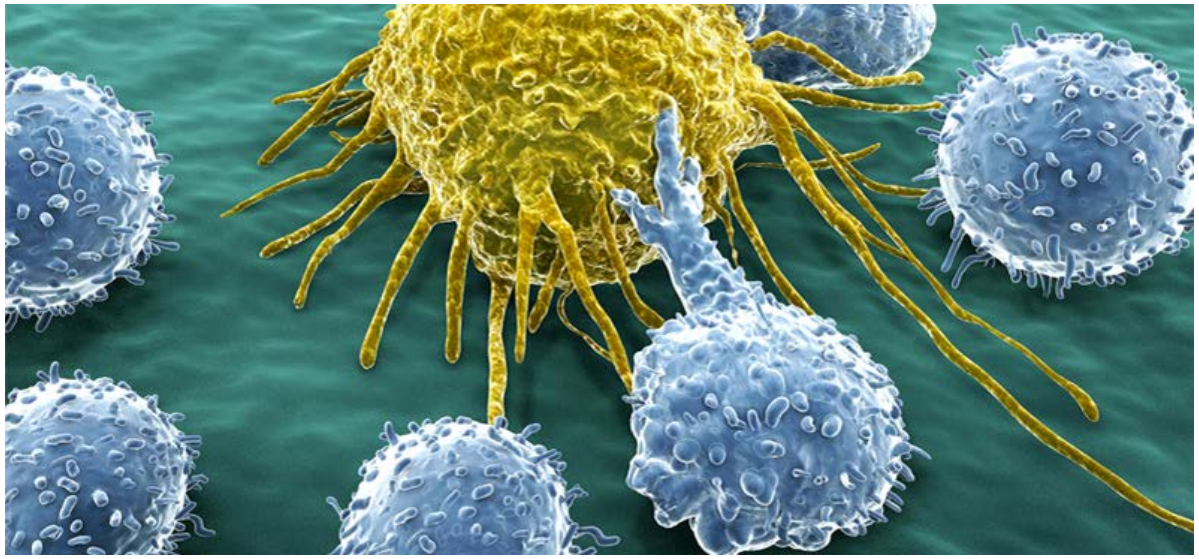
[Reproduced with permission Wolchok, 2009]

Accurate Evaluation of Clinical Response

Immunotherapies do not exhibit the same patterns of response as traditional chemotherapies

Applying chemotherapy-based response assumptions to immunotherapy trials can result in:

- Inaccurate interpretation of the response
- Premature termination of therapy
- Unnecessary removal of patients from clinical trials



Immune-related Response Criteria

RECIST1.1 remains the gold standard for evaluating treatment response in solid tumors

- However, new lesions or flare equals progressive disease under RECIST1.1 guidelines
- Inaccurate interpretation of response can result in premature termination of therapy and patient removal from a trial

Need new response criteria

- **Immune-related response criteria (irRC)**, 2009
  - Based on WHO criteria
- **Immune-related RECIST (irRECIST)**, 2013
  - Combines elements of irRC and RECIST
- **Immune RECIST (iRECIST)**, 2017
  - Standardizes and validates immune response criteria
- All account for novel response patterns seen with immunotherapies

iRECIST 2017

Seymour et al. Lancet Oncol 2017;18:e143-52

- Developed by the RECIST working group
- Standardizes and validates immune response criteria
- Addresses key questions about tumor assessment with immunotherapy

- Resetting the bar if RECIST Progressive Disease (PD) is followed at next time point (TP) by tumor shrinkage
- New overall response is defined as “iUPD” or immune unconfirmed progressive disease

iRECIST/RECIST 1.1

RECIST 1.1	iRECIST
Definition measurable, non measurable lesion	Unchanged
Definition target and non target	Unchanged
Measurement of nodal lesion	Unchanged
Calculation of sum of diameters (SoD)	Unchanged
Definition of CR,PR,SD and duration	Unchanged
Confirmation of CR and PR	Unchanged
Definition of progression TL and NTL	Unchanged

RECIST 1.1	iRECIST
Management of new lesions	New : iSoD sum of diameters for new lesion target
Response after RECIST progression	New: to take into account flare effect
Confirmation of progression required	New: new definition rules
Reason why progression cannot be confirmed	New: must be provided when patient continue in the trial
Clinical status	New: taken into account at clinical evaluation

