Immune therapy in melanoma

Tumor Immunology 101

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Disclosures

- Advisory board for Genoptix, BMS

- There will be discussion about the use of products for non-FDA approved indications in this presentation.

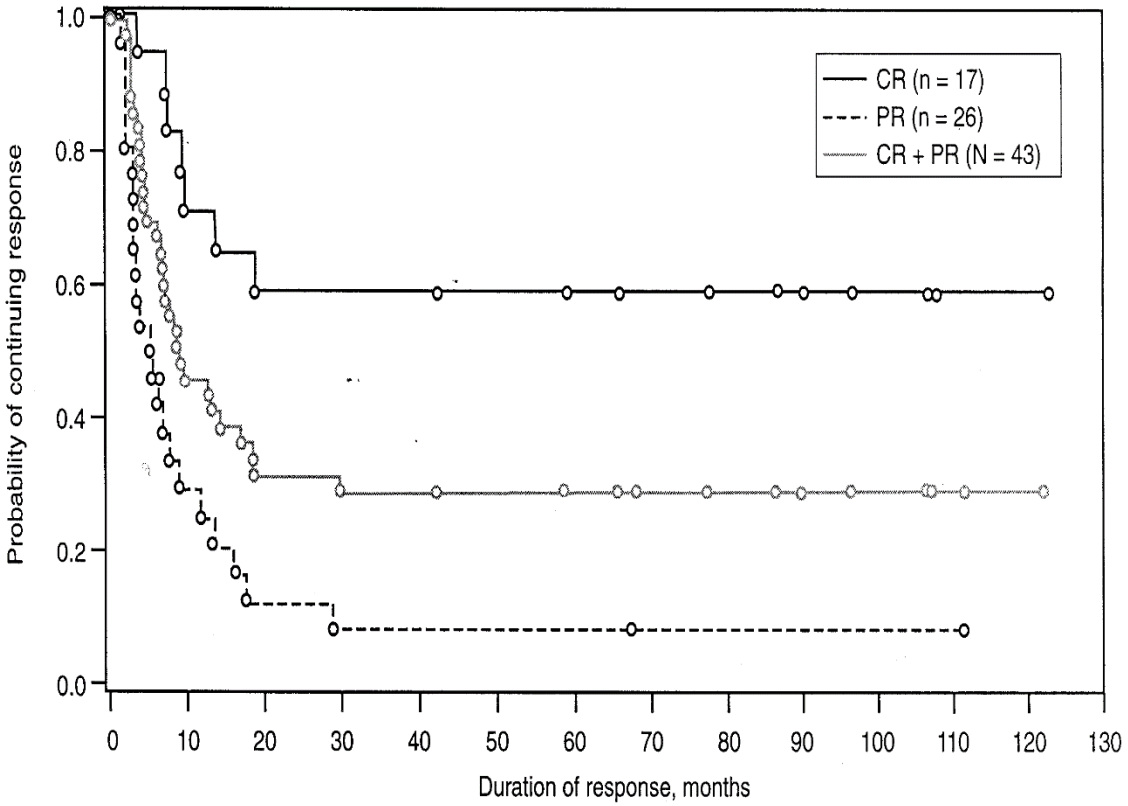
Outline

- **High-dose IL-2**
- Ipilimumab
- Anti-PD-1/PD-L1
- Combinations/future directions

High-dose IL-2

- First clearly effective immune therapy in cancer
- Prolonged responses in a subset
- Severe acute toxicities
  - Limits use to otherwise healthy patients
  - Multiorgan dysfunction/SIRS
  - Limited to experienced centers
  - May (still) be an option in carefully selected patients

High Dose IL-2



- RR: 16% (43 / 270)
  - Some large volume and visceral
  - Most soft tissue and lung
- Durable responses
  - Median 8.9 mos
  - CR: not reached
- Survival
  - Median 12 mos
  - 11% >@ 5yrs

