MADRID 2014 ESMO congress

Clinical evaluation of response to immunotherapy

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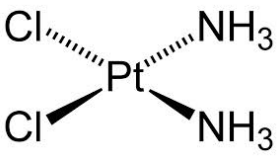
Disclosures

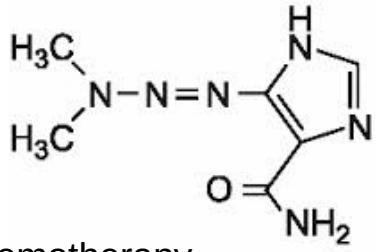
- Consultancy role:
  - BMS; MSD; GSK; Roche
- Research grants:
  - BMS; GSK; MSD

Aim of presentation

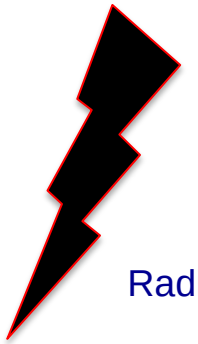
- Highlight the differences in MOA of IT compared to targeted therapy of chemotherapy
- Summarize the response types observed with IT
- Discuss the evaluation possibilities

MOA of cancer treatments





chemotherapy



Radiotherapy

DNA damage

Cell death

MOA of cancer treatments

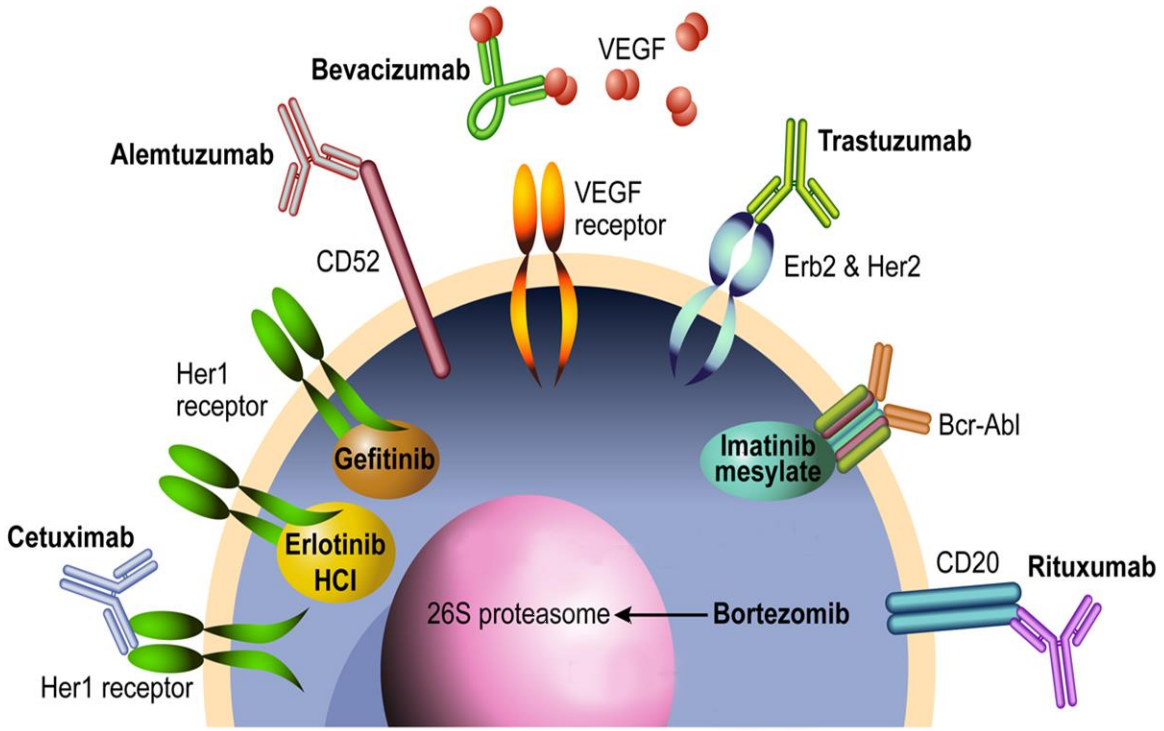
Targeted agents

↓

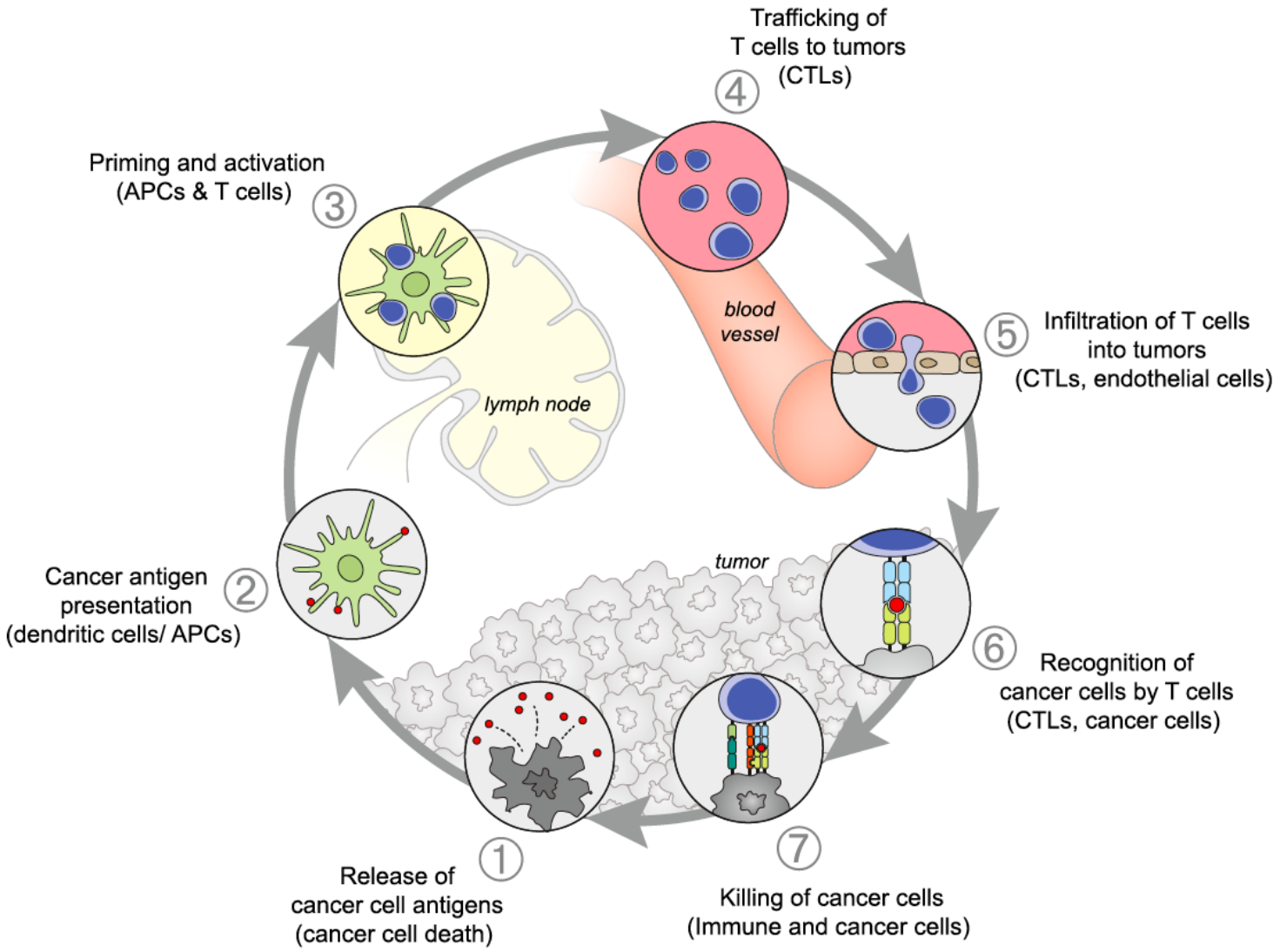
Inhibition of mutated or overexpressed proteins in cancer cells

↓

Cell death or stop of cell growth

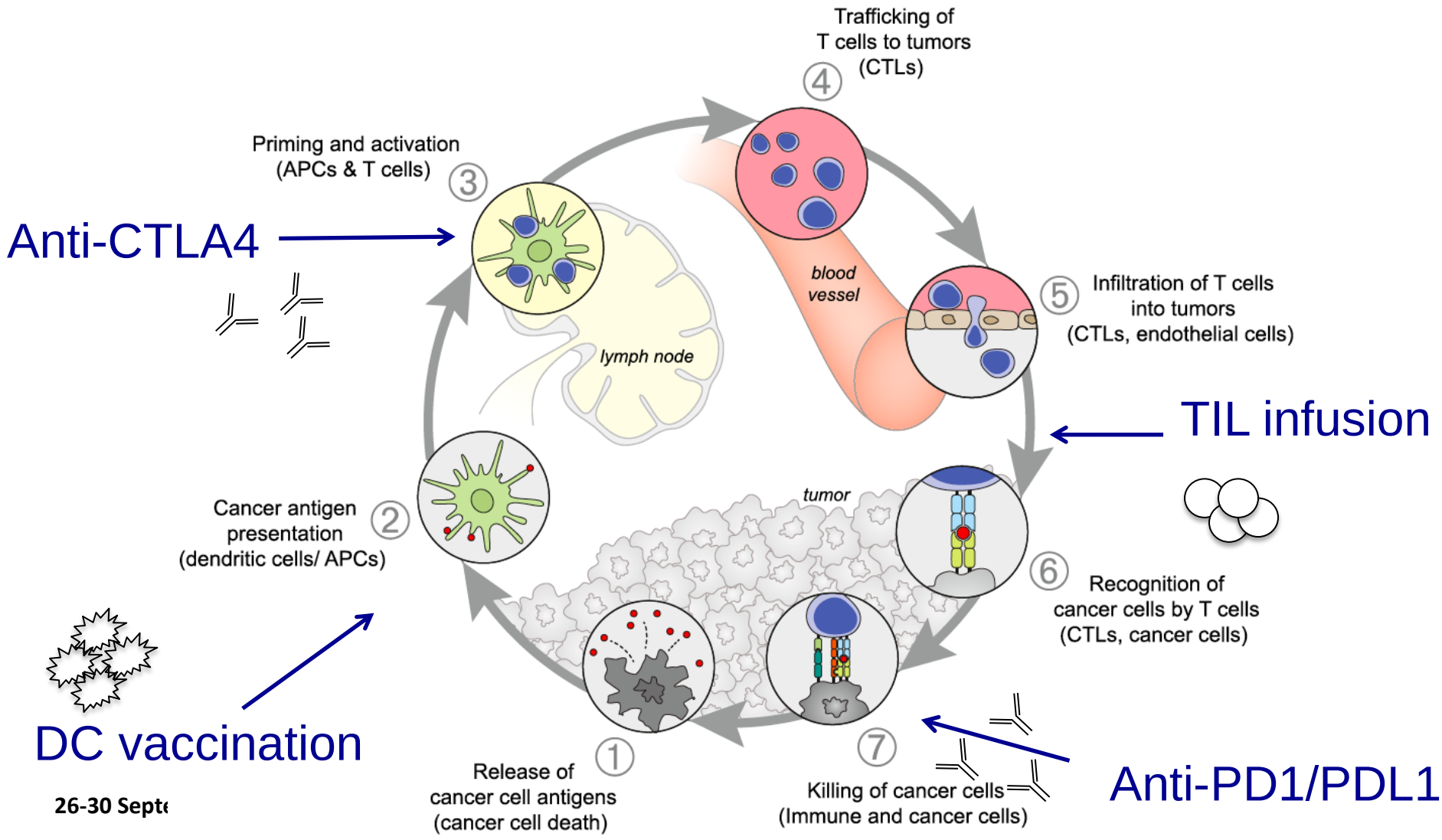


MOA of cancer treatment



Chen & Mellman Immunity 2013

MOA of cancer treatment



IT versus TT or CT

- Targeted and chemotherapy work directly
  - Target tumor cells (and normal cells)
- Immunotherapy works indirectly
  - Stimulates cells from the immune system
    - Anti-CTLA4
    - Anti-PD1/PD-L1
    - DC vaccination or other vaccine platforms
  - Augments the pool of tumor-specific T cells
    - TIL therapy
    - TCR of CAR gene therapy

