Immune-Related Radiographic Response Criteria

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Presenter Disclosure Information

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The following relationships exist related to this presentation:

No Relationships to Disclose

Educational Objectives of this session

- Develop an understanding of the various radiographic and clinical response criteria
- Define response and progression
- Realize the concept of iUPD, iCPD, iPR, iCR, within iRECIST
- Practical considerations

Timeline of radiographic criteria

Year	Criteria	Journal
1981	WHO	Cancer
2000	RECIST	Eur J Cancer
2009	RECIST 1.1	JNCI
2009	irRC	Clin Cancer Res
2013	irRECIST	Clin Cancer Res
2017	iRECIST	Lancet Oncology
2018	imRECIST	J Clin Oncol

Why monitor response?

- Surrogate for clinical outcome, including PFS and OS
- PFS is dependent on clinical and radiologic criteria
- PFS may be a surrogate for OS
- Assess early and easily
- Discontinue an ineffective intervention

What makes immunotherapy different requiring new criteria?

- A novel MOA, including concept of immune infiltration
- Delayed onset of tumor regression
- Persistent benefit beyond drug delivery, including PR/CR
- d/c at first suggested PD may be premature
- New criteria better only if its application leads to improved outcomes

Highlights of various “immune” based criteria

	RECIST 1.1	irRC	irRECIST	iRECIST	imRECIST
Measurement modality	Unidimensional	Bi-dimensional	Unidimensional	Unidimensional	Unidimensional
Baseline lesion size	≥ 10mm	5mm x 5mm	≥ 10mm	≥ 10mm	≥ 10mm
Baseline lesion number	5 lesions in total; 2 per organ	10 lesions in total; 5 per organ	5 lesions in total; 2 per organ	5 lesions in total; 2 per organ	5 lesions in total; 2 per organ
Appearance of new lesions	PD	Incorporated in the sum of the measurements	Incorporated in the sum of the measurements	iUPD; not incorporated into sum; may turn into iCPD	Incorporated in the sum of the measurements
CR	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions	Disappearance of all lesions
PR	≥ 30% decrease from baseline	≥ 50% decrease from baseline	≥ 30% decrease from baseline	≥ 30% decrease from baseline	≥ 30% decrease from baseline
SD	Neither CR nor PD is met	Neither CR nor PD is met	Neither CR nor PD is met	Neither CR nor PD is met	Neither CR nor PD is met
PD	≥ 20% increase; minimum of 5mm	≥ 25% increase	≥ 20% increase; minimum of 5mm	≥ 20% increase; minimum of 5mm	≥ 20% increase; minimum of 5mm
Confirmation of PD	Not applicable	Yes	Yes; 4-12 weeks	Yes; 4-8 weeks	Yes - at least 4 weeks

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irRC (immune related response criteria)

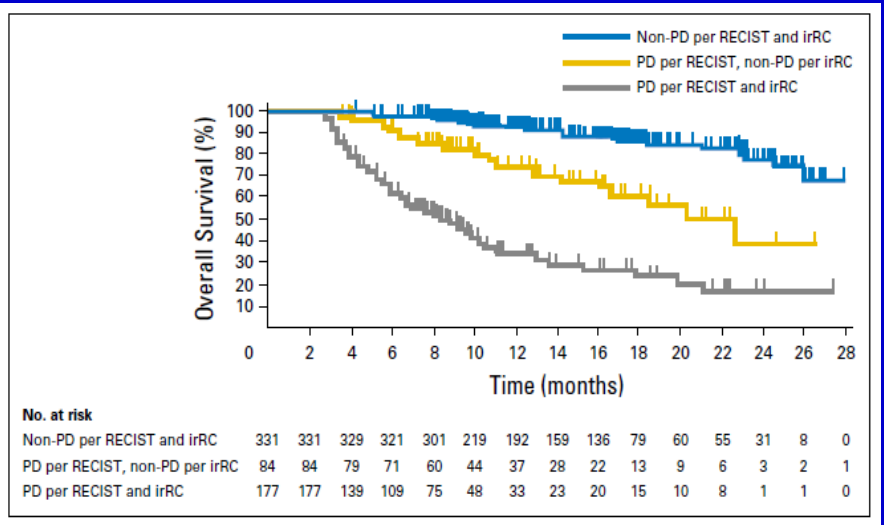
First described

- **Ipilimumab in melanoma (2009)**

Validation

- **Pembrolizumab in melanoma**
- **OS:**

No PD in both criteria (>26 mo) > PD RECIST/SD irRC (22.5 mo) > PD in both (8.4 mo)