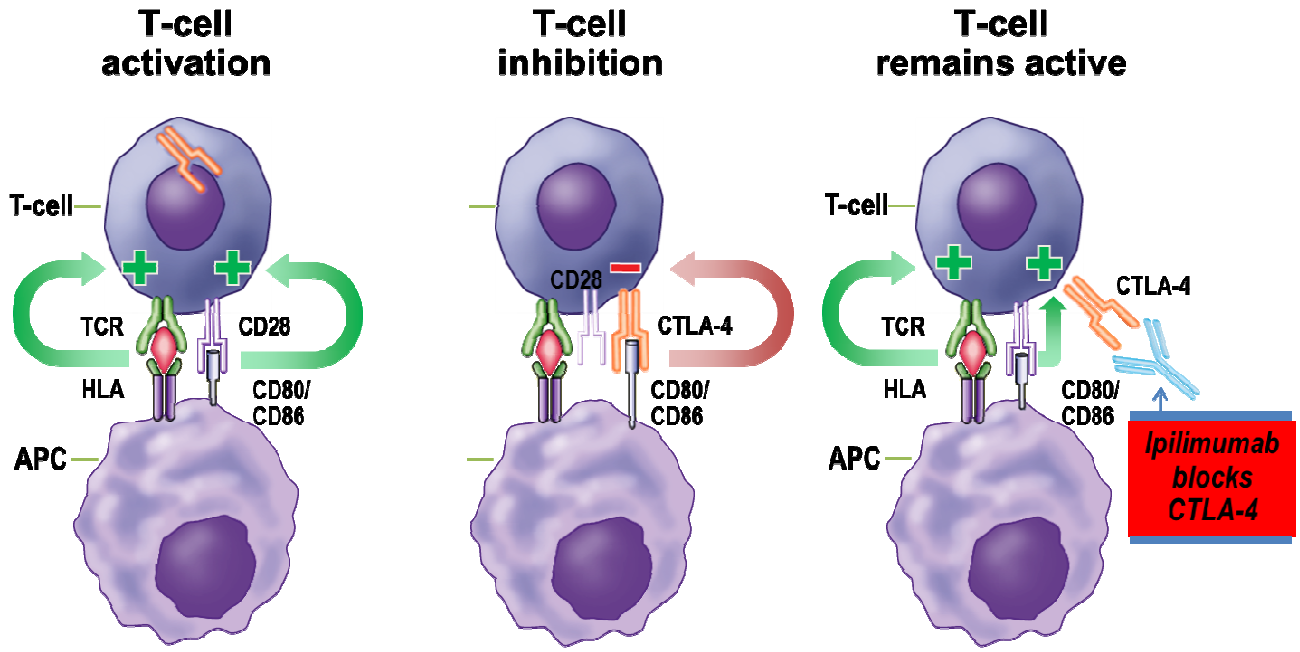
***Atkins et al JCO, 1999 (N=270)**

Outline

- High-dose IL-2
- **Ipilimumab**
- Anti-PD-1/PD-L1
- Combinations/future directions

Ipilimumab

- Monoclonal antibody to CTLA-4
- First “immune checkpoint inhibitor”
- Unleashes suppressed immune responses



Adapted from O’Day et al. Plenary session, ASCO 2010.

Ipilimumab

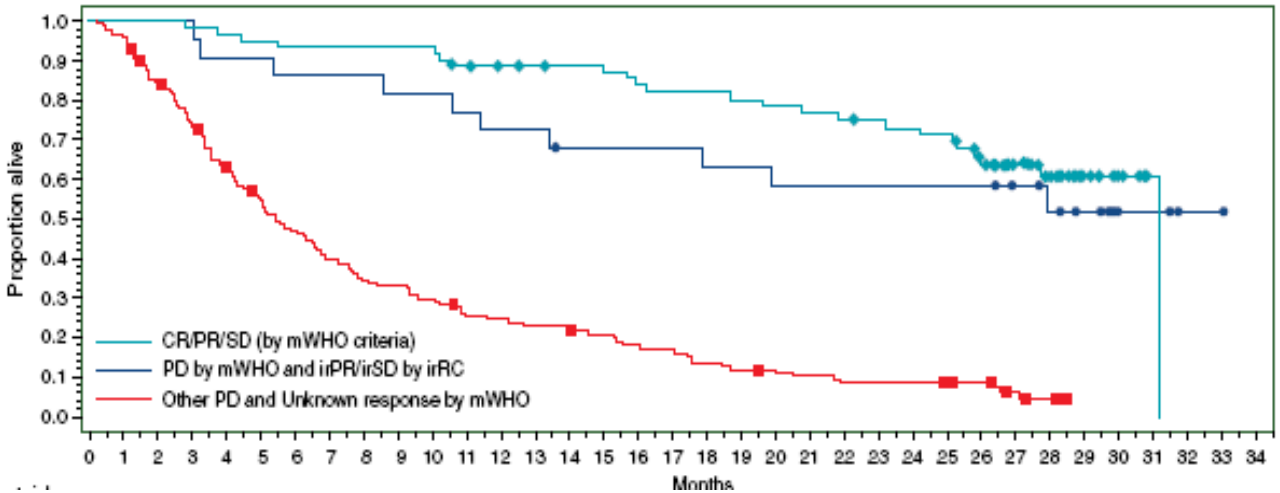
- First agent to improve survival in advanced melanoma (compared to vaccine)
- Median OS 10 vs. 6.4 months, $p < 0.001$
- Also improved survival in combination with dacarbazine
- Low response rates (10-15%)

Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

Hodi et al NEJM 2010

Ipilimumab

- Unconventional responses
  - Could have classic responses or stable/slow regression
  - Could also have responses after new lesions or growth in existing lesions
  - "Pseudoprogression" – rarely symptomatic and usually within first 3 months



Wolchok et al, *Clin Cancer Res*, 2009

Ipilimumab

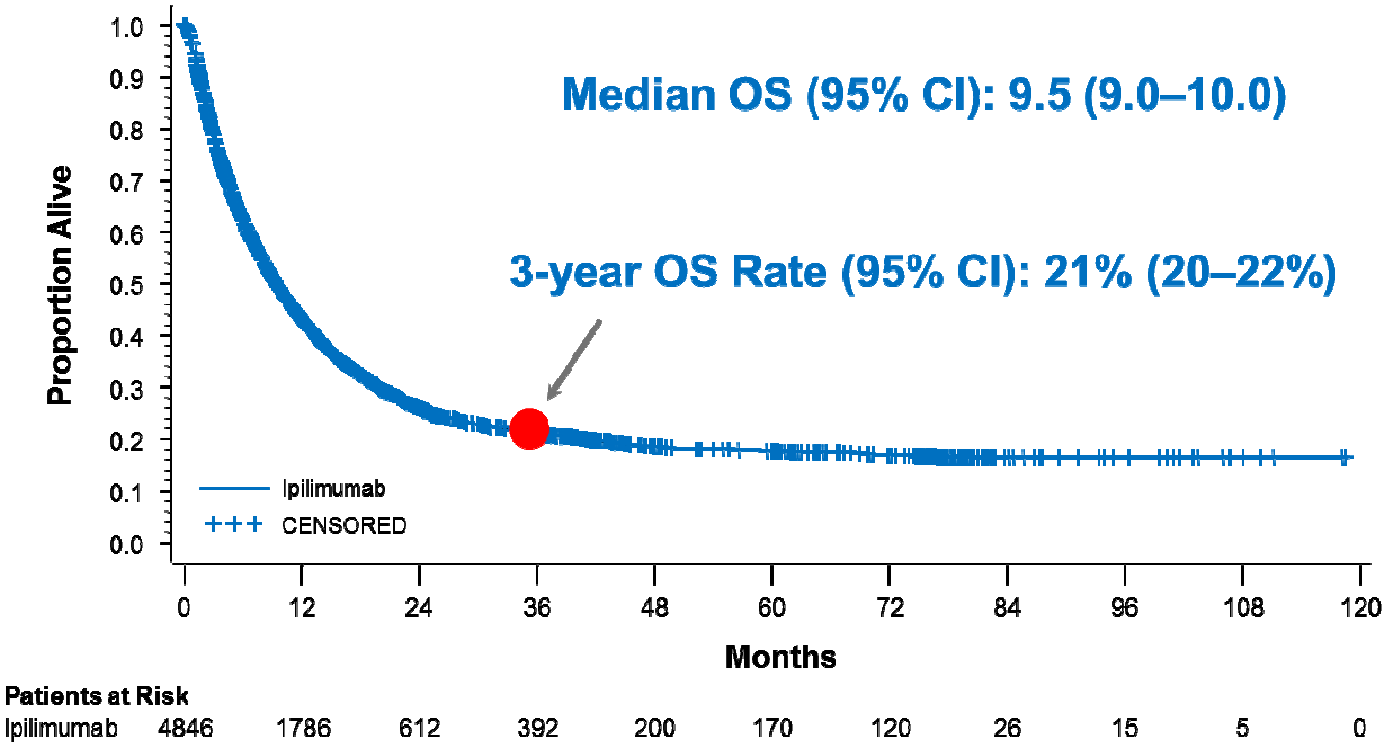
- Unconventional toxicities (immune related)