Time-to-response to treatment

- Chemotherapy: if present usually within 6 weeks (2 courses)
- Targeted therapy:
  - BRAFi (+MEKi) within days, mostly within 2 weeks (PET)
- Immunotherapy: highly variable
  - Ipilimumab: weeks to months
  - Anti-PD1/PD-L1: weeks to months
  - TIL: weeks to months

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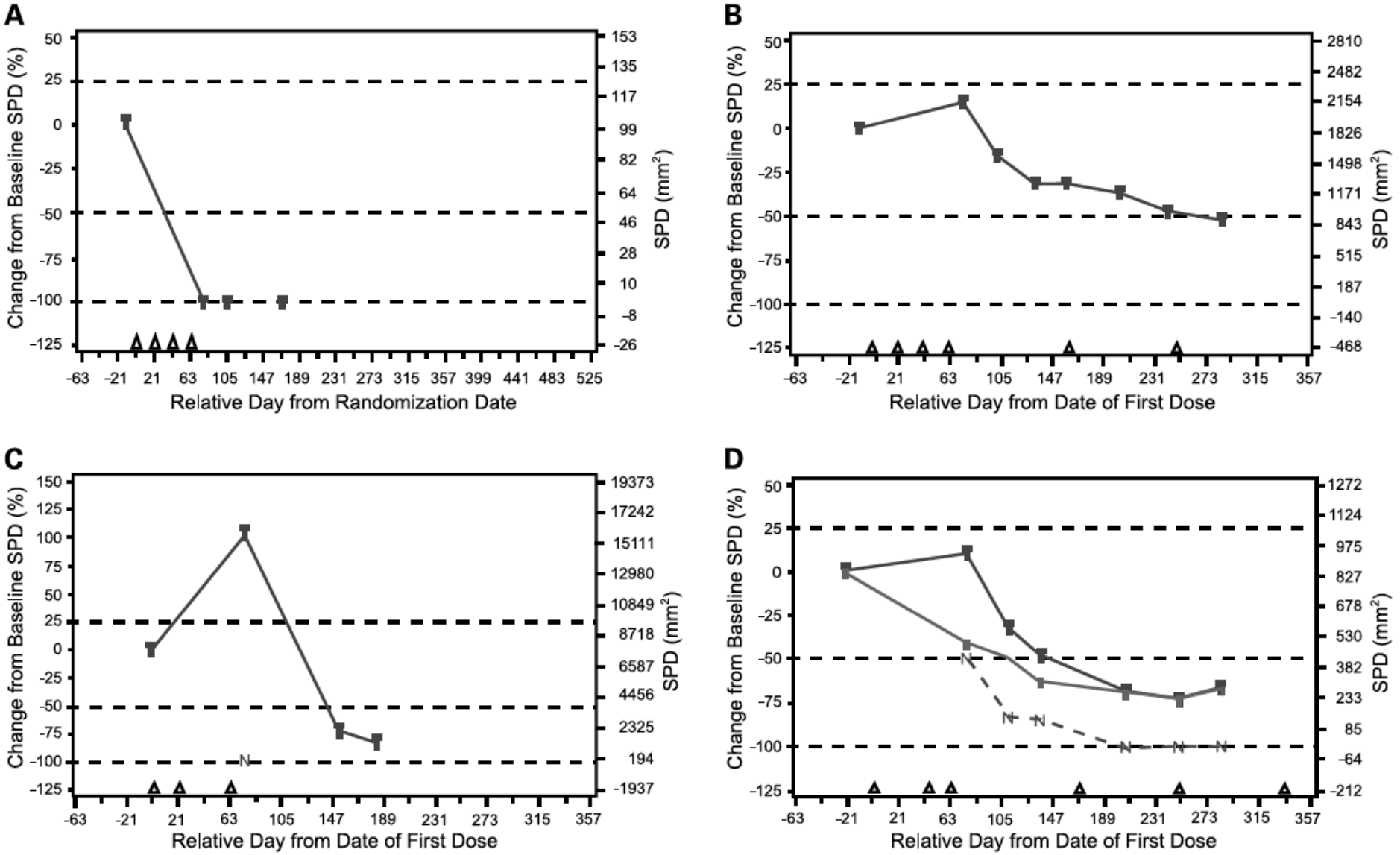
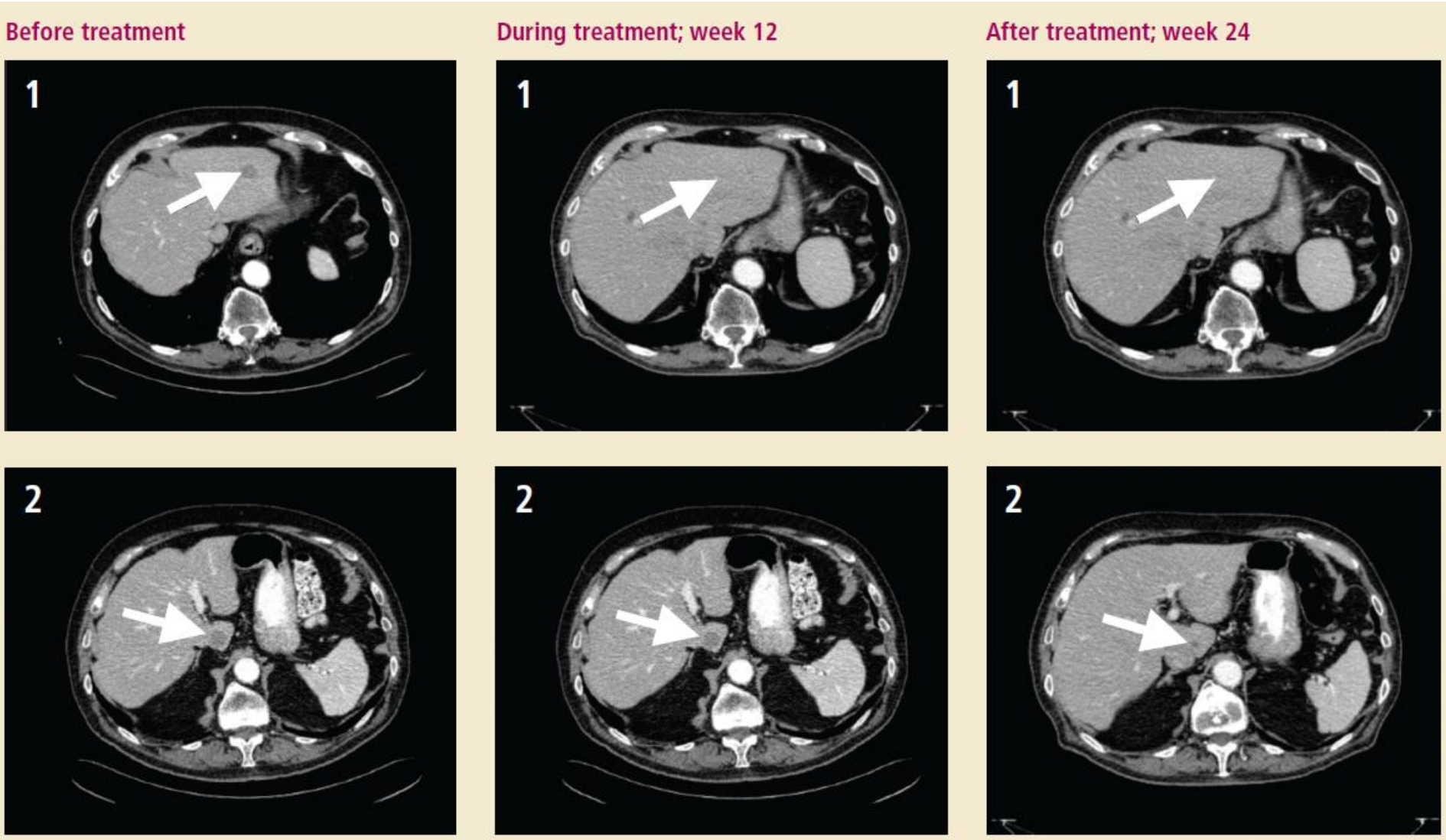
Patterns of response to ipilimumab



