Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the treatment of melanoma

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Advances in Cancer Immunotherapy™ - New Jersey
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Society for Immunotherapy of Cancer (SITC)

- Research funding from Amgen and Merck
- Recent scientific advisory board member for Amgen

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Topics of Discussion

- Overview of Targeted Versus Immunotherapy
- Interleukin-2
- Ipilimumab
- Pembrolizumab and Nivolumab
- Biomarkers

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Key Randomized Trials for Stage IV Melanoma

Table 4. Key Randomized Trials for Stage IV Melanoma.*

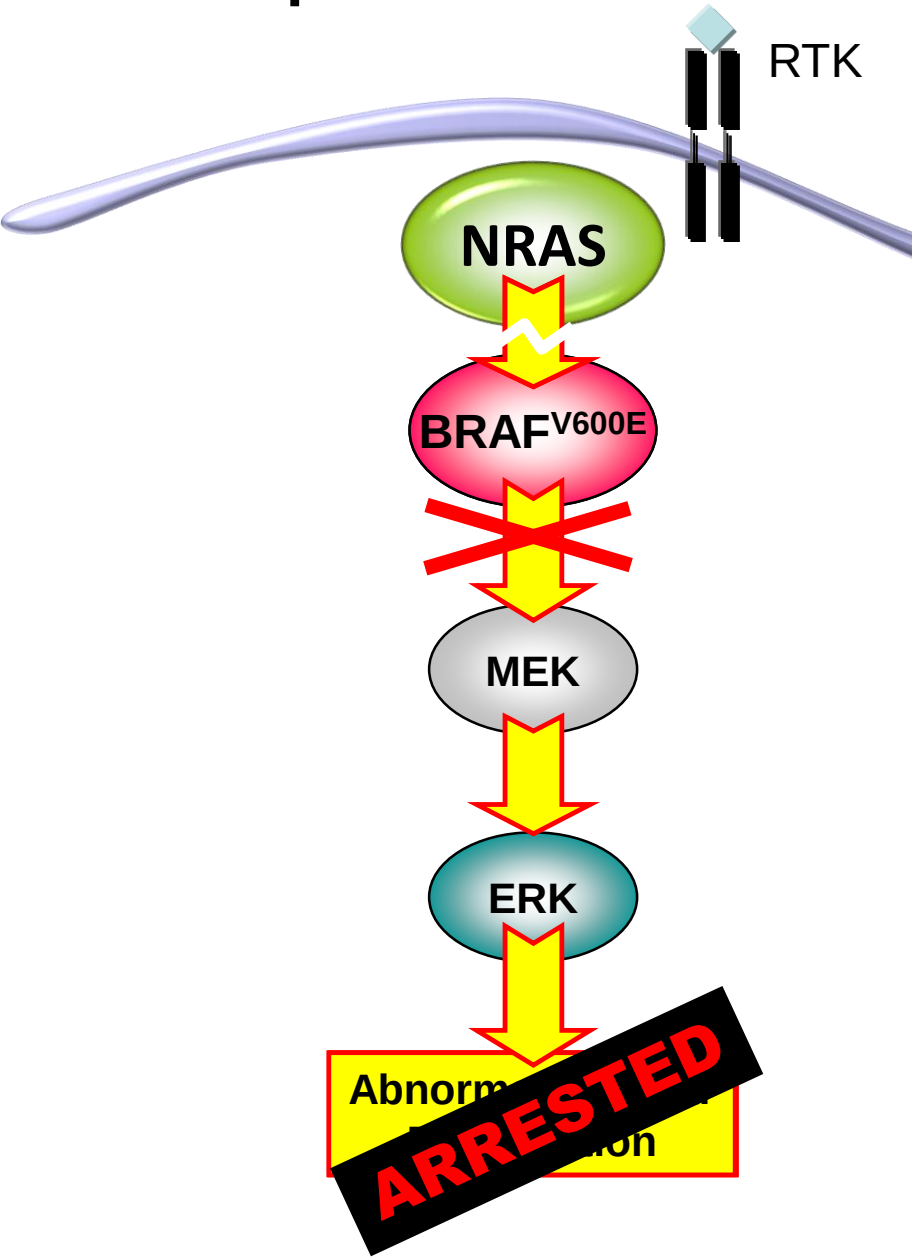
Study	Trial Regimen	No. of Patients	Response Rate	Median Survival
			%	*mo*
Costanzi et al.	Carmustine, hydroxyurea, and dacarbazine with or without BCG	256	29	With BCG, 6.7; without BCG, 6
	versus			
	Dacarbazine and BCG	130	18	6.9
Buzaid et al.	Cisplatin, vinblastine, and dacarbazine	46	24	6
	versus			
	Dacarbazine	45	11	5
Chapman et al.	Cisplatin, dacarbazine, carmustine, and tamoxifen	108	18	7
	versus			
	Dacarbazine	118	10	7
Cocconi et al.	Dacarbazine and tamoxifen	60	28†	10.7‡
	versus			
	Dacarbazine	52	12	6.4
Rusthoven et al.	Cisplatin, dacarbazine, carmustine, and tamoxifen	98	30	Men, 6.4; women, 6.9
	versus			
	Cisplatin, dacarbazine, and carmustine	97	21	Men, 6.4; women, 7.1
Falkson et al.	Dacarbazine and interferon alfa	30	53	17.6§
	versus			
	Dacarbazine	30	18	9.6
Falkson et al.	Dacarbazine, interferon alfa with or without tamoxifen	126	16	With tamoxifen, 9.5; without tamoxifen, 9.3
	versus			
	Dacarbazine with or without tamoxifen	129	21	With tamoxifen, 8; without tamoxifen, 10
Keilholz et al.	Interleukin-2 (decrescendo regimen) and interferon alfa	66	18	9
	versus			
	Cisplatin, interleukin-2, and interferon alfa	60	35; overall survival same	9
Rosenberg et al.	Cisplatin, dacarbazine, and tamoxifen	52	27	15.8
	versus			
	Cisplatin, dacarbazine, tamoxifen, high-dose interleukin-2, and interferon alfa	50	44; overall survival worse	10.7
Eton et al.	Cisplatin, vinblastine, and dacarbazine	92	25	9.5
	versus			
	Cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa (sequential)	91	48	11.8
Keilholz et al.	Cisplatin, dacarbazine, and interferon alfa	180	23	9.0
	versus			
	Cisplatin, dacarbazine, interferon alfa, and interleukin-2	183	21	9.0
Atkins et al.	Cisplatin, vinblastine, and dacarbazine	201	11	8.7
	versus			
	Cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa (concurrent)	204	17	8.4