% of Patients			
irAE	**Ipi + gp100 N=380**	**Ipi +pbo N=131**	**gp100 + pbo N=132**
All grades			
Any	**57**	**60**	**32**
Dermatologic	**39**	**42**	**17**
GI	**31**	**28**	**14**
Endocrine	**3**	**8**	**2**
Hepatic	**2**	**3**	**4**

Hodi et al NEJM 2010

Ipilimumab

- Unconventional outcomes



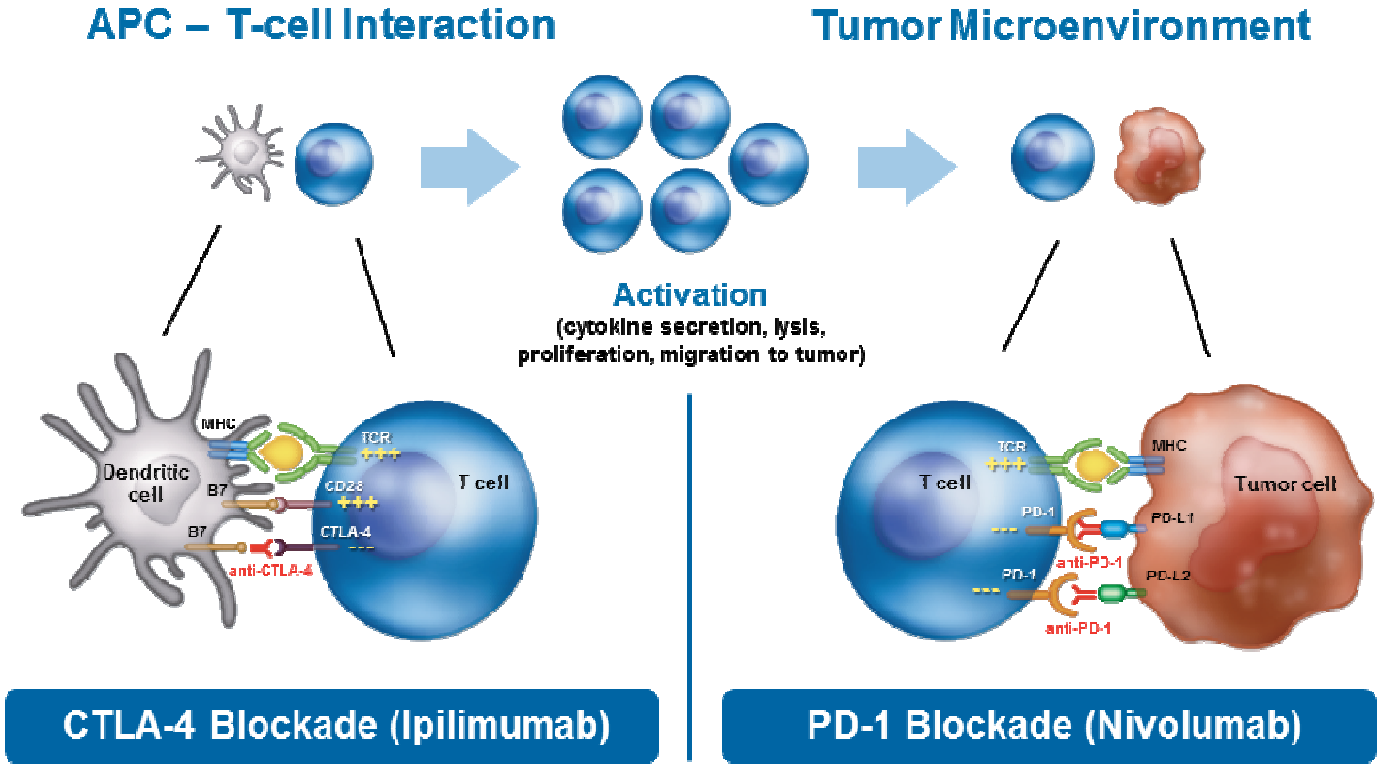
Schadendorf et al, ESMO, 2013

Outline

- High-dose IL-2
- Ipilimumab
- **Anti-PD-1/PD-L1**
- Combinations/future directions

Anti-PD-1/PD-L1

- Monoclonal antibody to PD-1 or PD-L1
- Improved response rates/survival
- Improved toxicity profile