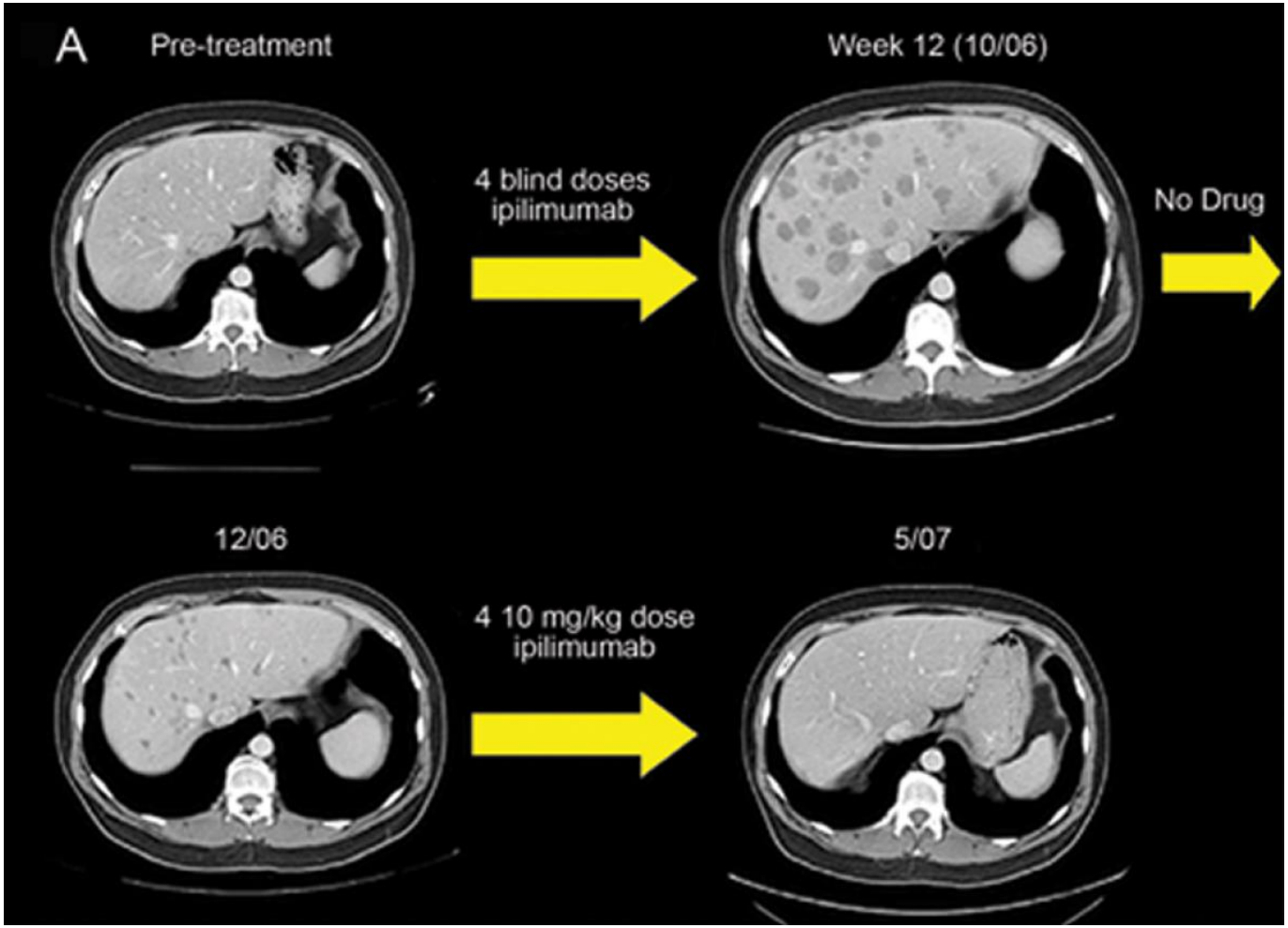
Wolchok et al., Clin Canc Res 2009

Response patterns with ipilimumab



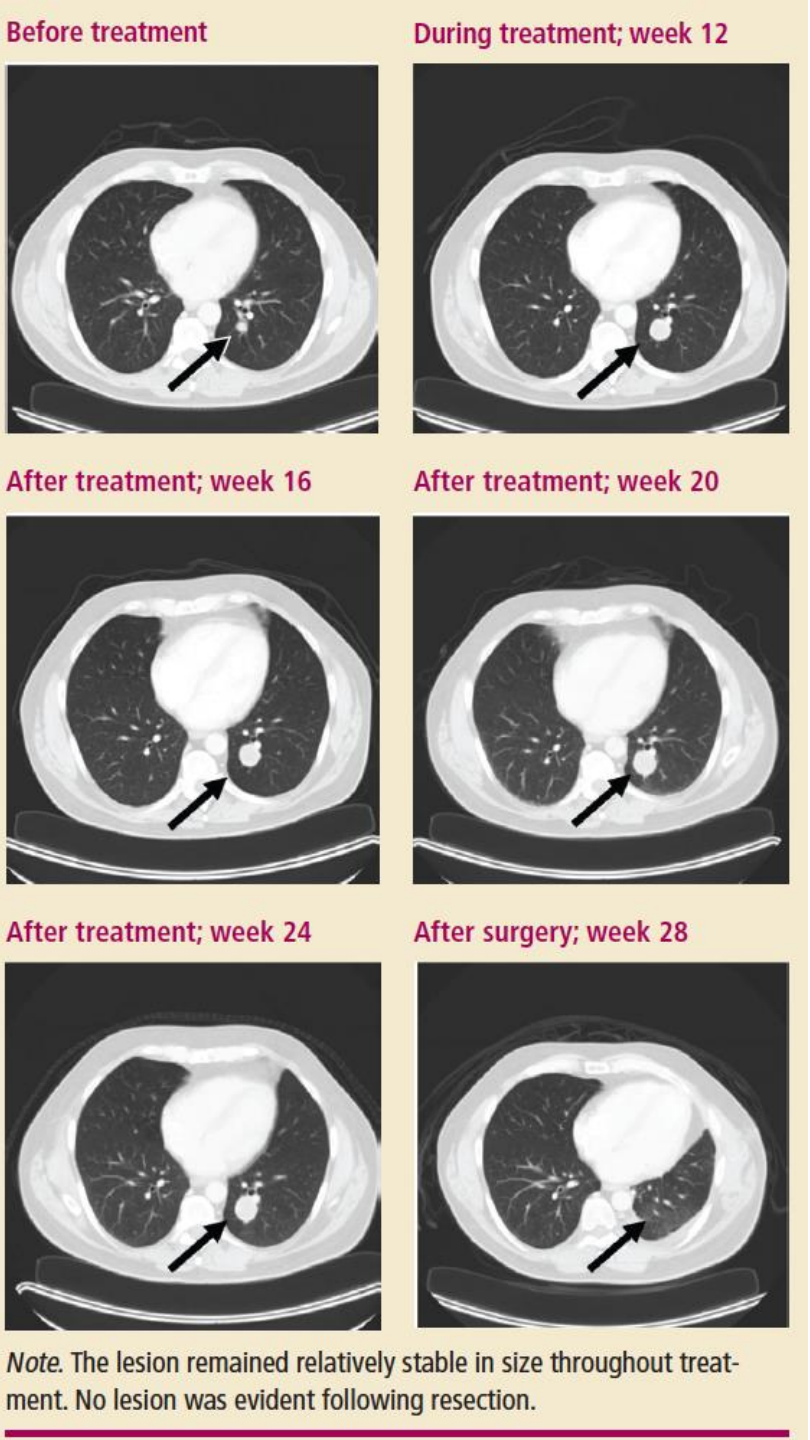
Ledezma et al. J Clin Oncol Nurs 2011

Response patterns with ipilimumab

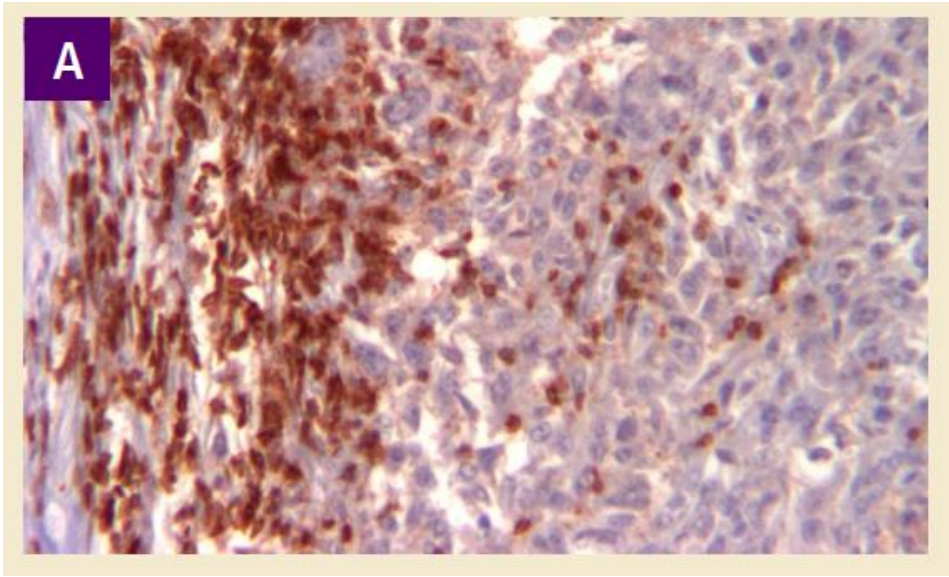


Saenger and Wolchok Cancer Immunity 2008

Response pattern following ipilimumab treatment



Note. The lesion remained relatively stable in size throughout treatment. No lesion was evident following resection.

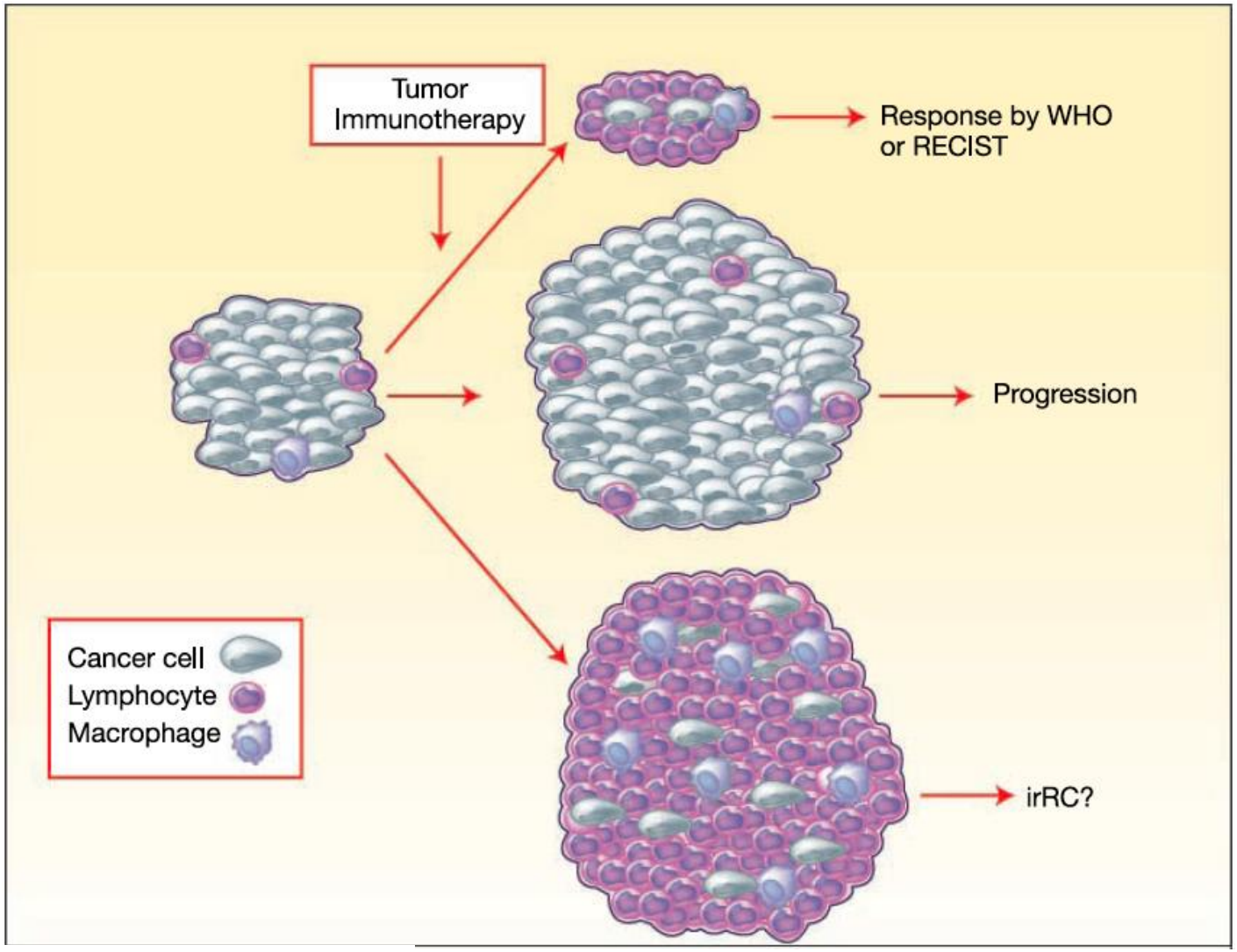


Dense infiltrate of T cells in resected lesion

esmo.org

Ledezma et al. J Clin Oncol Nurs 2011

Is progression truly progression?