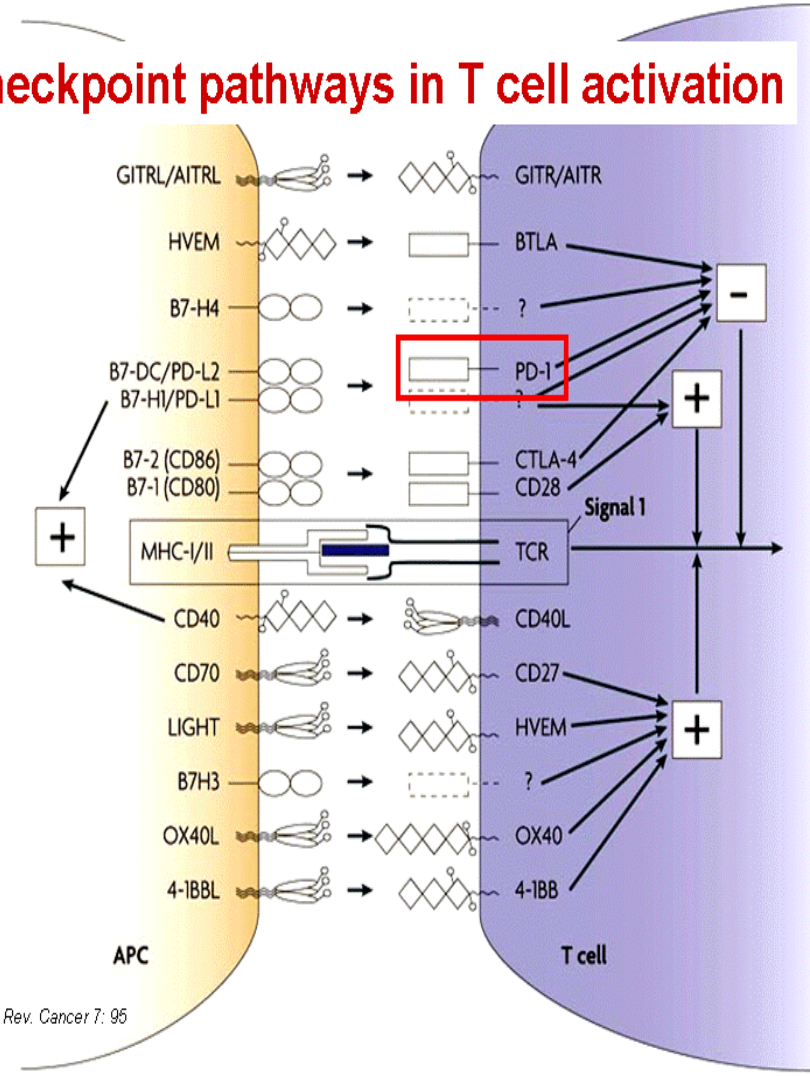
* All study data are taken from Atkins et al.[86] BCG denotes bacille Calmette–Guérin.
† P=0.03.
‡ P=0.02.
§ P<0.01.

BOY, TIMES HAVE CHANGED

The NEW ENGLAND JOURNAL of MEDICINE

Landscape of Melanoma Therapy in 2014





Acknowledgement: Keith Flaherty

Targeted Versus Immunotherapies

Targeted therapies: Manipulating the Tumor

- BRAF and MEK Inhibition

(oral tyrosine kinase inhibitors)

- Chronic toxicities, often

predictable

- High response rate
- Predictive Biomarkers
- Inevitable resistance with much insight but more to learn

Immunotherapies: Manipulating the Immune System

- Cytokines (IL-2) and immune checkpoint inhibition (anti- CTLA-4,Pd-1 antibodies)
- Mostly manageable but some “fast and furious” toxicities
- Low(er) response rate
- Predictive Biomarkers?
- Durable responses; but resistance?

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IN THE BEGINNING….

INTERLEUKIN-2
(a brief recap)

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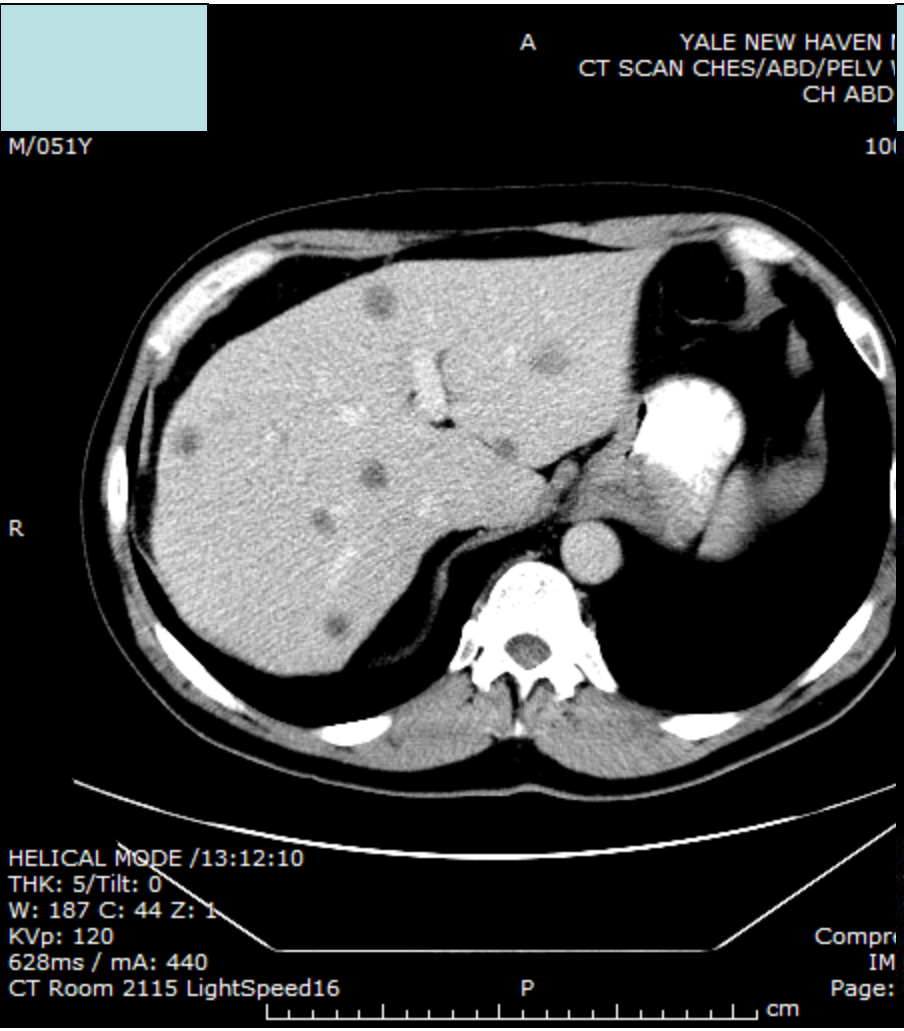