Adapted from Wolchok J, ASCO 2015

Anti-PD-1/PD-L1

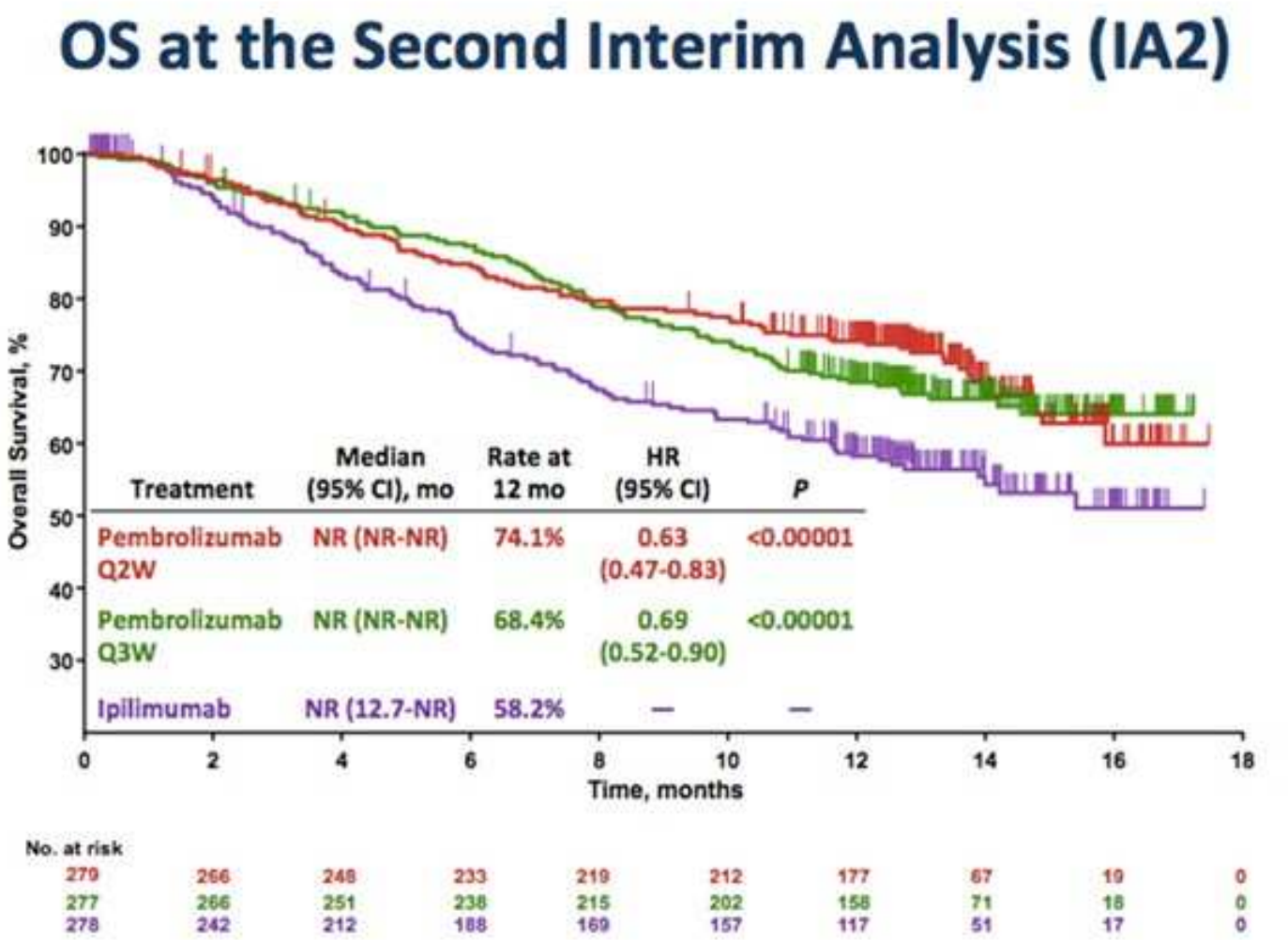
- Nivolumab (BMS-936558): Anti-PD-1
- Pembrolizumab (MK-3475): Anti-PD-1
- Atezolizumab (MPDL3280a): Anti-PD-L1
- Each showed response rates of 25-40% in phase I trials, often heavily pre-treated
- Less common atypical immune responses
- More rapid and frequent responses
- Favorable toxicity profiles

Pembrolizumab vs. Ipilimumab

- 834 patients naïve to anti-PD-1 or ipilimumab
- Randomized to 2 doses of pembro vs. ipi
- Improved outcomes with pembrolizumab
  - Response rates (33 vs. 12%)
  - 6-month PFS (47% vs. 27%)
  - 12-month OS (~71% vs. 58%)
  - Grade 3/4 AEs (12% vs. 19%)
  - All p-values < 0.05
- **Pembrolizumab is preferred over ipilimumab as first-line immune therapy (off label)**