Ribas et al. Clin Canc Res 2009

Cancer Therapy: Clinical

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 Cancer Res 2009

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Immune related Response Criteria

	WHO	irRC
New, measurable lesions (i.e., ≥5 × 5 mm)	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions (i.e., <5 × 5 mm)	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

Wolchok et al., Clin Cancer Res 2009

….simplify irRC from bidimensional

WHO based irRC

	Bidimensional assessment (the original irRC (7))
Measurable lesions	≥5 × 5 mm^2 by bidimensional measurements
Measurement of each lesion	The longest diameter × the longest perpendicular diameter (cm^2)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any
Response assessment	PD: ≥25% increase from the nadir PR: ≥50% decrease from baseline CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.
Confirmation	Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD

Nishino et al., Clin Canc Res 2013

....simplify irRC from bidimensional to unidimensional…

WHO based irRC RECIST 1.0 based irRC

	Bidimensional assessment (the original irRC (7))	Unidimensional assessment
Measurable lesions	≥5 × 5 mm^2 by bidimensional measurements	≥10 mm in the longest diameter
Measurement of each lesion	The longest diameter × the longest perpendicular diameter (cm^2)	The longest diameter (cm)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any	The sum of the longest diameters of all target lesions and new lesions if any
Response assessment	PD: ≥25% increase from the nadir PR: ≥50% decrease from baseline CR: Disappearance of all lesions	PD: ≥20% increase from the nadir PR: ≥30% decrease from baseline CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.	
Confirmation	Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD	

Nishino et al., Clin Canc Res 2013

Best immune related response according to 2-dimensional vs 1-dimensional measurement

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: $\kappa_w = 0.881$.

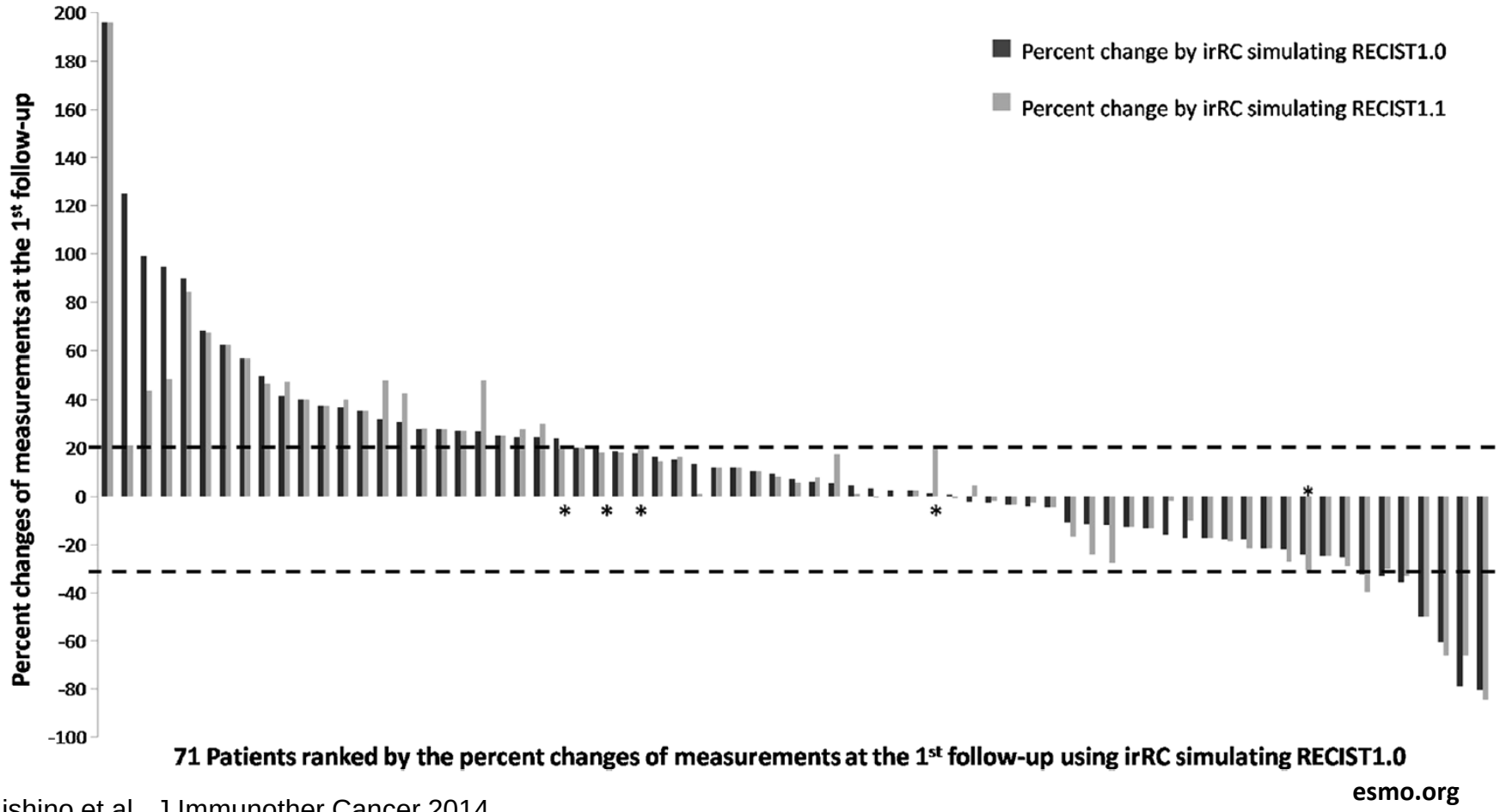
Nishino et al., Clin Canc Res 2013

RECIST 1.0 vs RECIST 1.1

- 10 lesions
- Max 5 per organ
- Min. size clinical lesion: 20 mm
- Not mentioned

- 5 lesions
- Max 2 per organ
- Min. size clinical lesion 10 mm
- LN target lesion ≥15 mm

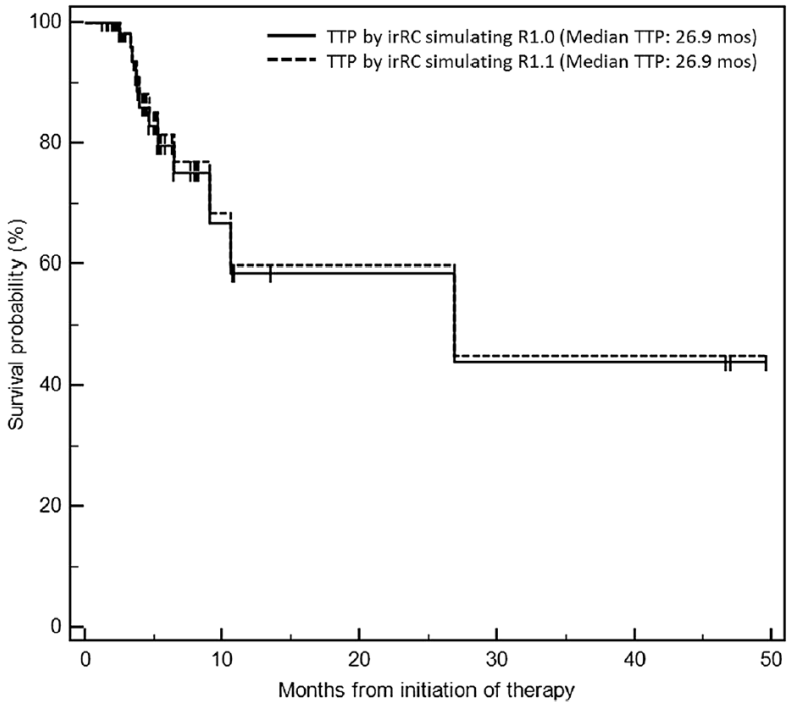
irRC, but now based on RECIST 1.1

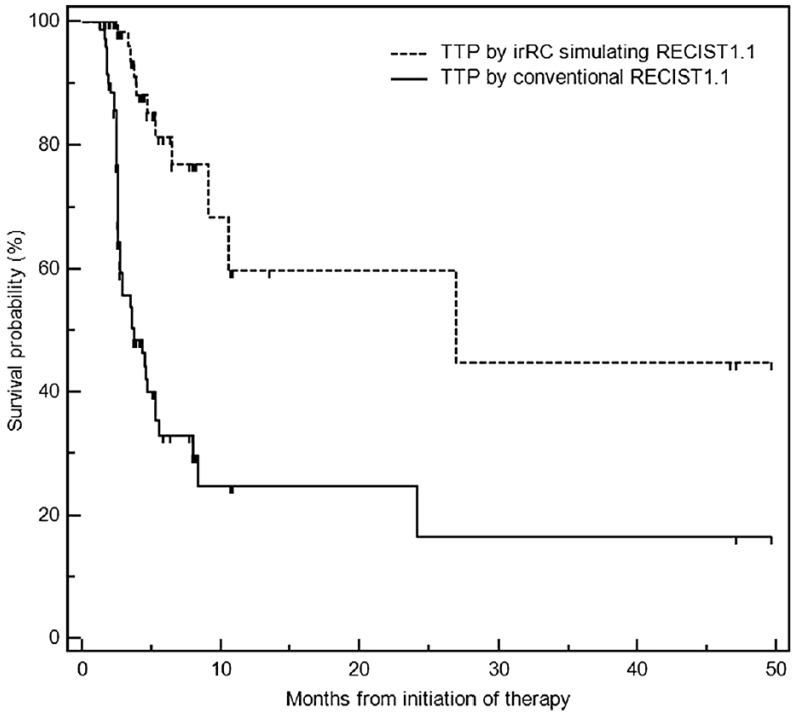


esmo.org

Nishino et al., J Immunother Cancer 2014

RECIST 1.1 based irRC capture patterns of response to immunotherapy



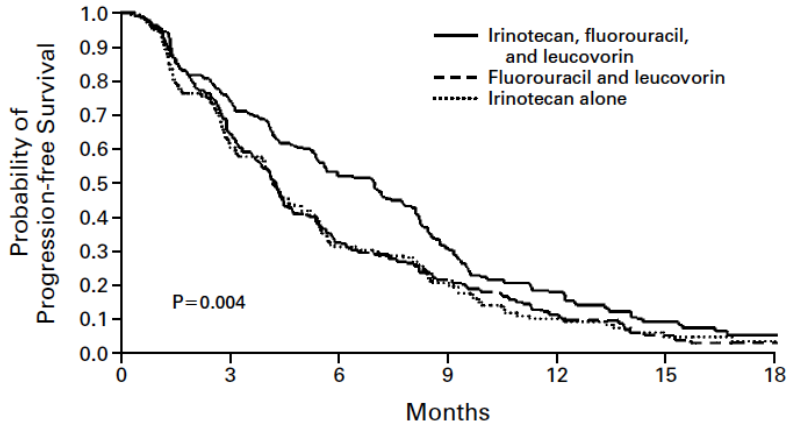


Nishino et al., J Immunother Cancer 2014

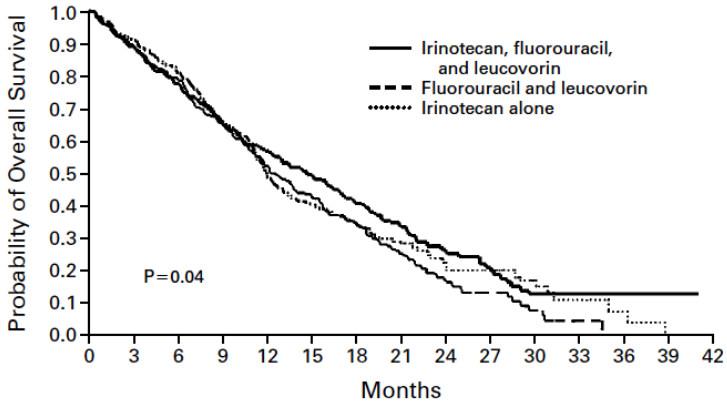
Which parameter should we measure for response evaluation to IT

- Objective response?
- Progression free survival?
- Overall survival?
  - Median
  - Survival at 3 years
  - ?