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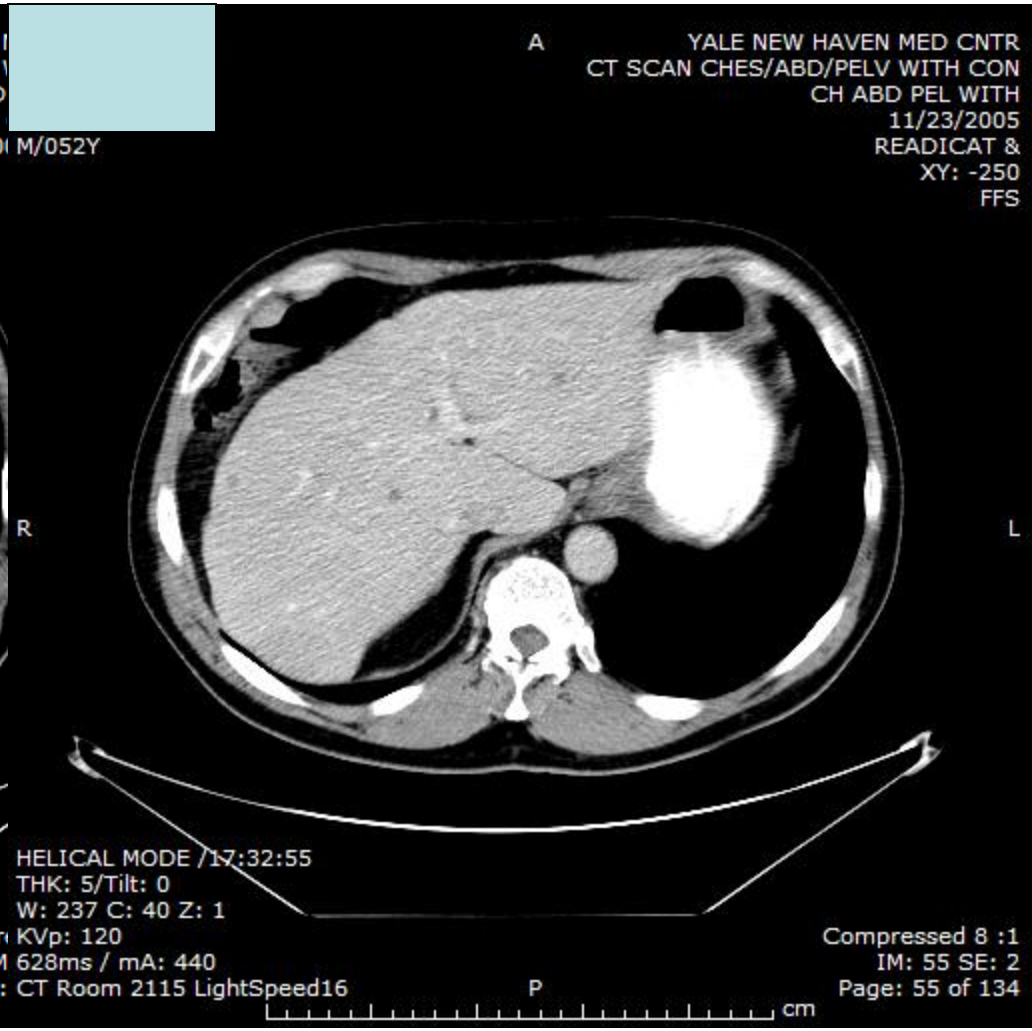

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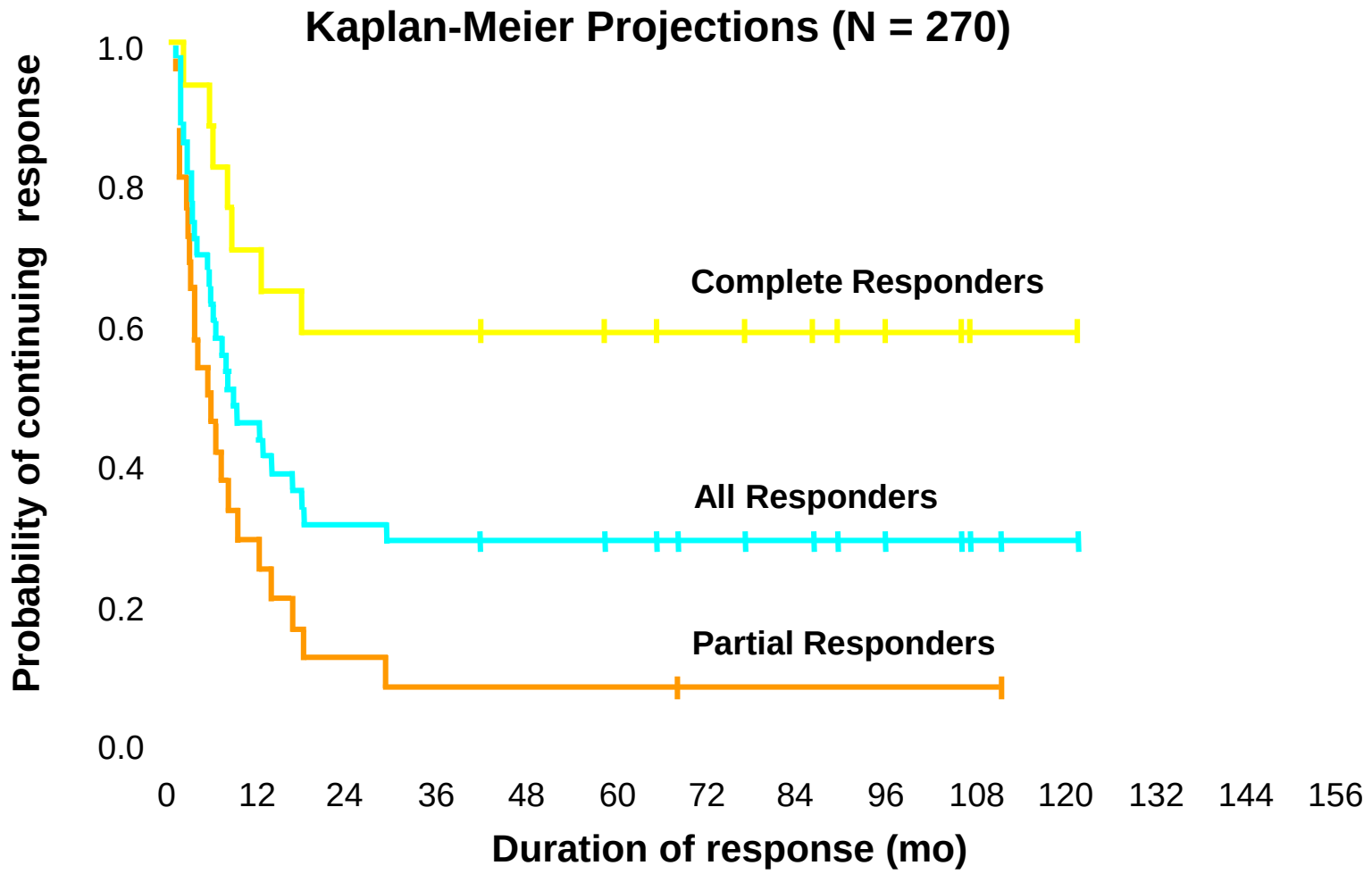
High-dose IL-2 induces durable objective clinical responses in 15-20%



Data on file. Chiron Corporation. Acknowledgement, H. Kaufman

In the Beginning…. IL-2

Atkins et al, J Clin Oncol, 1999

Number of Patients	**270**
Responders	**43 (16%)**
Complete Responders	**17 (6%)**
Durable Responses > 24 months	**12 (4.4%)**
Median Survival	**12 months**
Median duration of response	**8.9 months**
Durable Ongoing Responses > 24 months (in months) **(staging based on disease site only)**	**CR: 24,40,41,59,62,65,72,86, 103,106 (all M1a/b)** **PR: 55,92 (both M1c)** **+Salvage Surgery (4/5 M1c): survival: 54,60,64,66,87,103**
Treatment-related deaths (all sepsis-related)	**6 (2.2%)**