Robert et al NEJM 2015

Pembrolizumab vs. Ipi



Ribas et al, AACR 2015

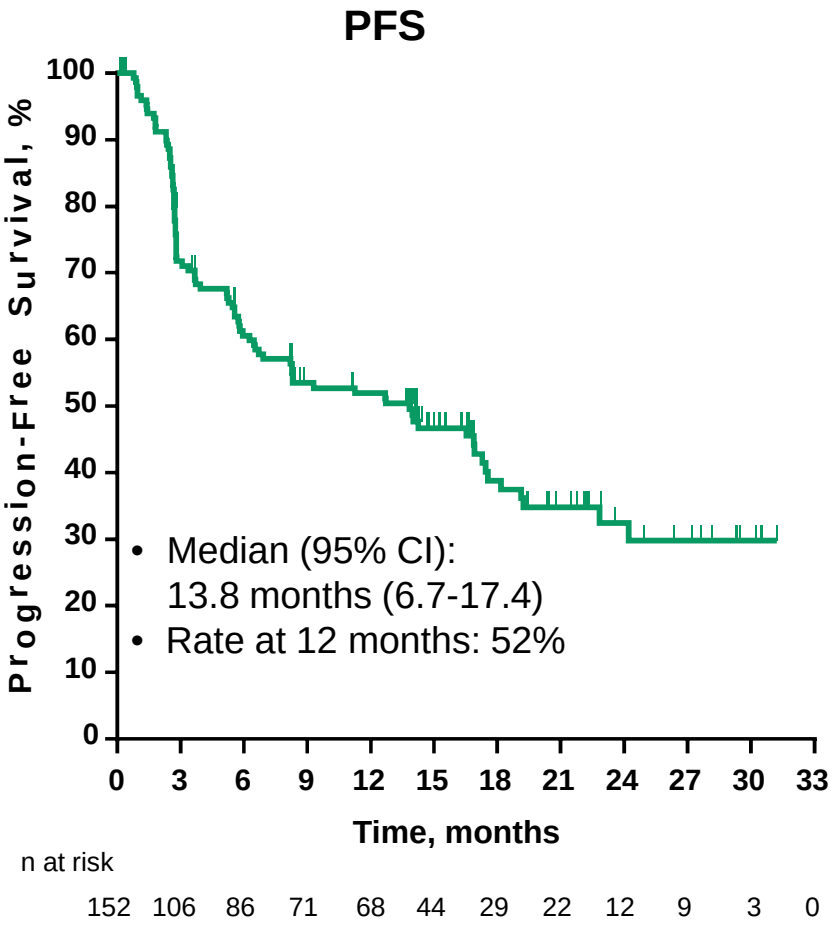
Pembrolizumab as First-Line Therapy[a]

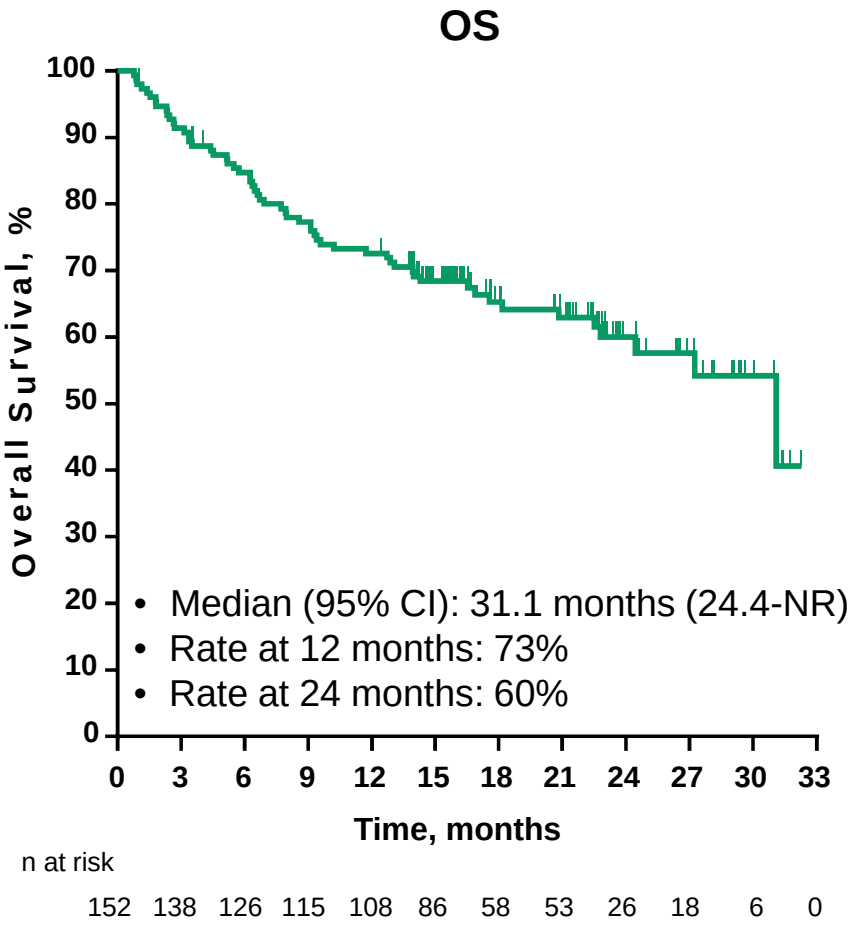
	Total (N = 133)
Complete response, % (95% CI)	13.5 (8.2-20.5)
ORR, % (95% CI)	45.1 (36.5-54.0)
DCR, % (95% CI)	60.9 (52.1-69.2)

Courtesy of A Daud, ASCO 2015

[a]Excludes patients with ocular melanoma.
Analysis cut-off date: October 18, 2014.

Kaplan-Meier Estimates of PFS and OS in Treatment-Naive Patients (n = 152[a])





Courtesy of A Daud, ASCO 2015

[a]Excludes patients with ocular melanoma.
Analysis cut-off date: October 18, 2014.

AEs of Interest Based on Immune Etiology

Adverse Event, n (%)	Any Grade	Grade 3-4
Hypothyroidism	49 (7.5)	1 (0.2)
Hyperthyroidism	15 (2.3)	2 (0.3)
Pneumonitis[a]	18 (2.7)	2 (0.3)
Colitis[b]	11 (1.7)	7 (1.1)
Hepatitis[c]	4 (0.6)	2 (0.3)
Nephritis[d]	3 (0.5)	2 (0.3)
Uveitis[e]	6 (0.9)	0 (0.0)

- Some reported skin rashes may have been immune-mediated
- Other immune-mediated events observed in >2 patients: thyroiditis (n = 6); hypophysitis, hypopituitarism, pruritus, and rash (n = 3 each); autoimmune thyroiditis, myositis, and rash generalized (n = 2 each)

Courtesy of A Daud, ASCO 2015

[a]Includes interstitial lung disease of grade 1-2. [b]Includes colitis microscopic and enterocolitis. [c]Includes autoimmune hepatitis. [d]Includes renal failure. [e]Includes iridocyclitis and iritis.
Analysis cut-off date: April 18, 2014.