Chemotherapy



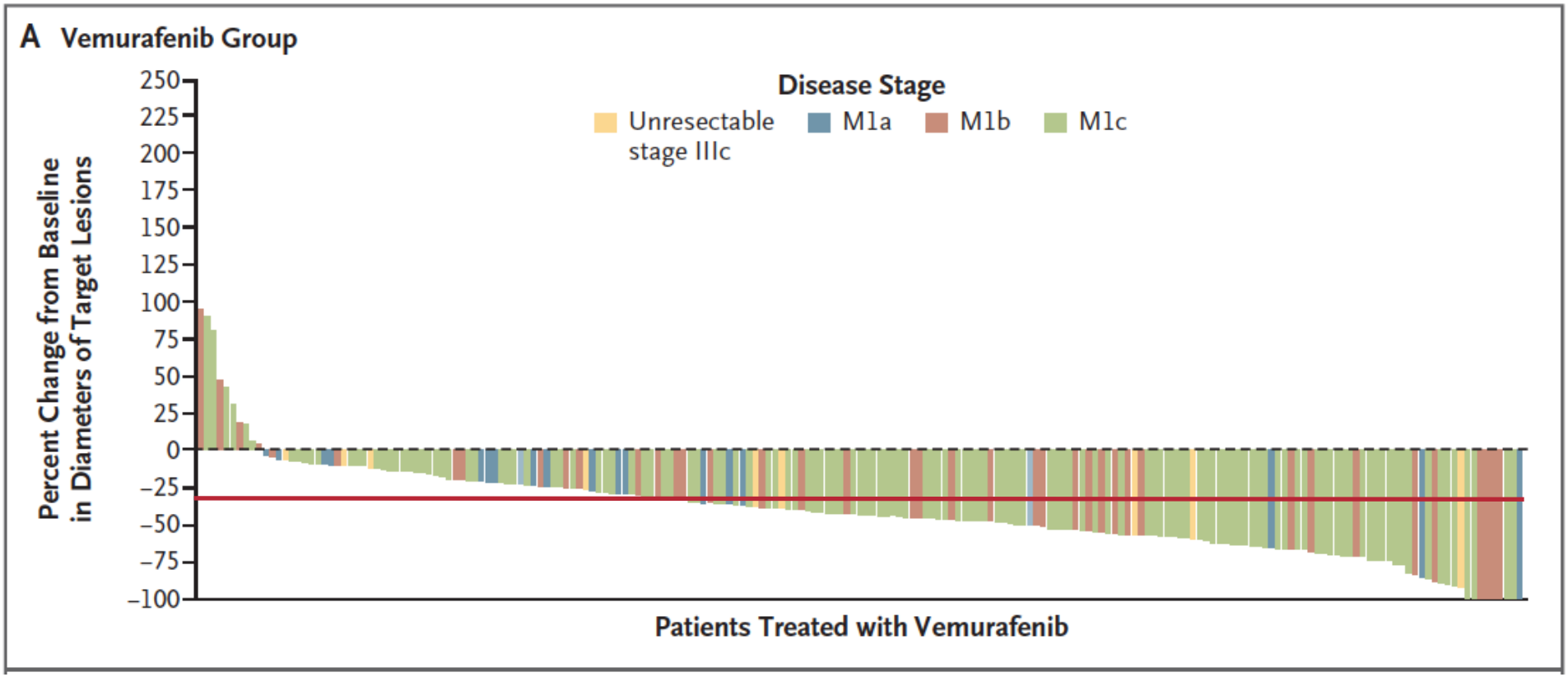
No. at Risk							
Irinotecan, fluorouracil, and leucovorin	231	154	99	49	23	11	5
Fluorouracil and leucovorin	226	124	54	32	15	5	2
Irinotecan alone	226	112	51	29	12	4	1



No. at Risk								
Irinotecan, fluorouracil, and leucovorin	231	178	129	84	33	10	3	1
Fluorouracil and leucovorin	226	175	116	72	23	5	0	0
Irinotecan alone	226	181	110	69	28	11	2	0

Saltz et al., NEJM 2000

Targeted therapy



Chapman et al., N Engl J Med 2011

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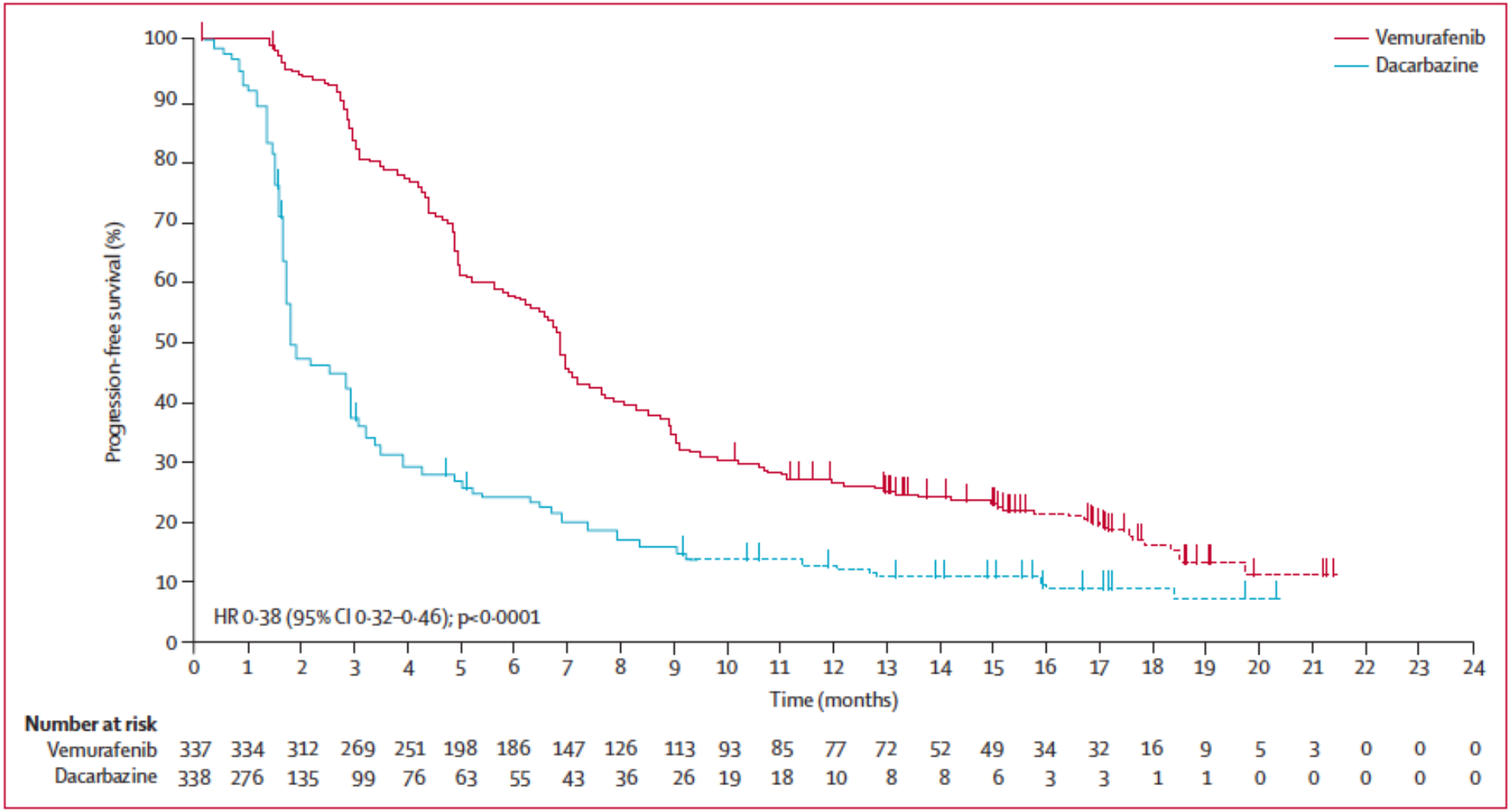
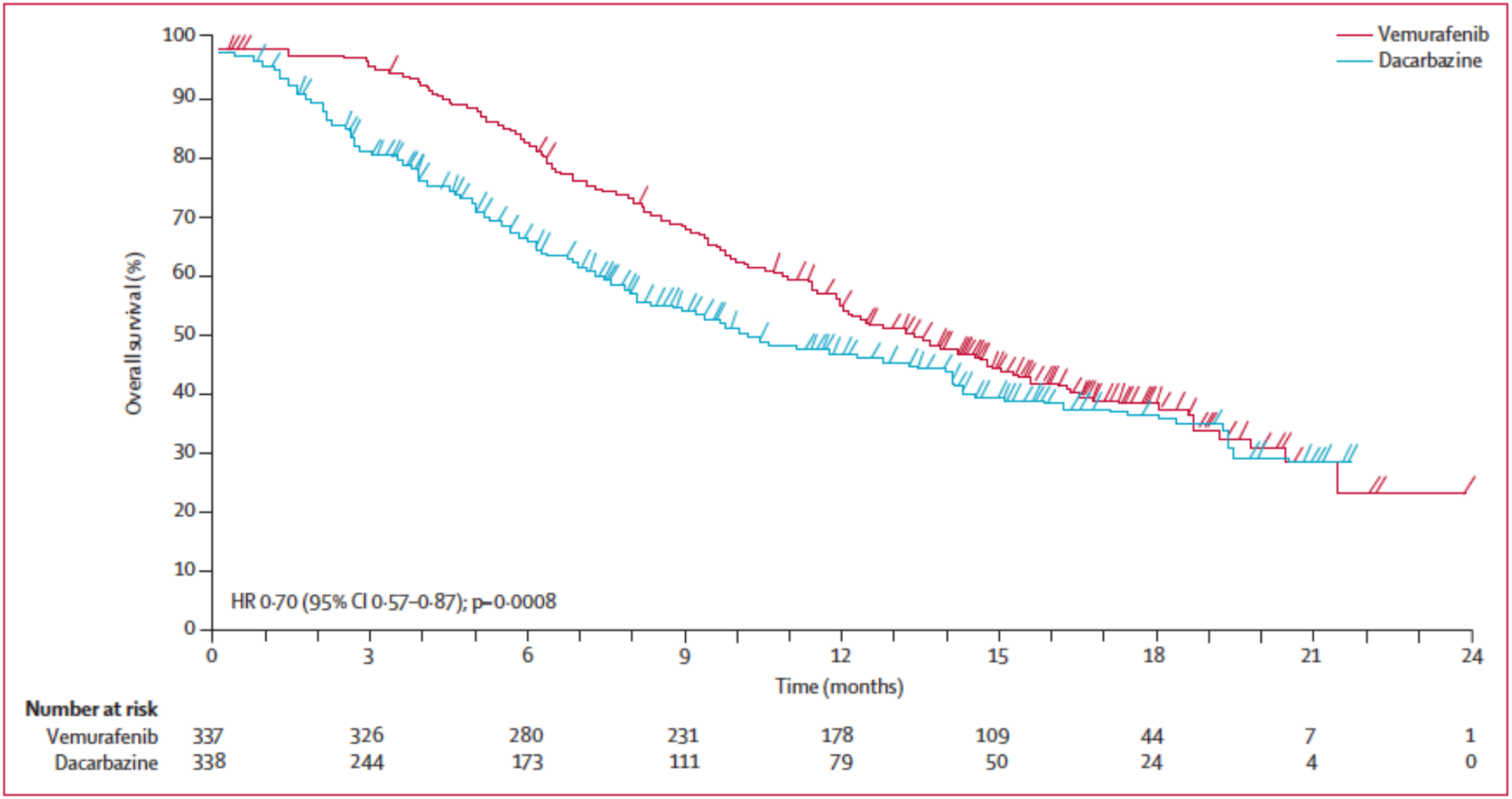
Short duration of response