Major drawback

Used bi dimensional measurements; more error prone

Wolchcok, Clin Cancer Res, 2009
Hodi, J Clin Oncol, 2016

irRECIST (immune related RECIST)

A model to convert irRC (bidimensional) to irRECIST (unidimensional)

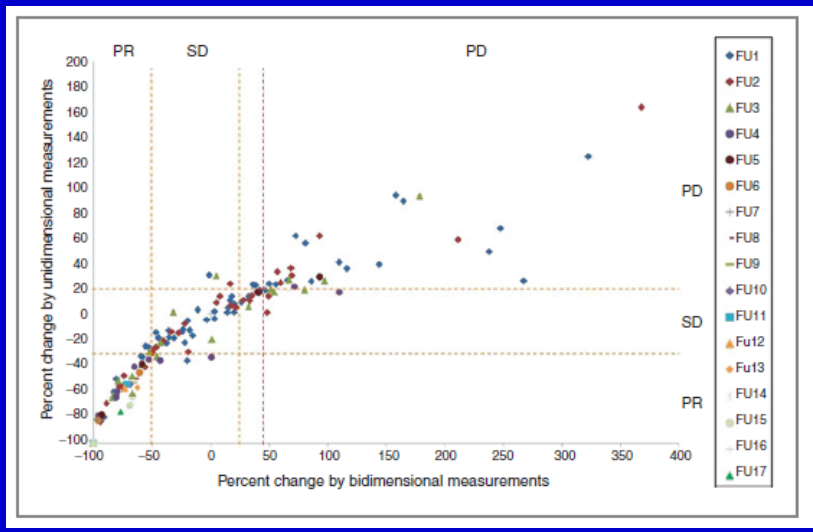


Table 2. Best immune-related response according to bidimensional versus unidimensional assessment

Best response by unidimensional assessment	Best response by bidimensional assessment			
	irCR	irPR	irSD	irPD
irCR	1	0	0	0
irPR	0	7	0	0
irSD	0	0	41	3
irPD	0	0	1	4

NOTE: $\kappa_w = 0.881$.