Outline

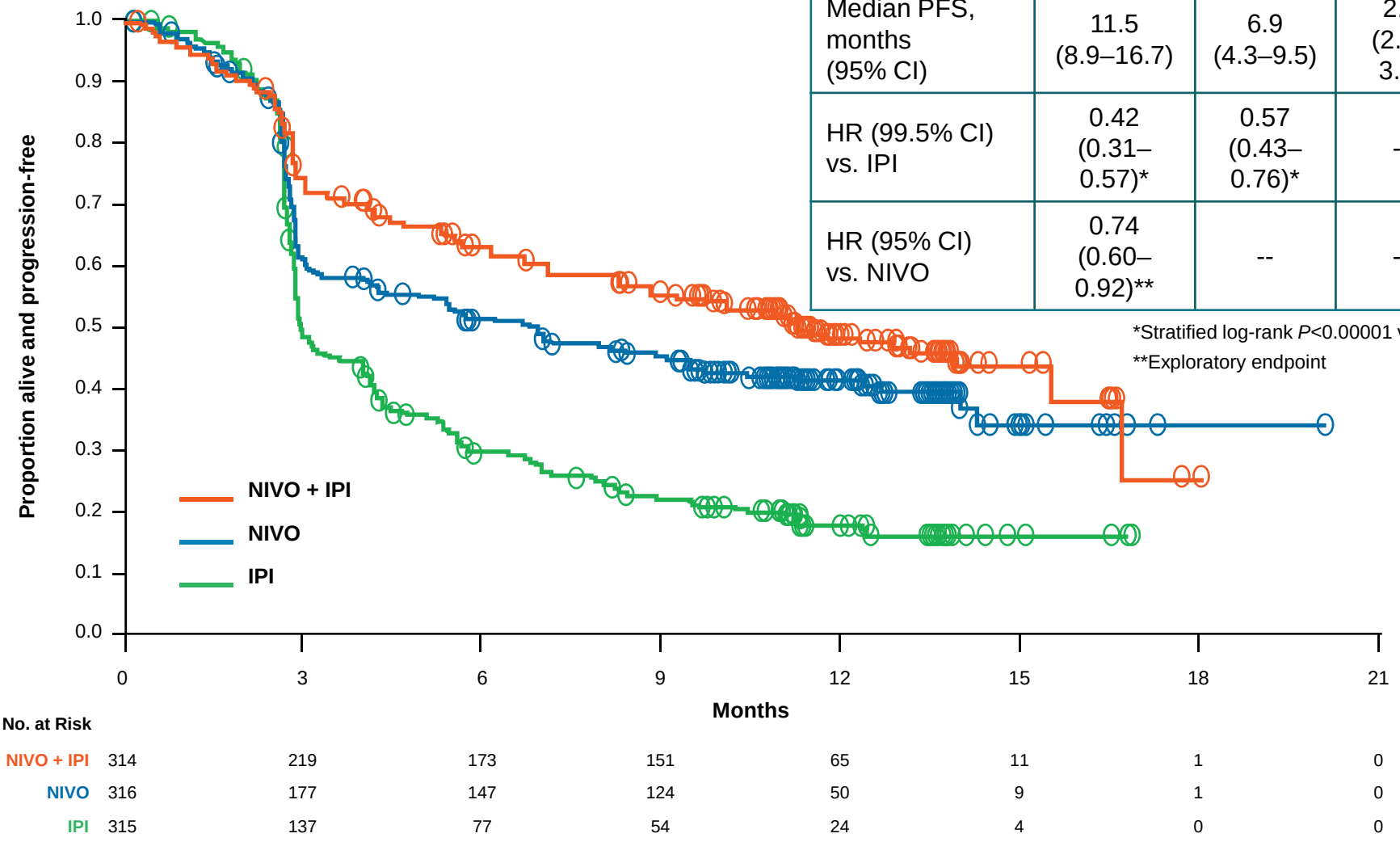
- High-dose IL-2
- Ipilimumab
- Anti-PD-1/PD-L1
- **Combinations/future directions**