- First RECIST PD is iUPD
- iUPD confirmed 4-8weeks
- Treatment past PD only considered if patient is clinically stable

New Progression Confirmation Rules: iRECIST

iCPD: immune confirmed progressive disease

Worsening in lesion category

iUPD TL ≥ 20% SoD + ≥5mm SoD ↗ = iCPD

iUPD NTL Unequivocal ↗ + Any ↗ = iCPD

iUPD NL + NLT ≥5mm iSoD ↗ / NL NT / Any ↗ = iCPD

Worsening in other lesion category

iUPD TL ≥ 20% SoD + NTL Unequivocal ↗ = iCPD

OR

\+ NL = iCPD

iUPD NTL Unequivocal ↗ + TL ≥ 20% SoD = iCPD

OR

\+ NL = iCPD

TL = target lesion
SoD = sum of diameters for all target lesions
iSod = immune sum of diameters for new lesion target
iUPD = immune unconfirmed progressive disease

iCPD = immune confirmed progressive disease
NTL = non target lesion
NL = new lesion
NLT = new lesion target
NL NT = new lesion non target

Statistical Considerations

iRECIST progression

- iUPD subsequently confirmed
  - The date used is the first UPD date

- iUPD never confirmed
  - If a subsequent iSD, iPR or iCR is seen, the initial iUPD is ignored
  - Otherwise, iUPD date is used

irRC/ irRECIST /iRECIST Comparison

- All account for delayed response and flare effect by repeat imaging up to 12 weeks after treatment
- All allow for the presence of new lesions

irRC

- Bidimensional measurements (longest diameter x the longest perpendicular diameter)
- Rarely used today

irRECIST

- Unidimensional measurements (longest diameter) have been shown to have less variability
- PD thresholds for irRECIST and RECIST are aligned, allowing for comparisons to be made between trials and to historical data
- **Most trials today evaluate response using irRECIST and RECIST 1.1**

iRECIST

- Unidimensional measurements (longest diameter)
- PD thresholds for iRECIST and RECIST are aligned
- Progression confirmation rules are defined
- Resetting the bar if PD is followed at the next TP by tumor shrinkage (iUPD must occur again)
- **Will be most used going forward**

Response Criteria Comparison

	irRC	irRECIST	RECIST 1.1	iRECIST
Lesion Measurement	Bidimensional	Unidimensional	Unidimensional	Unidimensional
Baseline Lesion Size	5 mm X 5 mm	≥ 10 mm	≥ 10 mm	≥ 10 mm
Baseline Lesion Number	10 lesions total, 5 per organ	5 lesions total, 2 per organ	5 lesions total, 2 per organ	5 lesions total, 2 per organ
Appearance of New Lesions	Incorporated into TTB	Incorporated into TTB	Always represents PD	iUPD
Response	**CR** = disappearance of all lesions **PR** ≥ 50% decrease from baseline TTB **SD** = when neither PR nor PD can be established **PD** ≥ 25% increase in the nadir of TTB	**CR** = disappearance of all lesions **PR** ≥ 30% decrease from baseline TTB **SD** = when neither PR nor PD can be established **PD** ≥ 20% increase in the nadir of TTB (minimum 5 mm)	**CR** = disappearance of all lesions **PR** ≥ 30% decrease from baseline TTB **SD** = when neither PR nor PD can be established **PD** ≥ 20% increase in the nadir of TTB (minimum 5 mm)	**CR** = disappearance of all lesions **PR** ≥ 30% decrease from baseline TTB **SD** = when neither PR nor PD can be established **PD** ≥ 20% increase in the nadir of TTB (minimum 5 mm)
Confirmation after first assessment	Yes	Yes, wait up to 12 weeks **to confirm PD to account for flare**	Yes, if response is primary endpoint	Yes 4-8 weeks

iRECIST: When to use

- Not treatment decision guidelines
- Internationally agreed recommendations
- Not **yet validated** response criteria

- Late phase/approval trial
  - RECIST 1.1 primary criteria
  - iRECIST exploratory criteria
- Early phase
  - Consider iRECIST as primary criteria because assessment is done via RECIST 1.1 until progression
    - Uses same thresholds as RECIST 1.1 at progression
    - iSoD is the only new concept

Thank You!

For all more information about how Median can assist you with your immunotherapy studies, contact:

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