IL-2 Grade 3-4 Toxicity

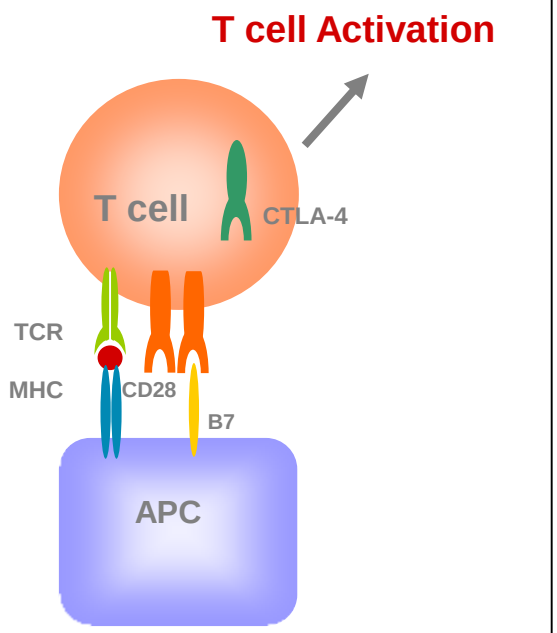
	NCI-SB HD IL-2	CWG HD IL-2
Median Doses per Course	12 (28)	68% (19 doses)
Death	0	1%
Hypotension	36.4%	56.8%
Pulmonary	4.2%	13.7%
CNS orientation	10.2%	14.7%
CNS consciousness	2.5%	
Infection	2.8%	3.2%
Nausea/vomiting	13.4%	9.5%
Diarrhea	9.2%	
Hyperbilirubinemia	3.2%	11.6%
ALT	3.2%	
Creatinine > 8.0 mg/dL	1.1%	13.7% (gr 3-4)
Oliguria (< 80 ml/8h)	12%	
Atrial Arrhythmia	4.2%	8.4% (all cardiac)
Malaise	20.5%	3.2%

IL-2: Key Unanswered Questions

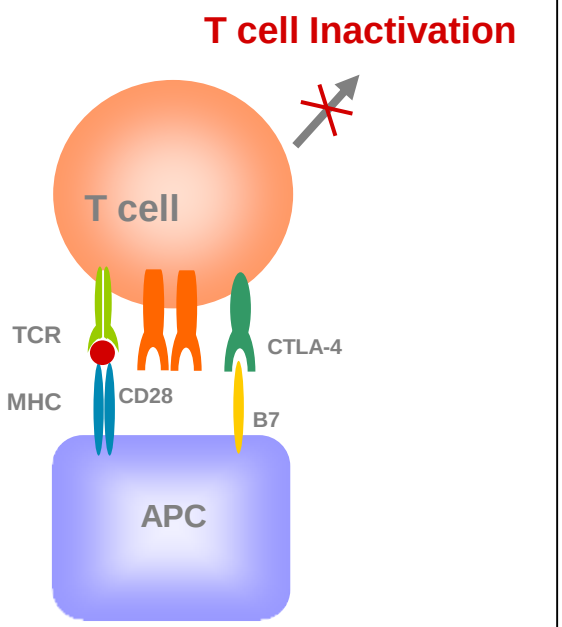
- How does IL-2 mediate tumor regression?
  - Why does IL-2 work in only 10-20% of patients?
  - Is there a way to predict IL-2 response prior to treatment?
- How does IL-2 mediate toxicity?
- Still discuss as a therapeutic possibility in appropriate patients especially in combination with newer agents
- Without firm mechanistic grasp, biomarker development is challenging

Blocking CTLA-4 Ligation Augments Immune Responses

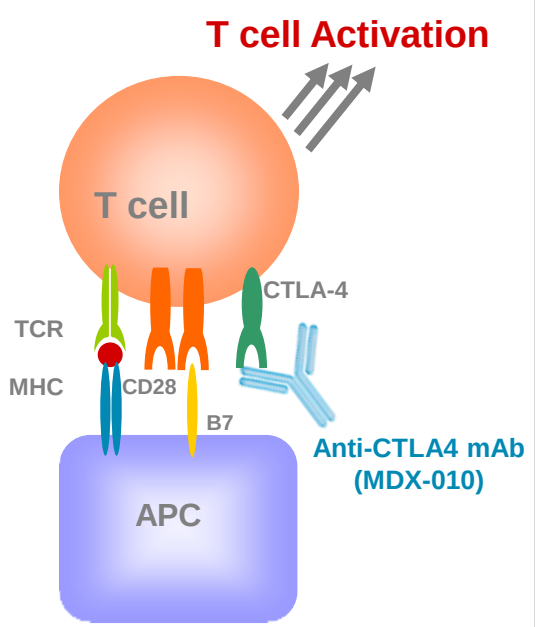
1. Co-stimulation via CD28 ligation transduces T cell activating signals



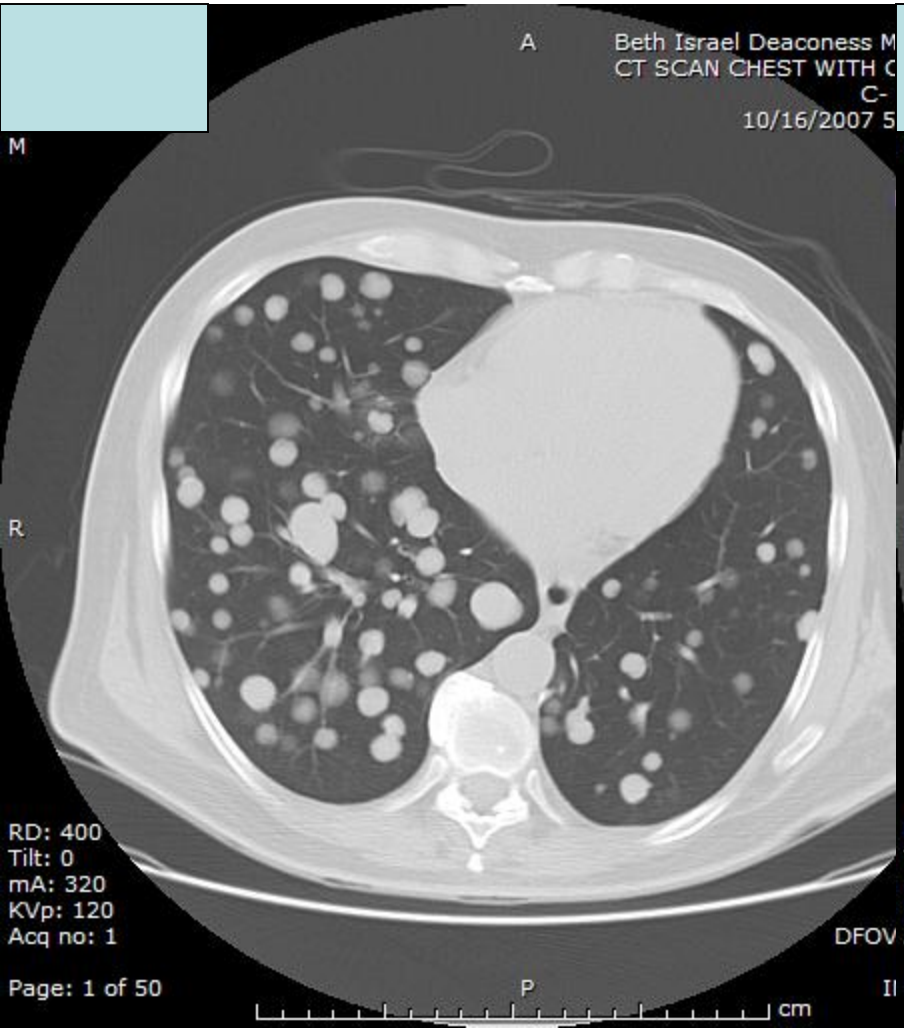
2. CTLA-4 ligation on activated T cells down-regulates T cell responses