Phase III trial: Nivolumab + Ipi vs. Nivo vs. Ipi

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

*Stratified log-rank *P*<0.00001 vs. IPI

**Exploratory endpoint



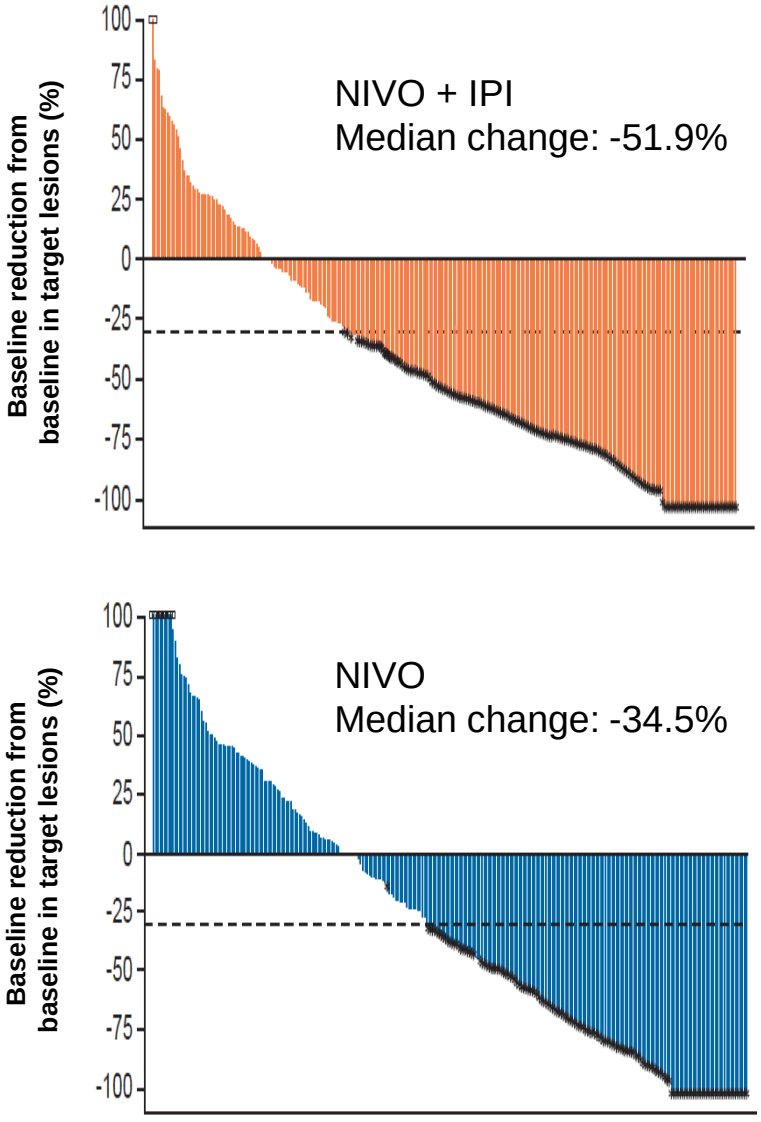
Adapted from Wolchok J, ASCO 2015

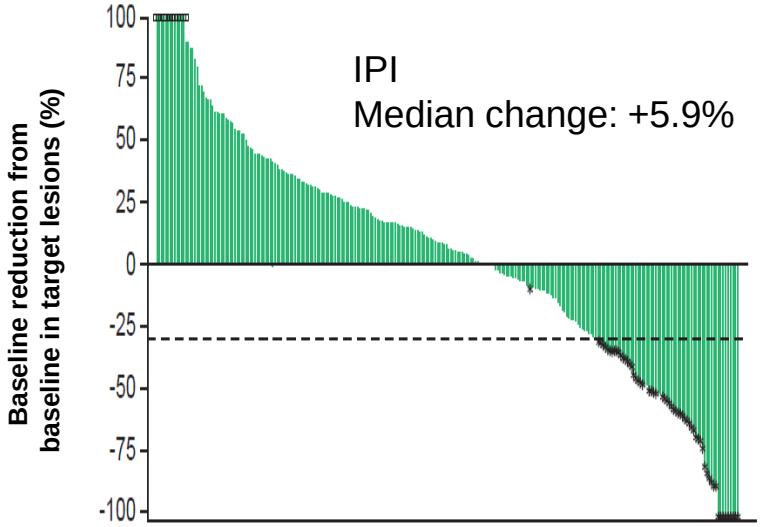
Response to Treatment

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	**57.6** (52.0–63.2)	**43.7** (38.1–49.3)	**19.0** (14.9–23.8)
Two-sided *P* value vs ipi	<0.001	<0.001	--
Best overall response %			
Complete response	11.5	8.9	2.2
Partial response	46.2	34.8	16.8
Stable disease	13.1	10.8	21.9
Progressive disease	22.6	37.7	48.9
Unknown	6.7	7.9	10.2

Adapted from Wolchok J, ASCO 2015
Larkin et al NEJM 2015

Tumor Burden Change From Baseline





Adapted from Wolchok J, ASCO 2015
Larkin et al NEJM 2015

Safety Summary

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

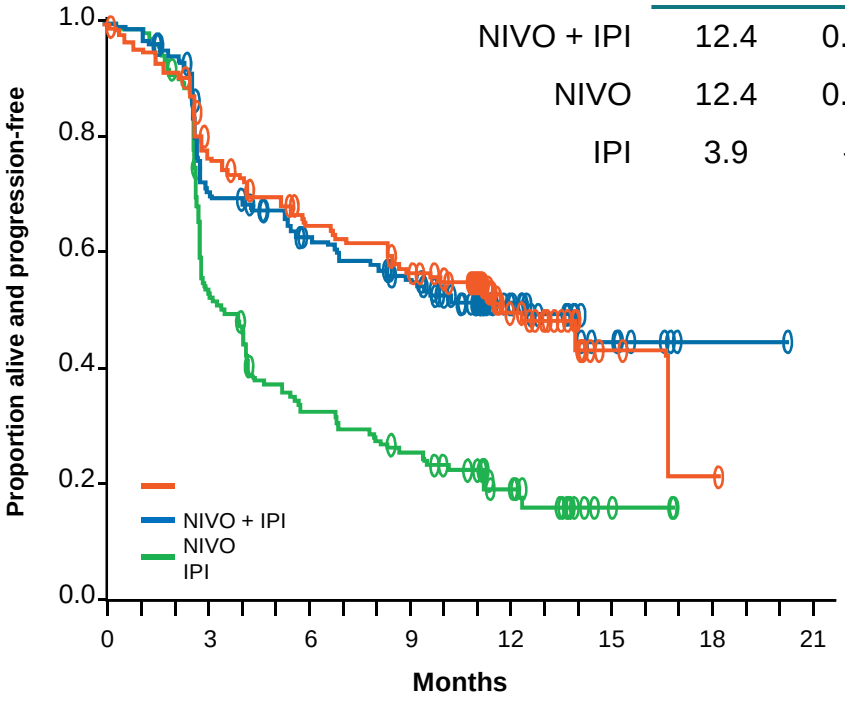
Adapted from Wolchok J, ASCO 2015
Larkin et al NEJM 2015

What is next?