McArthur Lancet Oncol 2014

Survival in BRIM-3 trial



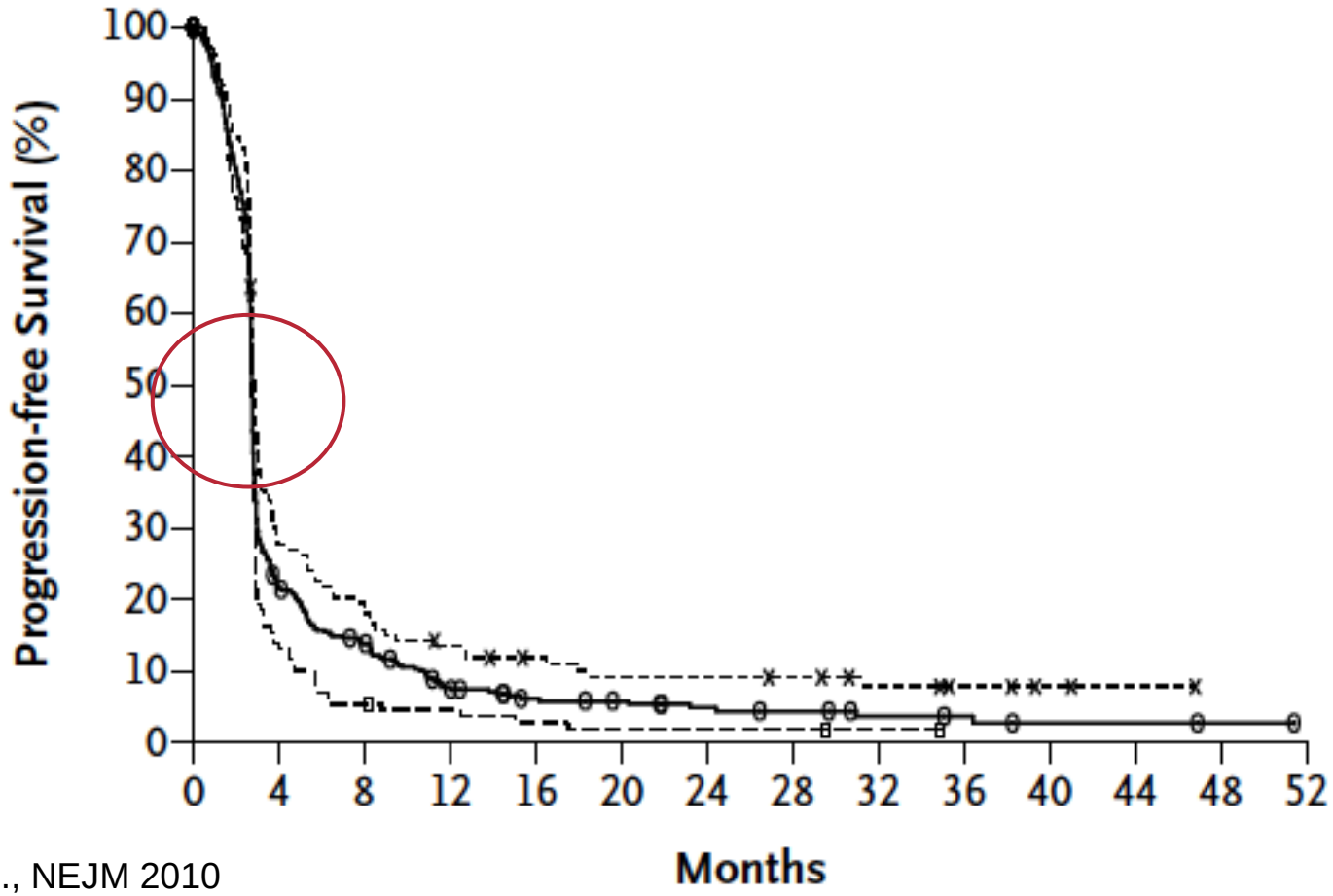
Mc Arthur Lancet Oncol 2014

Objective response to ipilimumab

Evaluation of therapy			
Induction			
Best overall response — no. (%)			
Complete response	1 (0.2)	2 (1.5)	0
Partial response	22 (5.5)	13 (9.5)	2 (1.5)
Stable disease	58 (14.4)	24 (17.5)	13 (9.6)
Progressive disease	239 (59.3)	70 (51.1)	89 (65.4)
Not evaluated	83 (20.6)	28 (20.4)	32 (23.5)
Best overall response rate — % (95% CI)	5.7 (3.7–8.4)	10.9 (6.3–17.4)	1.5 (0.2–5.2)
P value for comparison with gp100 alone	0.04	0.001	—
P value for comparison with ipilimumab alone	0.04	—	—
Disease control rate — % (95% CI)†	20.1 (16.3–24.3)	28.5 (21.1–36.8)	11.0 (6.3–17.5)
P value for comparison with gp100 alone	0.02	<0.001	—
P value for comparison with ipilimumab alone	0.04	—	—