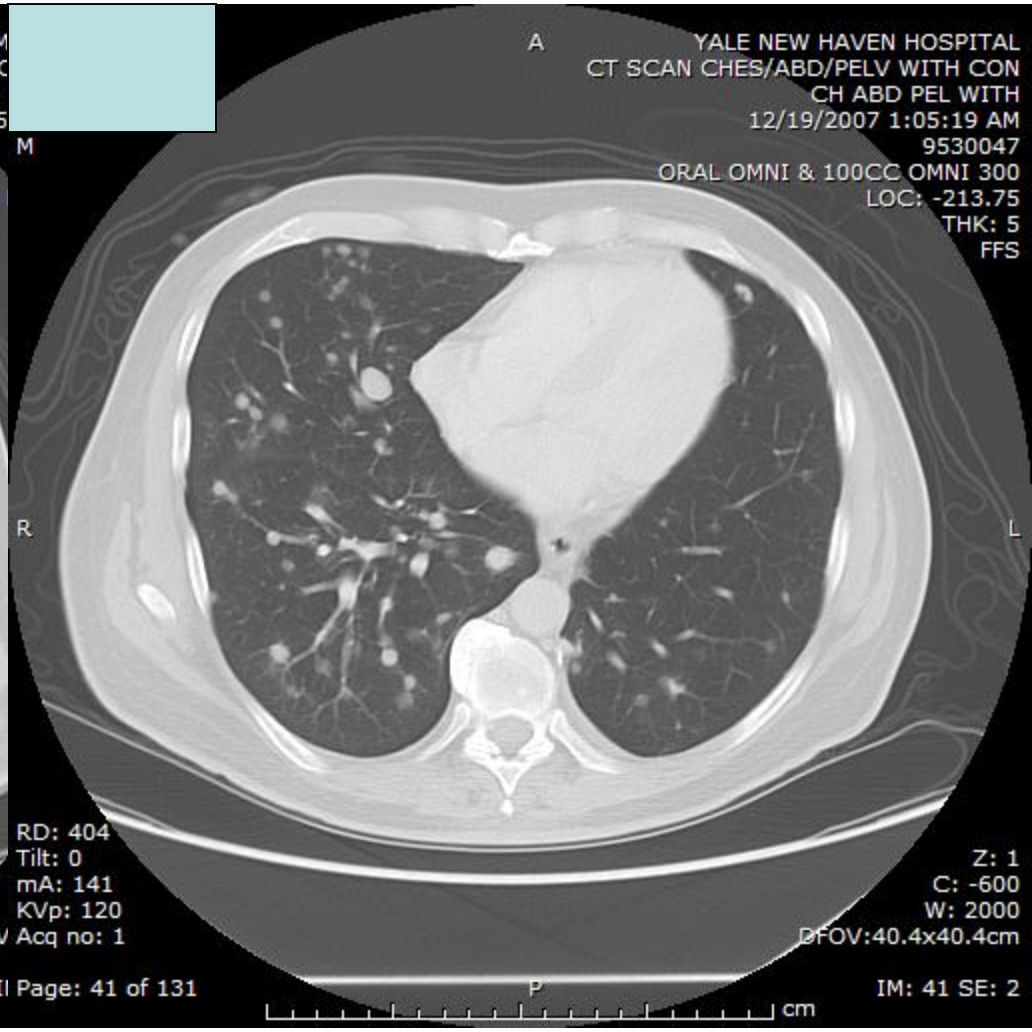


3. Blocking CTLA-4 ligation enhances T cell responses

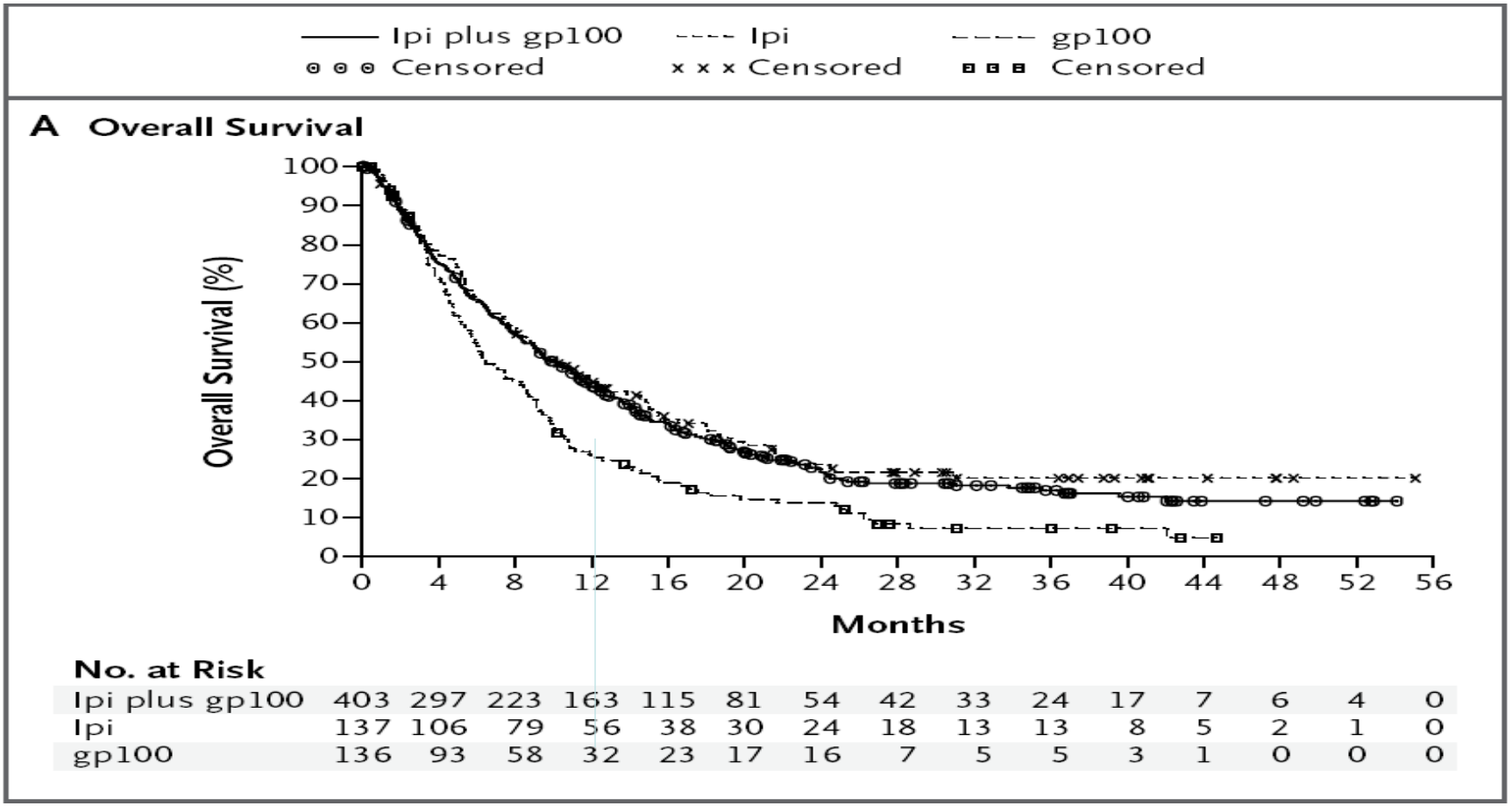


Response to Ipilimumab 10 mg/kg x 2 doses





No progression 5+ years

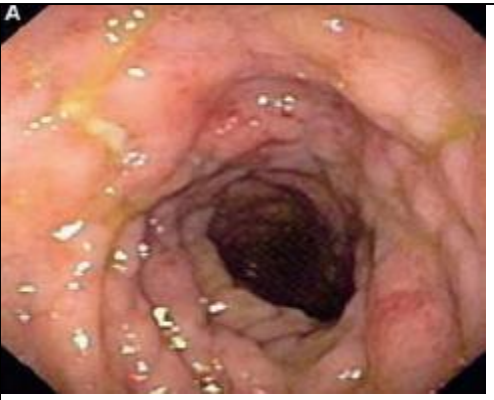


Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-yr	44%	46%	25%
2-yr	22%	24%	14%