- Combinations
  - Immune, targeted, injectable combinations
  - Augment activity, lessen toxicity?
- Biomarkers
  - Determine who gets single-agent vs. who gets combination

PFS by PD-L1 Expression Level (1%)

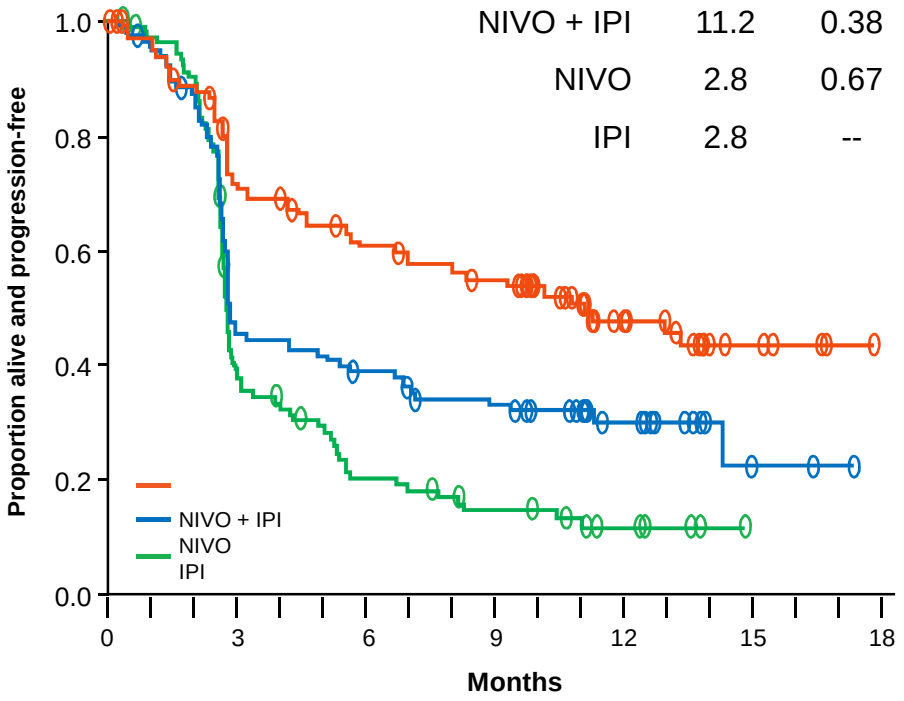
PD-L1 ≥1%*



	mPFS	HR
NIVO + IPI	12.4	0.44
NIVO	12.4	0.46
IPI	3.9	--

No. at Risk								
NIVO + IPI	155	113	91	78	32	4	1	
NIVO	171	115	97	83	34	7	1	0
IPI	164	83	47	36	16	3		

PD-L1 <1%*



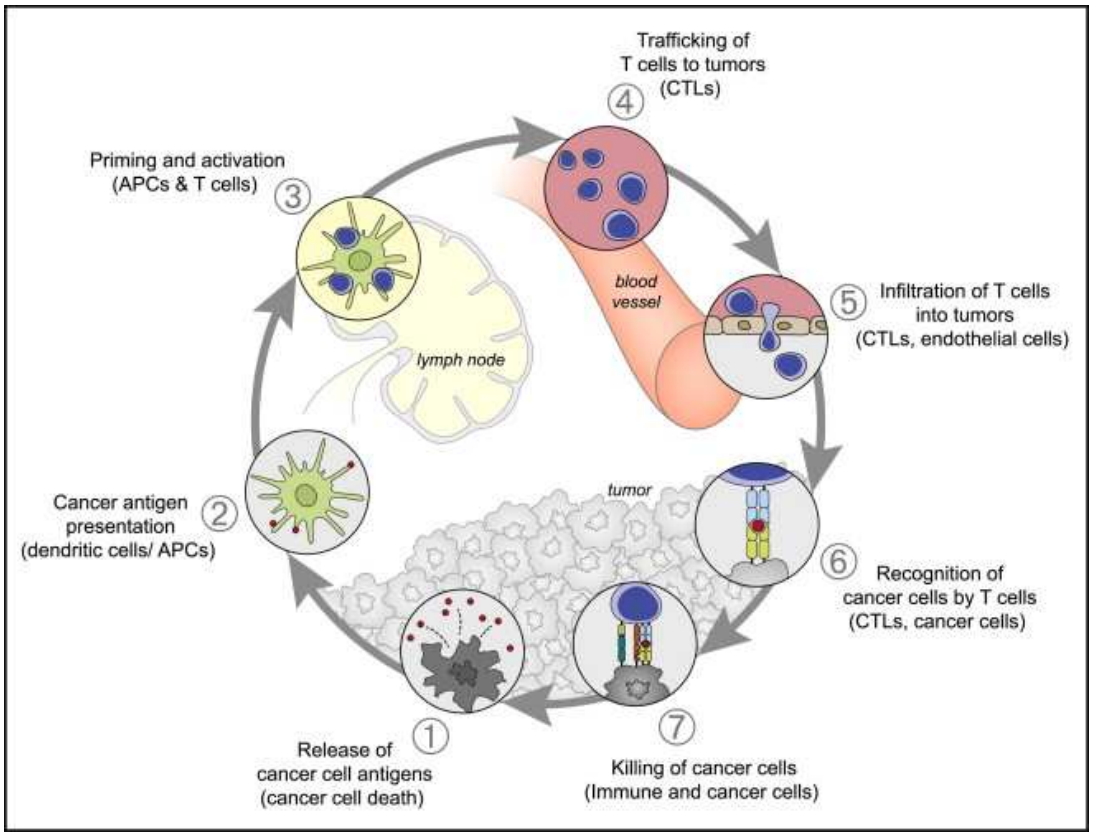
	mPFS	HR
NIVO + IPI	11.2	0.38
NIVO	2.8	0.67
IPI	2.8	--

No. at Risk							
NIVO + IPI	123	82	65	57	26	6	0
NIVO	117	50	42	34	13	2	0
IPI	113	39	19	12	5	0	

Adapted from Wolchok J, ASCO 2015
Larkin et al NEJM 2015

Biomarkers

- Mutational burden (tumor neoantigens)
- Antigen expression
- Infiltrating lymphocytes
- Immune checkpoints



Mellmen and Chen, Immunity 2013

Immune Therapy Conclusions

- IL-2 may still be an option for carefully considered patients
- Anti-PD-1 should generally be considered the first-line immune therapy approach for advanced melanoma
- Nivolumab + ipilimumab may be better than anti-PD-1 alone
  - Awaiting overall survival
  - Toxicity is worse (but manageable….)
  - Biomarkers will likely help stratify