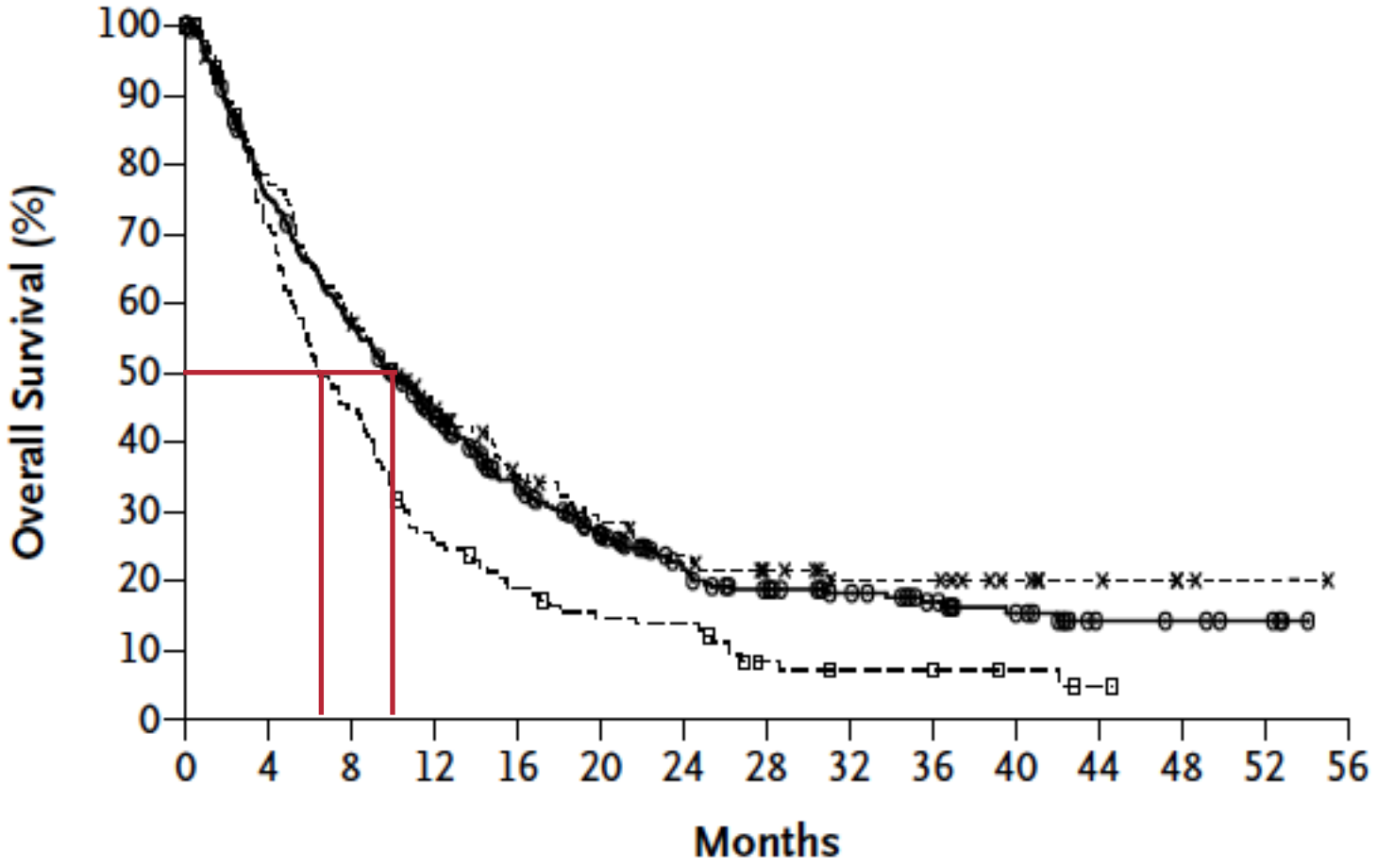
Hodi et al., NEJM 2010

Progression Free Survival



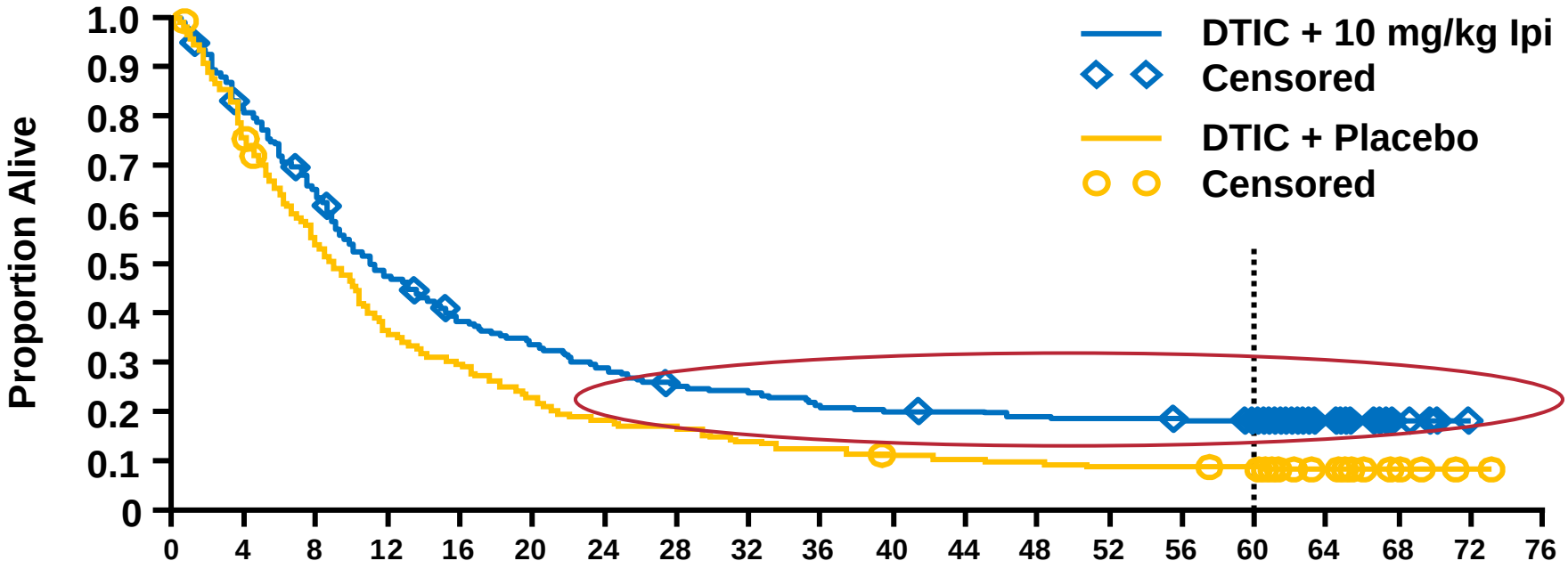
Hodi et al., NEJM 2010

Median overall survival



Hodi et al., NEJM 2010

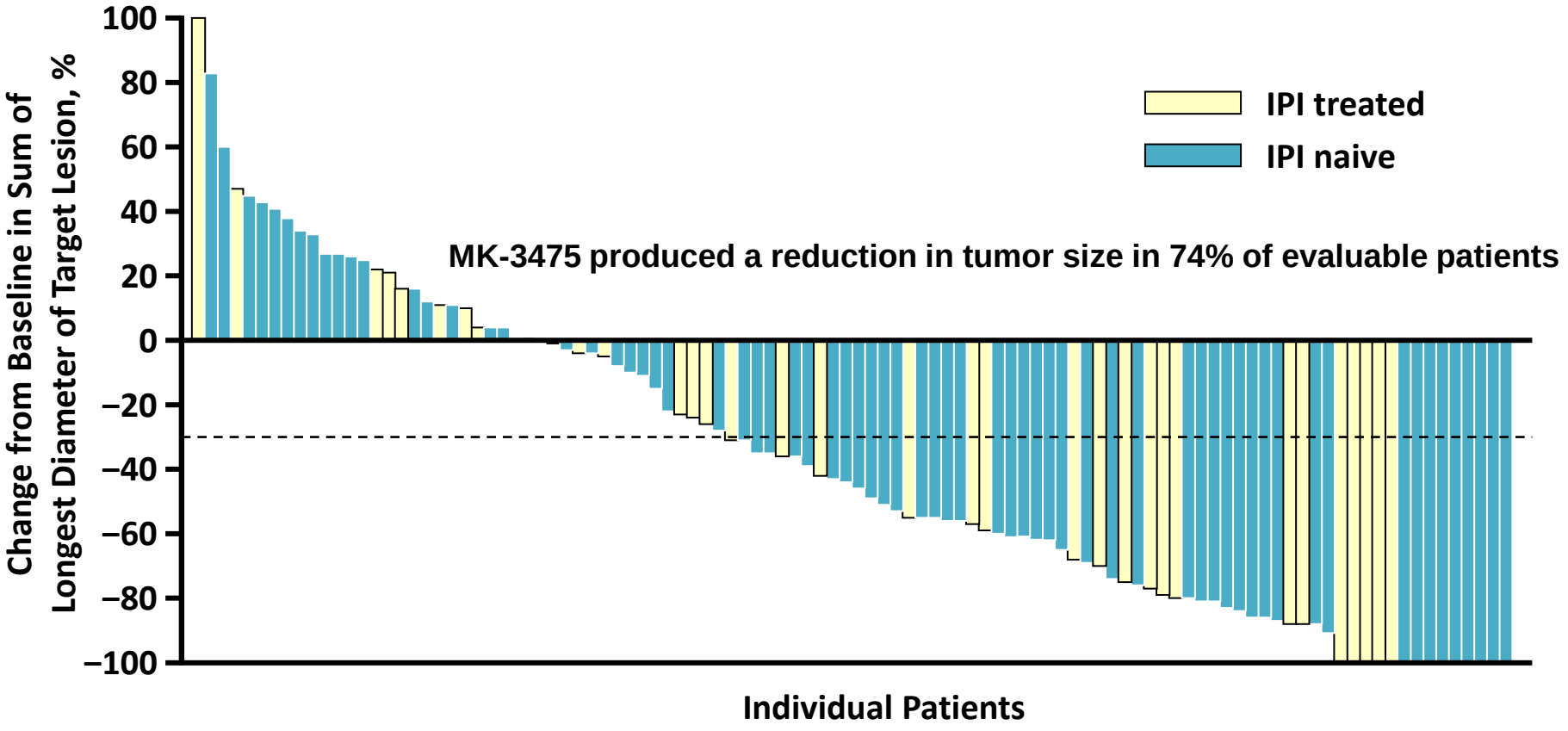
Long-term overall survival



Treatment Group	Overall survival rate, % [95% CI]				
	1-year	2-year	3-year	4-year	5-year
Ipi + DTIC (N=250)	47.6 [41.2-53.7]	28.9 [23.3-34.7]	**21.3 [16.3-26.6]**	**19.1 [14.4-24.3]**	**18.2 [13.6-23.4]**
Placebo + DTIC (N=252)	36.4 [30.4-42.4]	17.8 [13.3-22.8]	**12.1 [8.4-16.5]**	**9.7 [6.4-13.7]**	**8.8 [5.7-12.8]**

Maio et al ESMO 2013

Objective response of pembrolizumab



Ribas et al., ASCO 2014

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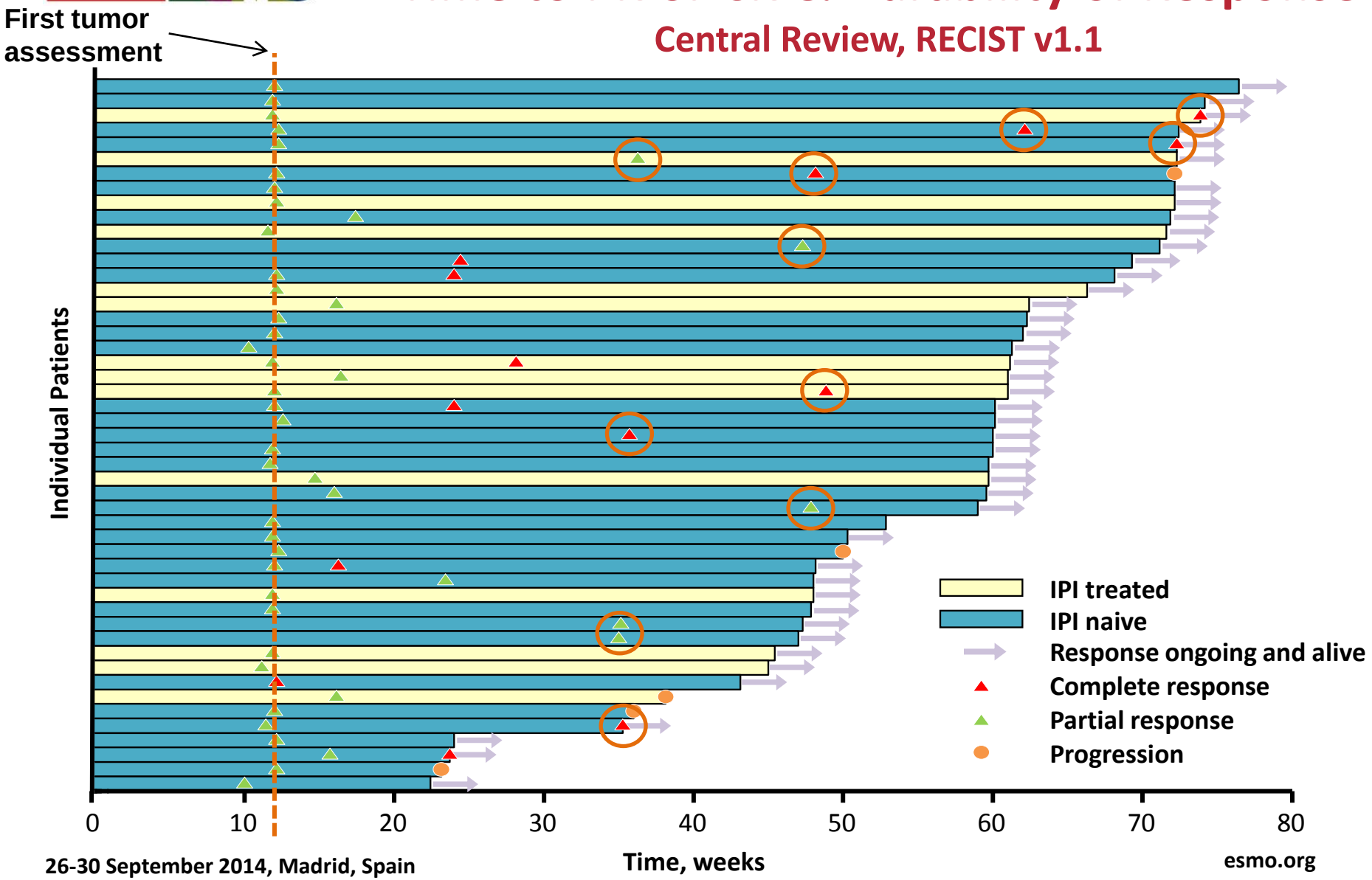
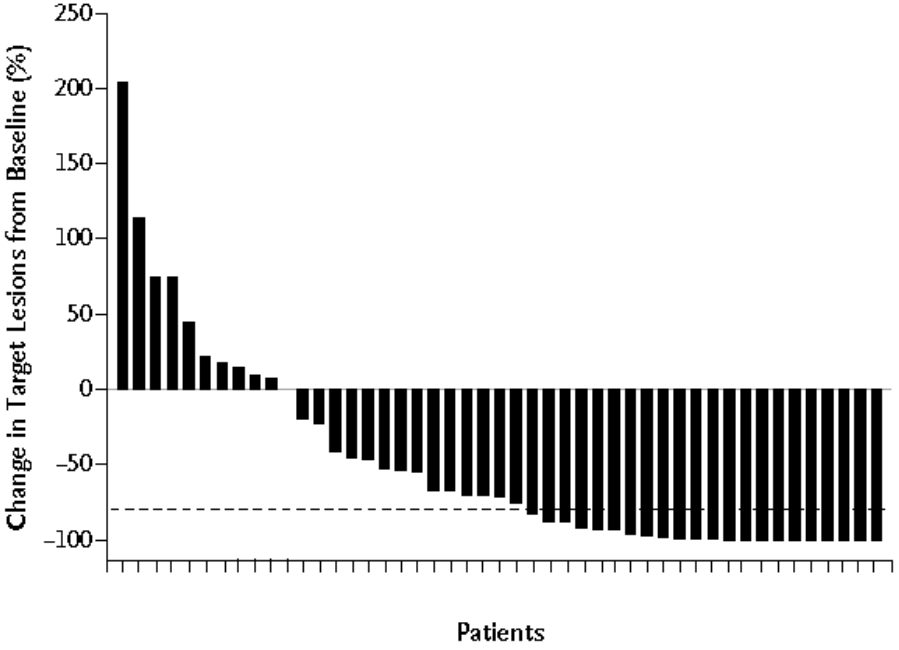
Time to PR or CR & Durability of Response