Major limitation

Similar to WHO:RECIST 1.1

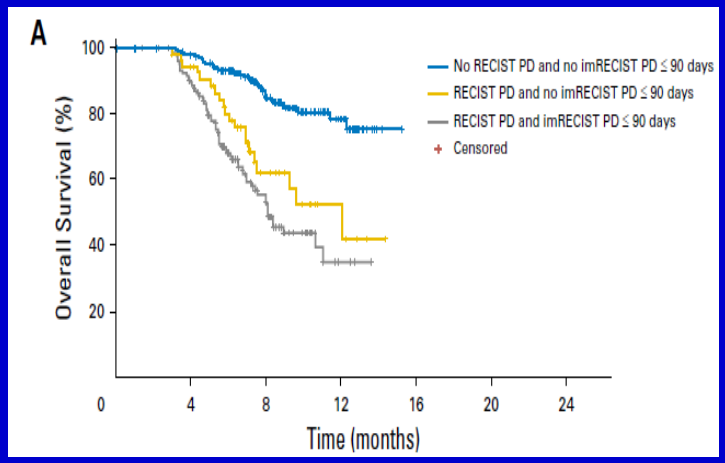
Not validated, rarely used

Nishino, Clin Cancer Res, 2013

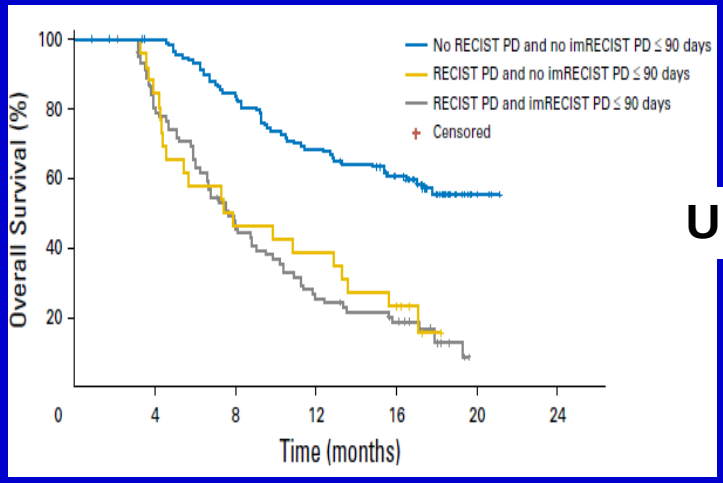
imRECIST (immune modified RECIST)

Based on atezolizumab data

- **PD on both criteria has worse OS than PD only on imRECIST in NSCLC (not in urothelial)**
- **New lesions is worse than TL progression**
- **RR ↑ 1-2%, PFS ↑ 0.5-1.5 mo**



NSCLC



Urothelial

Major limitation

Does imRECIST offer any benefit beyond iRECIST?

Hodi, J Clin Oncol, 2018

iRECIST (immune RECIST)

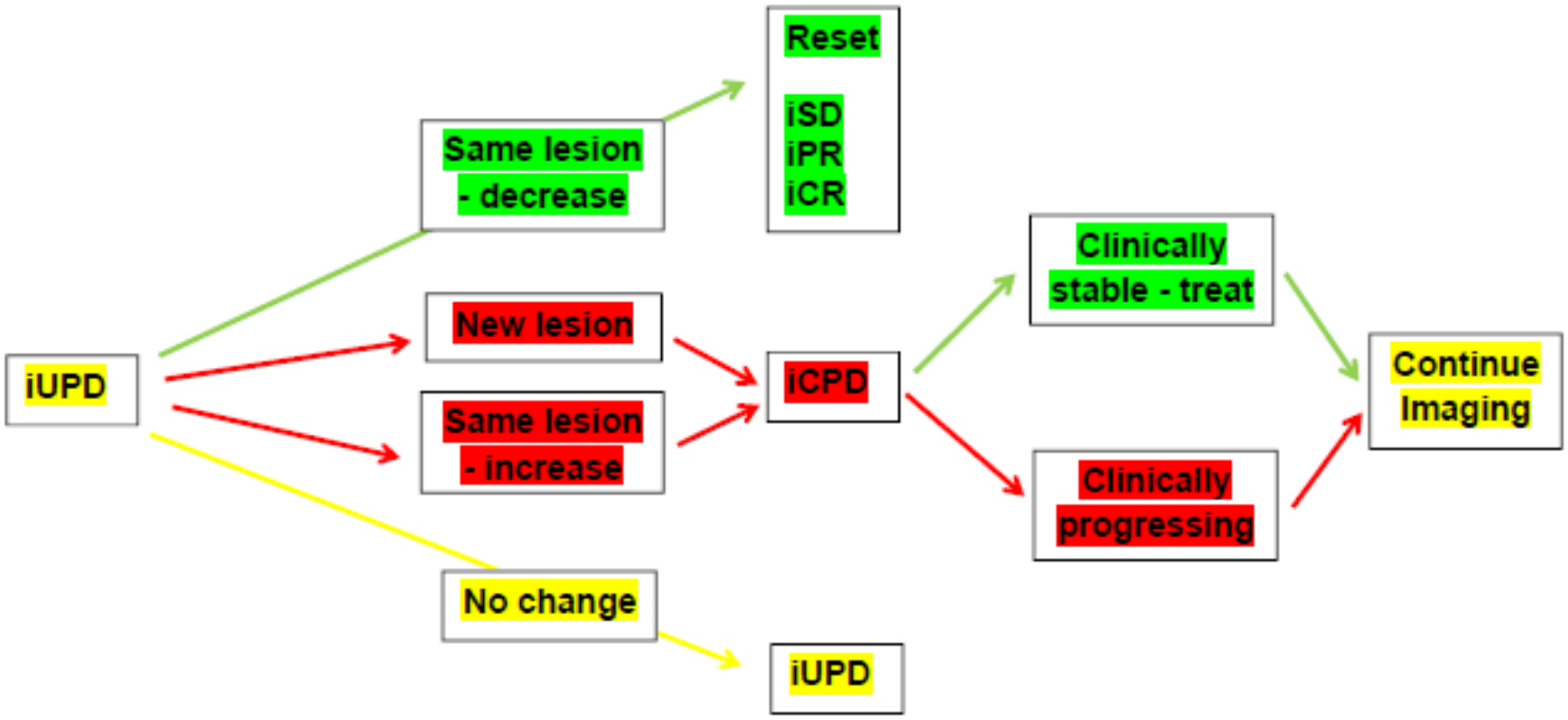
- To ensure uniformity across all trials, cooperative groups, industry, nations, continents, etc.
- Common theme,