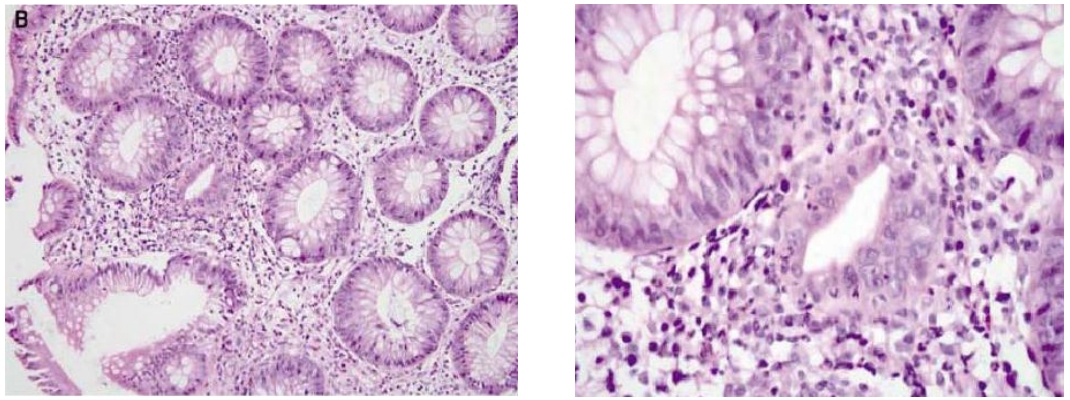
N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

N= 676; 3:1:1

But what about those pesky side effects?



Colonoscopic view of bowel edema and ulceration in the descending colon

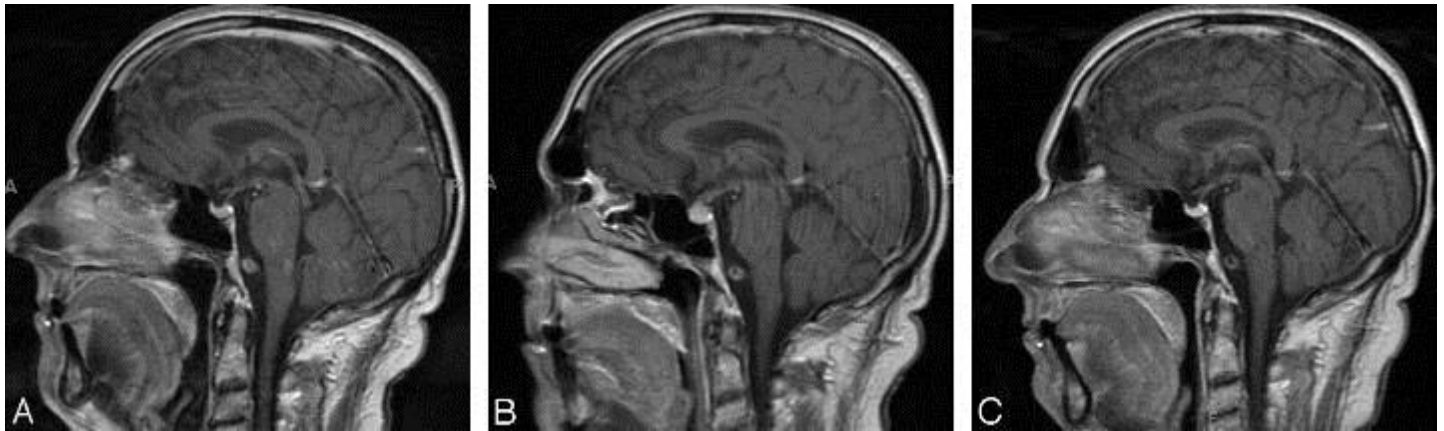


Histopathologic analyses show focal active colitis (left) with crypt destruction, loss of goblet cells, and neutrophilic infiltrates in the crypt epithelium (right)

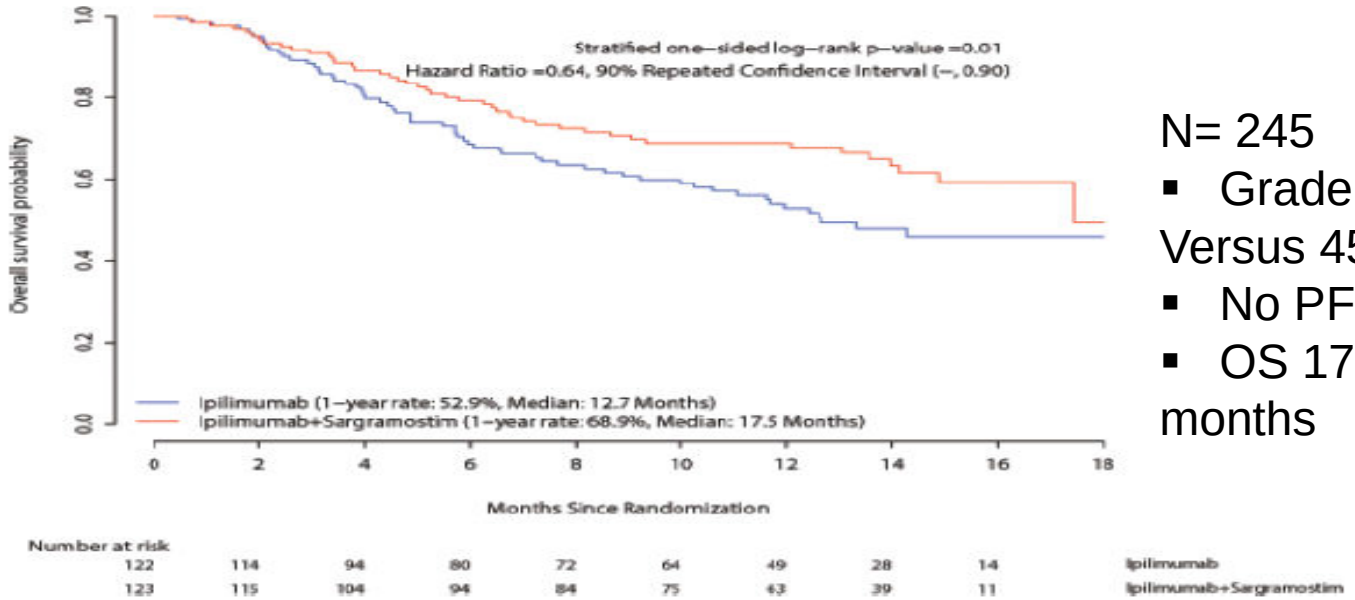
Maker AV, et al. Ann Surg Oncol 2005;12:1005-16