Central Review, RECIST v1.1

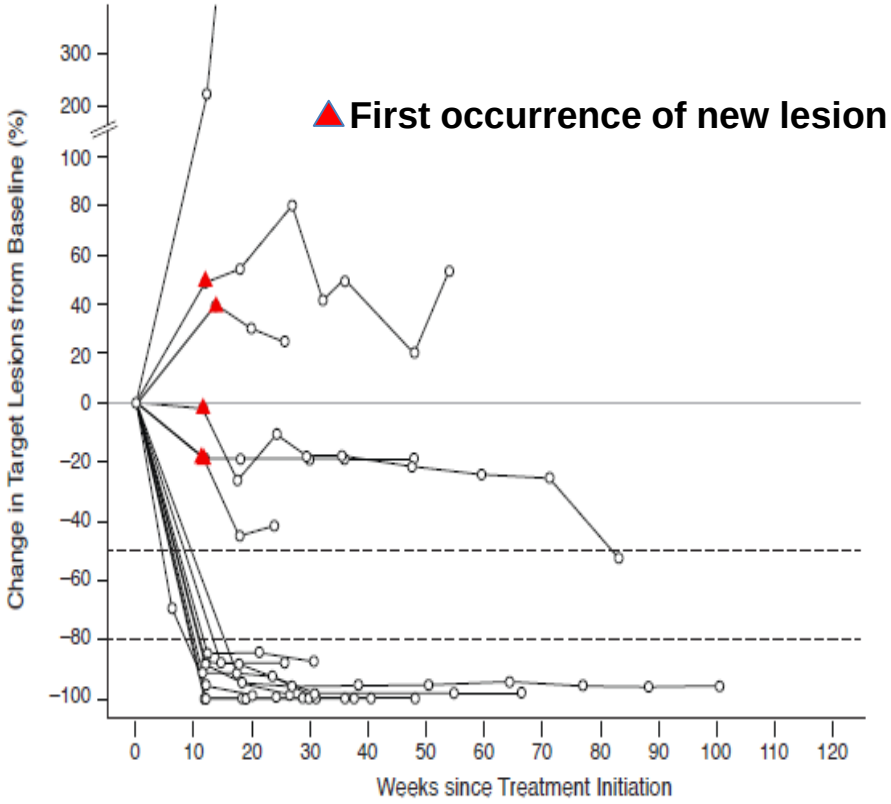


Ipilimumab + nivolumab

ORR: 40%



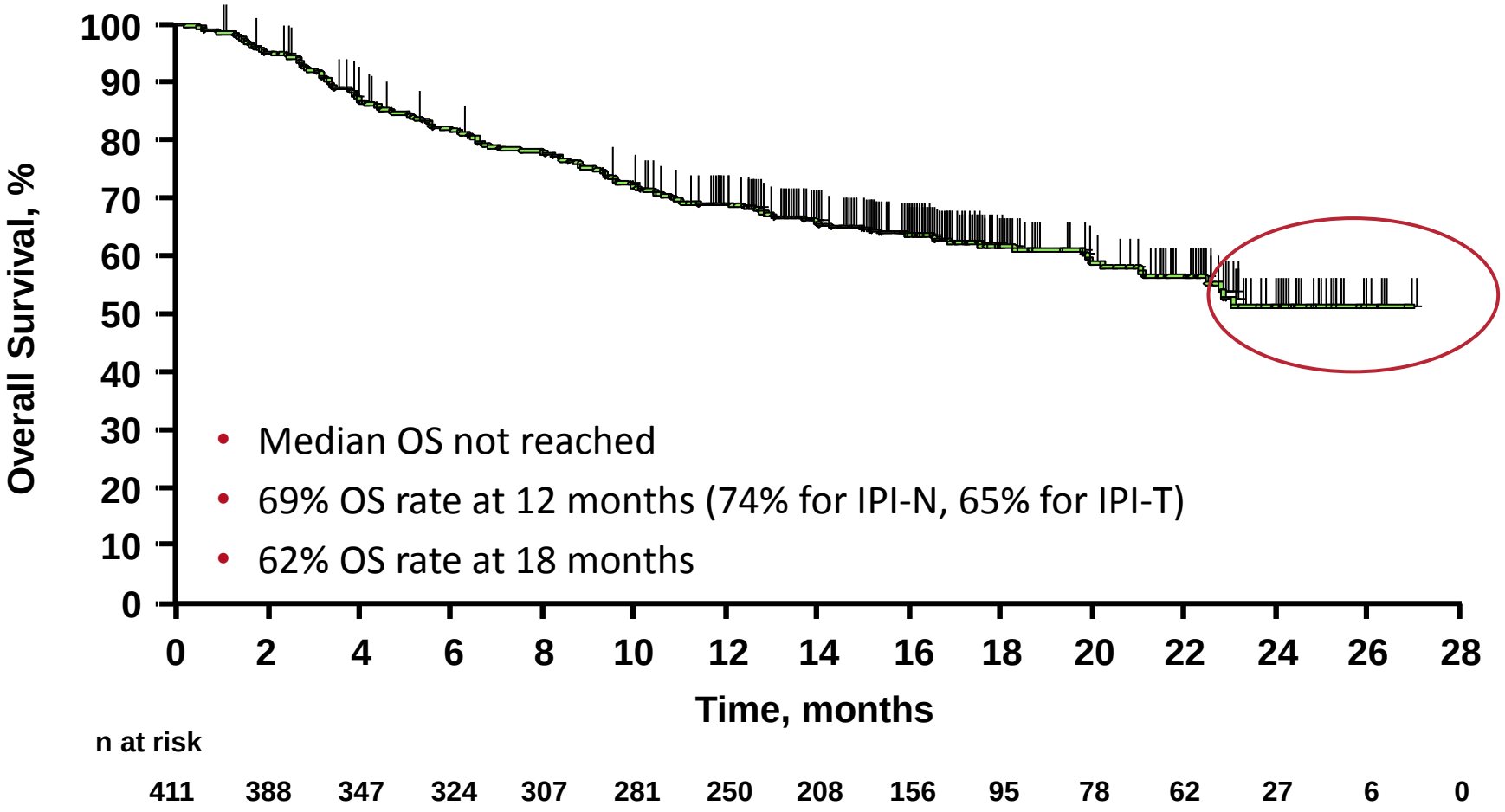
1 mg/kg nivolumab + 3 mg/kg ipilimumab



After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients still in response

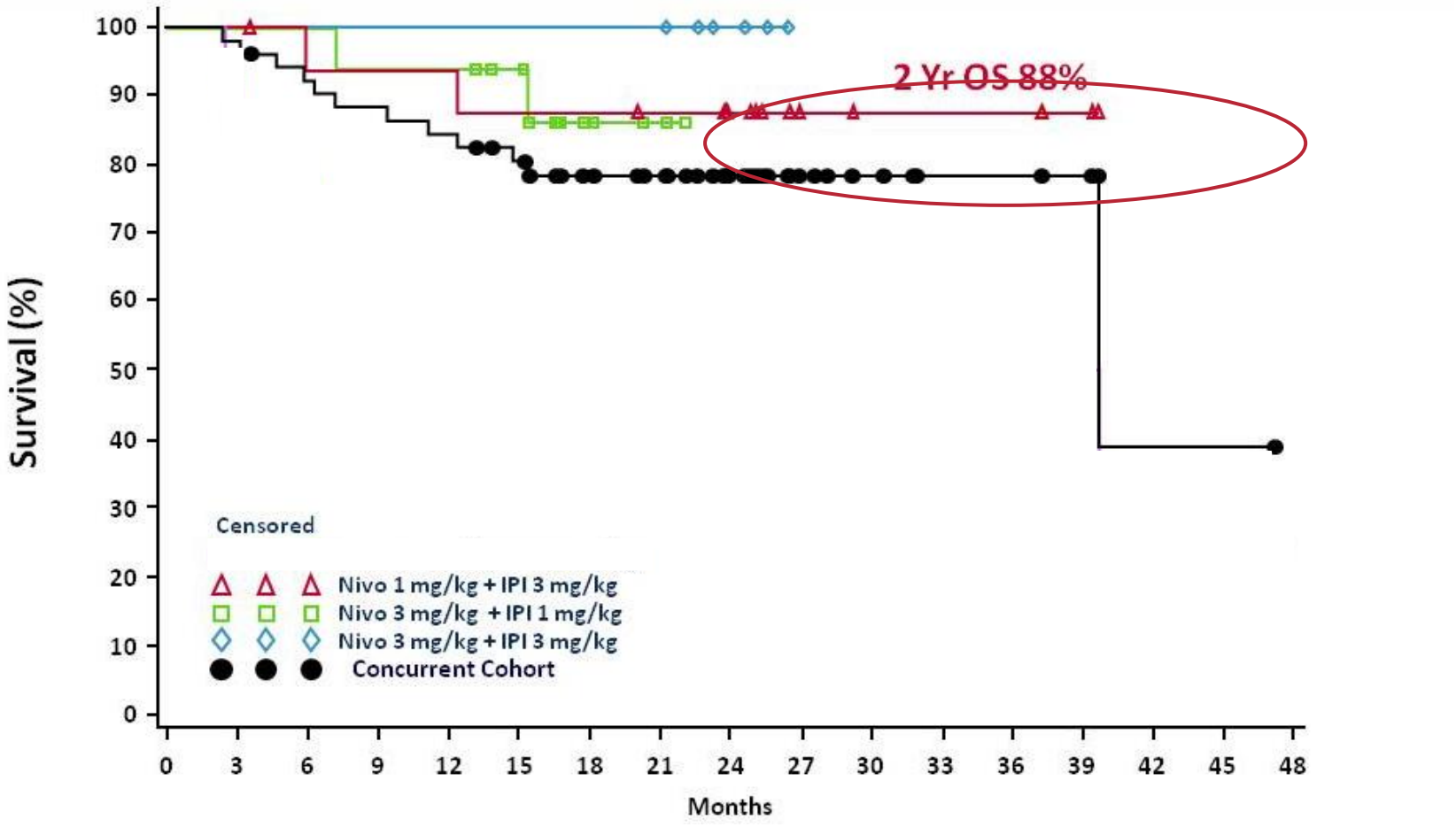
Wolchok et al. N Eng J Med 2013

Overall Survival of pembrolizumab



Ribas et al., ASCO 2014

Overall Survival with ipilimumab + nivolumab



Weber ASCO 2014

Conclusions

- Immunotherapy's mechanism of action is very different from classical chemotherapy or targeted therapy
- This is reflected by very different patterns and kinetics of response (mostly seen in ipi, much less in anti-PD1/PDL1 and ipi + nivo combination)
- In order to capture these different responses during clinical evaluations irRC have been developed (recently simplified to RECIST 1.1 based irRC)
- For anti-CTLA4 not ORR, PFS, nor median OS, but long-term survival was the most meaningful endpoint for clinical evaluation
- For anti-PD1/PD-L1 or ipi + nivo ORR and duration of response may be good endpoints, but long-term OS remains the most important endpoint for clinical evaluation