  RECIST 1.1 primary endpoints

  irRC and imRECIST for exploratory
- Major change is resetting the bar for PD after a iUPD does not convert to iCPD

Seymour, Lancet Oncology, 2017

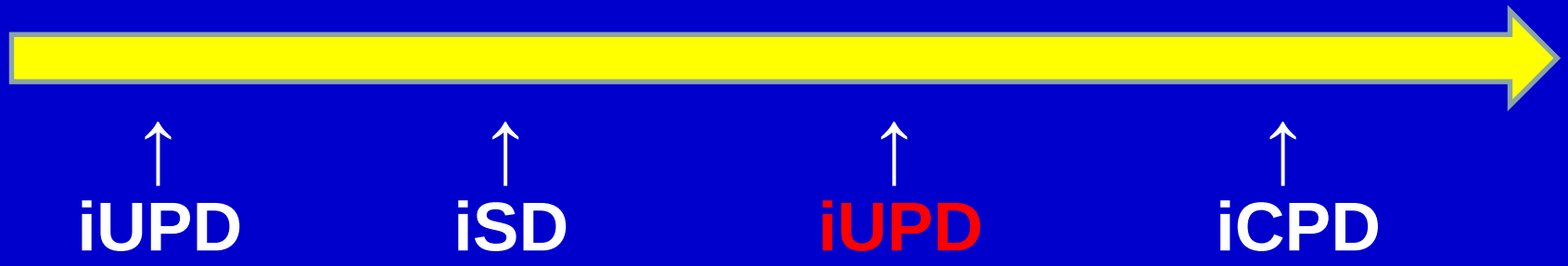
iUPD: The key new phenomenon in iRECIST



iUPD: immune Unconfirmed Progressive Disease (can have multiple iUPD)
iSD: immune Stable Disease
iPR: immune Partial Response
iCR: immune Complete Response
iCPD: immune Confirmed Progressive Disease

Key features of iRECIST

- If iUPD, and clinically stable, continue therapy
- Clinically stable includes
  - Stable performance status
  - No increase in disease related symptoms
  - No increase in need for managing symptoms
- New lesions are not added to sum of baseline
- Once iCPD, initial date of iUPD is date of PD



Recommendations of iRECIST

- **Not ready for treatment decision making**
- **Not prospectively validated**
- **Assess response on a calendar schedule, especially for comparative trials**
- **For registration trials, incorporate both**
  - **RECIST 1.1 for primary end points and**
  - **iRECIST for exploratory end points**
- **May use iRECIST in early phase trials**