K.J. Carpenter et al. AJNR Am J Neuroradiol 2009;30:1751-1753

- Colitis
- Hypophysitis
- Any-itis

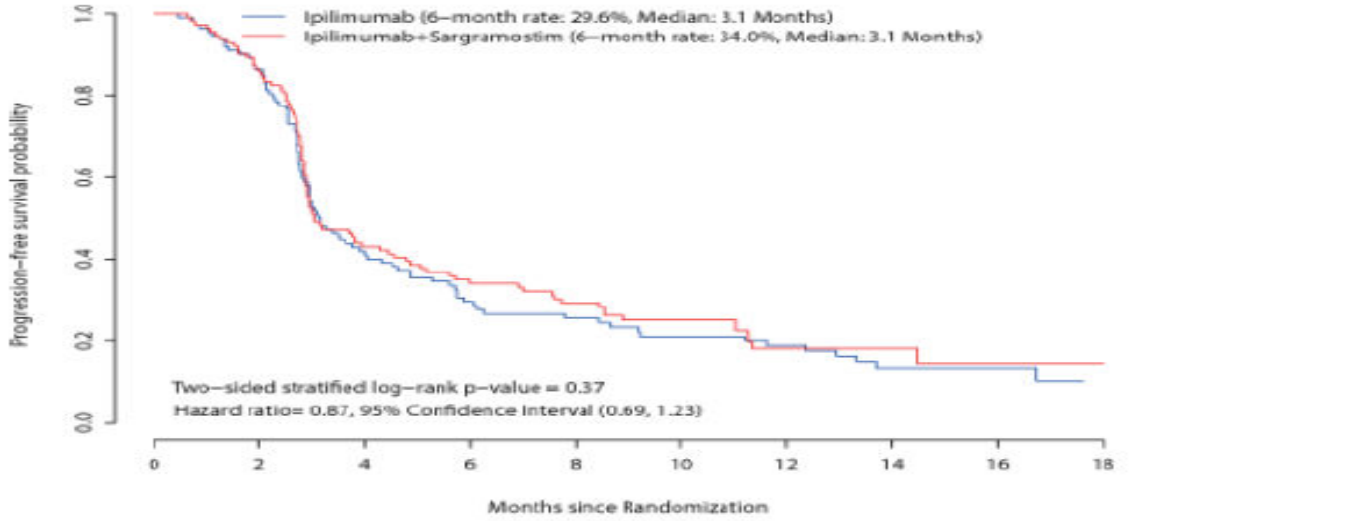


ECOG 1608



Number at risk

122	114	94	80	72	64	49	28	14	Ipilimumab
123	115	104	94	84	75	63	39	11	Ipilimumab+Sargramostim



Number at risk

122	97	46	29	25	19	15	8	5	Ipilimumab
123	99	49	36	31	22	10	7	4	Ipilimumab+Sargramostim

N= 245

- Grade 3-5 Ae's: 58% ipi alone

Versus 45% combo

- No PFS difference (3.1 mos)
- OS 17.5 versus 12.7 months

Adjuvant ipilimumab?

EORTC 1871 (234 ipi, 294 placebo)

- Ipilimumab 10 mg/kg versus placebo, X 4 doses, then q3 months for 3 years
- Stage III patients (20% IIIA)
- RFS significantly increased compared with placebo (median 26 versus 17 months with 3 year RFS 46.5 versus 34.8 per cent, HR 0.75, 95% CI 0.64-0.90)
- Significant toxicity in 90.5 per cent of patients; 36.5 grade 3; 5.5 grade 4; 5 deaths
- Only 50% got first 12 weeks and 29% over one year of therapy

WAIT FOR THE OVERALL SURVIVAL DATA…..

What about interferon?

ECOG 1609

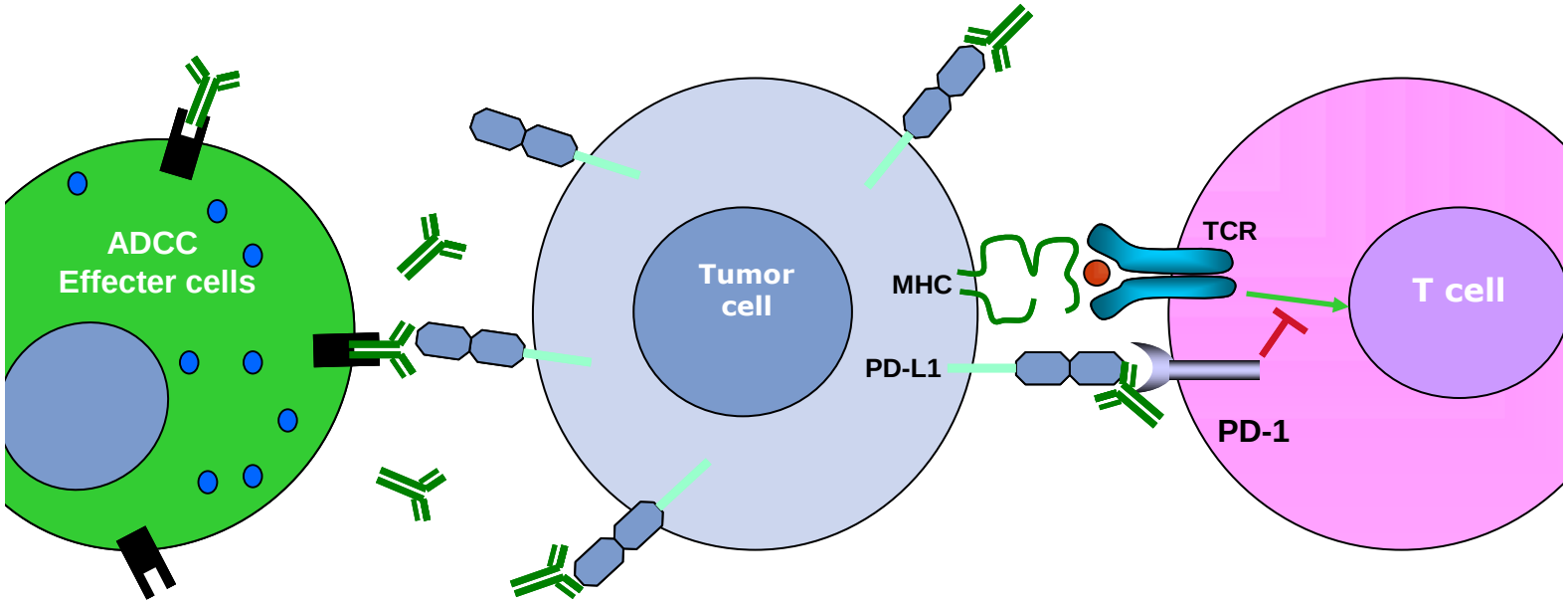
- **High dose interferon (traditional) schedule**
- **Ipilimumab 3 mg/kg**
- **Ipilimumab 10 mg/kg**

ACCRUED….STAY TUNED

Summary

- Ipilimumab prolongs survival in randomized phase III trials
- GM-CSF ameliorates toxicity?
- Adjuvant therapy prolongs PFS; OS data pending; toxicity not insignificant