Approved IO agents and clinical trials

Drug	Indication	Clinical condition	Primary end point	Secondary end point	Criteria	Independent Review	
Avelumab	Merkel Cell		ORR		RECIST 1.1	IRC	
	Urothelial	Post platinum	ORR,DOR		RECIST 1.1		
Durvalumab	Urothelial	Post platinum	ORR	DOR	RECIST 1.1	BIRC	
			PFS	OS	RECIST 1.1	BIRC	
Pembrolizumab	Melanoma	Unrectable	OS,PFS	ORR, DOR	RECIST 1.1	BIRC	
	NSCLC	Front line -single	PFS	OS, ORR	RECIST 1.1	BIRC	
	NSCLC	Front line -chemo	ORR	PFS, DOR, OS	RECIST 1.1	BIRC	beyond PD if stable
	NSCLC	Second line	OS, PFS	ORR, DOR	RECIST 1.1	BIRC	
	HNSCC	Post platinum	ORR		RECIST 1.1	BIRC	
	Hodgkin Disease	Relapsed/refractory	ORR, CR, DOR		IWG	BIRC	
	Medistinal NHL	Relapsed/refractory	ORR, CR, DOR		IWG	BIRC	
	Urothelial	Cisplatin ineligible	ORR, DOR		RECIST 1.1	BIRC	
	Urothelial	Post platinum	OS, PFS	ORR, DOR	RECIST 1.1	BIRC	
	MSI-H		ORR, DOR		RECIST 1.1	BIRC	
	Gastric	>2 lines of therapy	ORR, DOR		RECIST 1.1	BIRC	
	Cervical	Recurrent/metastatic	ORR,DOR		RECIST 1.1	BIRC	
Nivolumab	Melanoma	Front line	ORR, DOR		RECIST 1.1		
	Melanoma	Front line, BRAF WT	OS, Inv PFS	ORR	RECIST 1.1		
	Adjuvant		RFS				
	NSCLC	Second line - Squamous	OS, Inv ORR	PFS	RECIST 1.1		
	NSCLC	Second line - Non Sq	OS, ORR	PFS	RECIST 1.1		
	Small CLC	Third line	ORR, DOR		RECIST 1.1	BIRC	
	Renal	Second line	OS		RECIST 1.1	Inv. Assessed	
	Renal	Front line	OS, PFS, ORR		RECIST 1.1	IRRC	
	Hodgkin Disease	Relapsed/refractory	ORR	DOR	IWG	IRRC	
	HNSCC	Post platinum	OS	PFS, ORR	RECIST 1.1		beyond PD if stable
	Urothelial	Post platinum	ORR	DOR	RECIST 1.1	IRRC	
	CRC	MSI-H	ORR, DOR		RECIST 1.1	BIRC	
	Hepatocellular	Post sorafenib	ORR, DOR		RECIST 1.1	BIRC	

Approved IO agents and clinical trials

Drug	Indication	Clinical condition	Primary end point	Secondary end point	Criteria	Independent Review
Atezolizumab	Urothelial	Cisplatin ineligible	ORR, DOR, OS		RECIST 1.1	IRF
	Urothelial	Post platinum	OS, DOR		RECIST 1.1	BIRC
	NSCLC	Post platinum	OS	ORR, PFS	RECIST 1.1	Inv. Assessed
Cemiplimab	Cutaneous SCC	Metastatic or unresectable	ORR		RECIST 1.1	ICR
Ipilimumab	Melanoma	Unresectable	OS	ORR	Modified WHO	
	Melanoma	Adjuvant	RFS, OS			IRC
	Renal	Front line	OS, PFS, ORR		RECIST 1.1	IRRC
Tisagenlecleucel	B-ALL		CR			
	DLBCL				Lugano	IRC
Axicabtagene Ciloleucel	DLBCL	Relapsed/refractory	CR, DOR			IRRC
Talimogene laherparepvec	Melanoma	Recurrent	DRR	OS	modified WHO	IRC

Limitations of establishing criteria

- Can it be followed in the real world?
  - familiarity of care takers with established/new criteria
- Applicability of data
  - does data from one drug with an MOA apply to a different drug with its unique MOA
  - does tumor type matter - (eg. imRECIST, NSCLC vs. urothelial)
- PET without diagnostic CT not as reliable
- Too much information/paperwork for minimal increase in clinical benefit

What is now known and established

- Immune criteria clearly demonstrate an improvement in RR, PFS, OS over conventional criteria
- Responses are more durable
- More complicated, requiring education for implementation

Conclusions and take home points

- Immune therapy is distinct from traditional cytotoxic chemotherapy, in MOA and patterns of tumor response
- A clear need exists in refining response criteria
- Consensus statement led to iRECIST guidelines, that need validation
- Treatment beyond first progression may help a well defined subset of patients
- Current state of art requires traditional RECIST 1.1 for primary end points, and iRECIST for exploratory end points

Acknowledgments

- The SITC Organizing Committee for this opportunity
- Pioneers of immunotherapy, with the foresight to recommend innovative criteria
- Patients who volunteer for clinical trials that facilitate the forward march of the field