Targeting PD-1 and PD-L1 in the Tumor Microenvironment

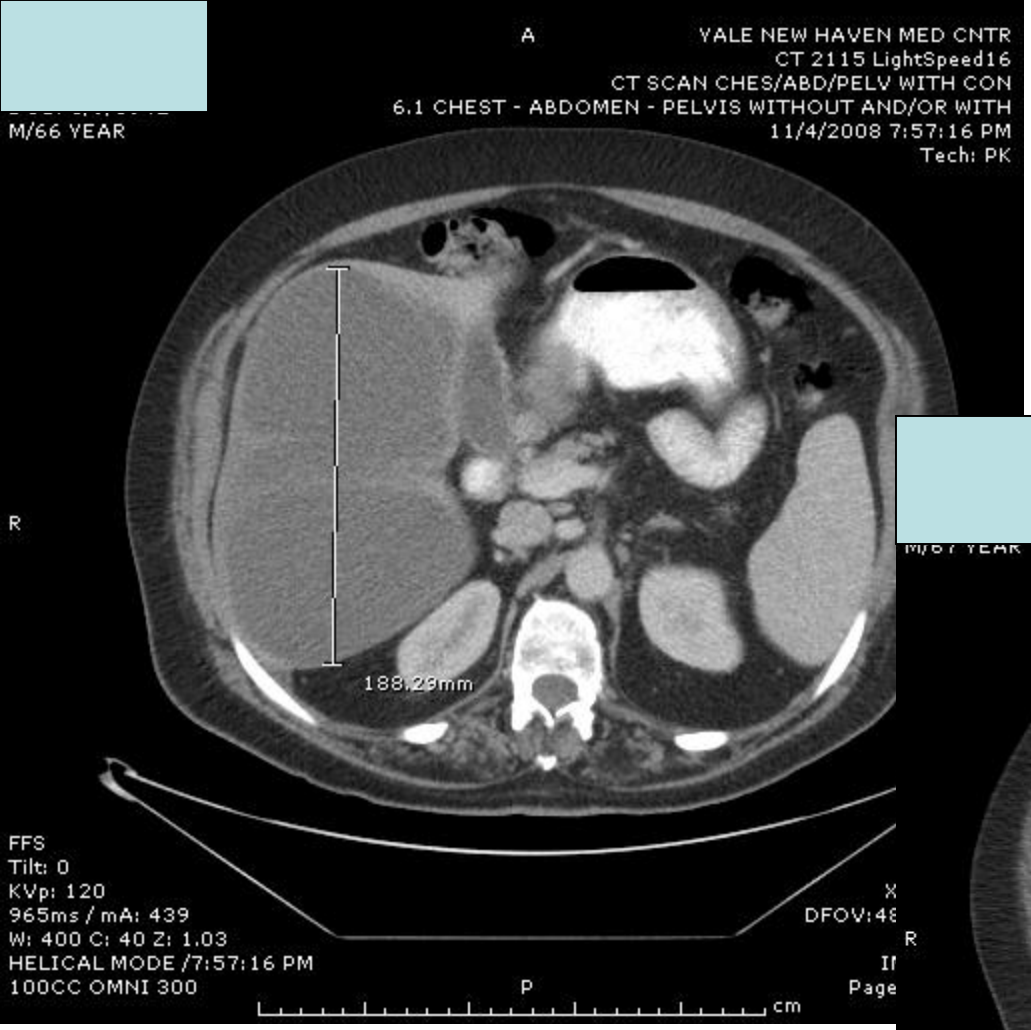


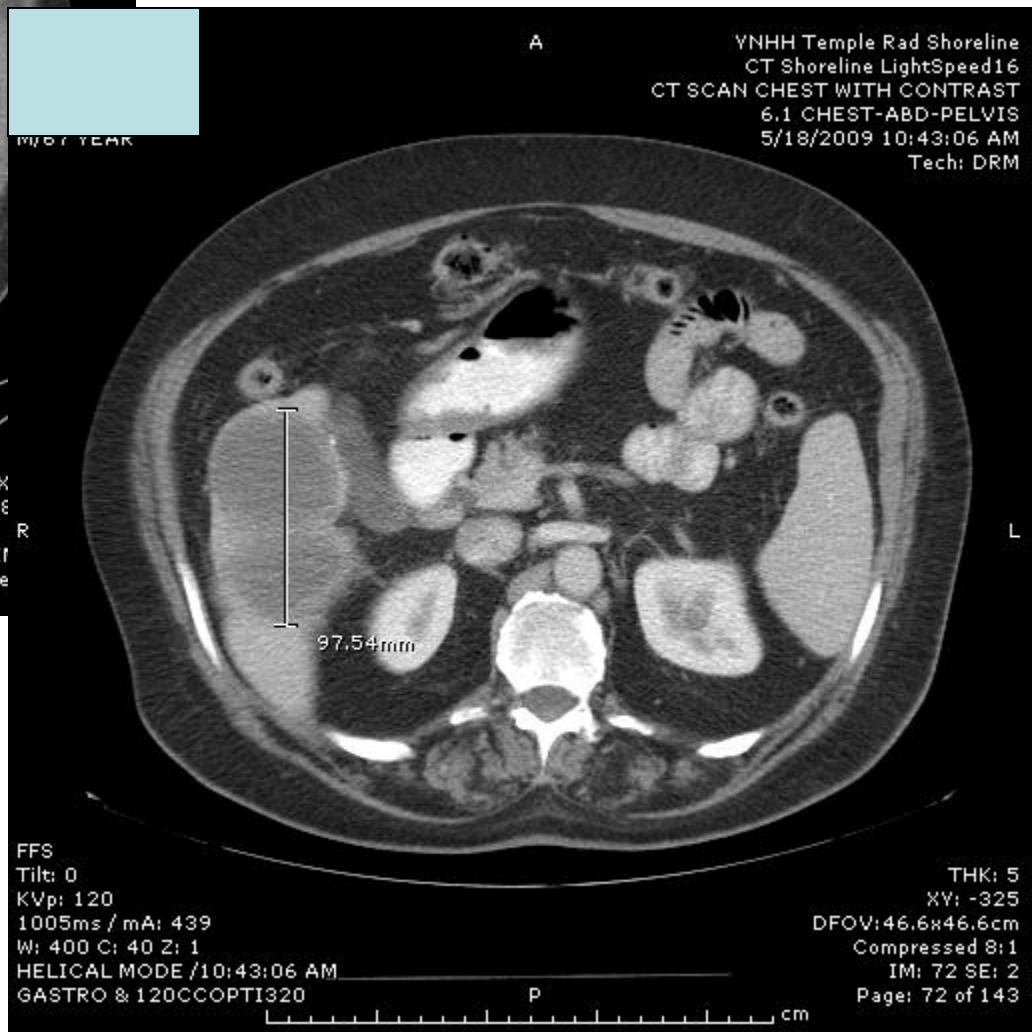
- PD L1 interacts with PD-1 to deliver a signal which inhibits T cell functions
- Blockade of PD-1/PD-L1 interaction releases T cells from immuno-suppression, therefore enhances anti-tumor immunity

Phase I trials of nivolumab, pembrolizumab, and combo of ipilimumab and nivolumab

Tumor type (dose, mg/kg)	No. pts	OR (CR/PR) (%)	Toxicities	Followup
Nivolumab (0.1-10 mg/kg q2wks)	107	32	13 (10)	Median OS: 17 mos 1yr-OS: 62% 2yr-OS: 48%
Pembrolizumab (10mg/kg q2wks, 10mg/kgq3 weeks; 2mg/kg q3weeks)	411	34	12% gr 3/4	1yr-OS: 69% 18 mos-OS: 62%
Ipi/nivo	53	42 (17/25)	Ae's: 90% Severe: 49%	I yr-OS: 94% 2 yr OS: 88%

Metastatic Melanoma,
Anti-PD1 1 mg/kg every other week

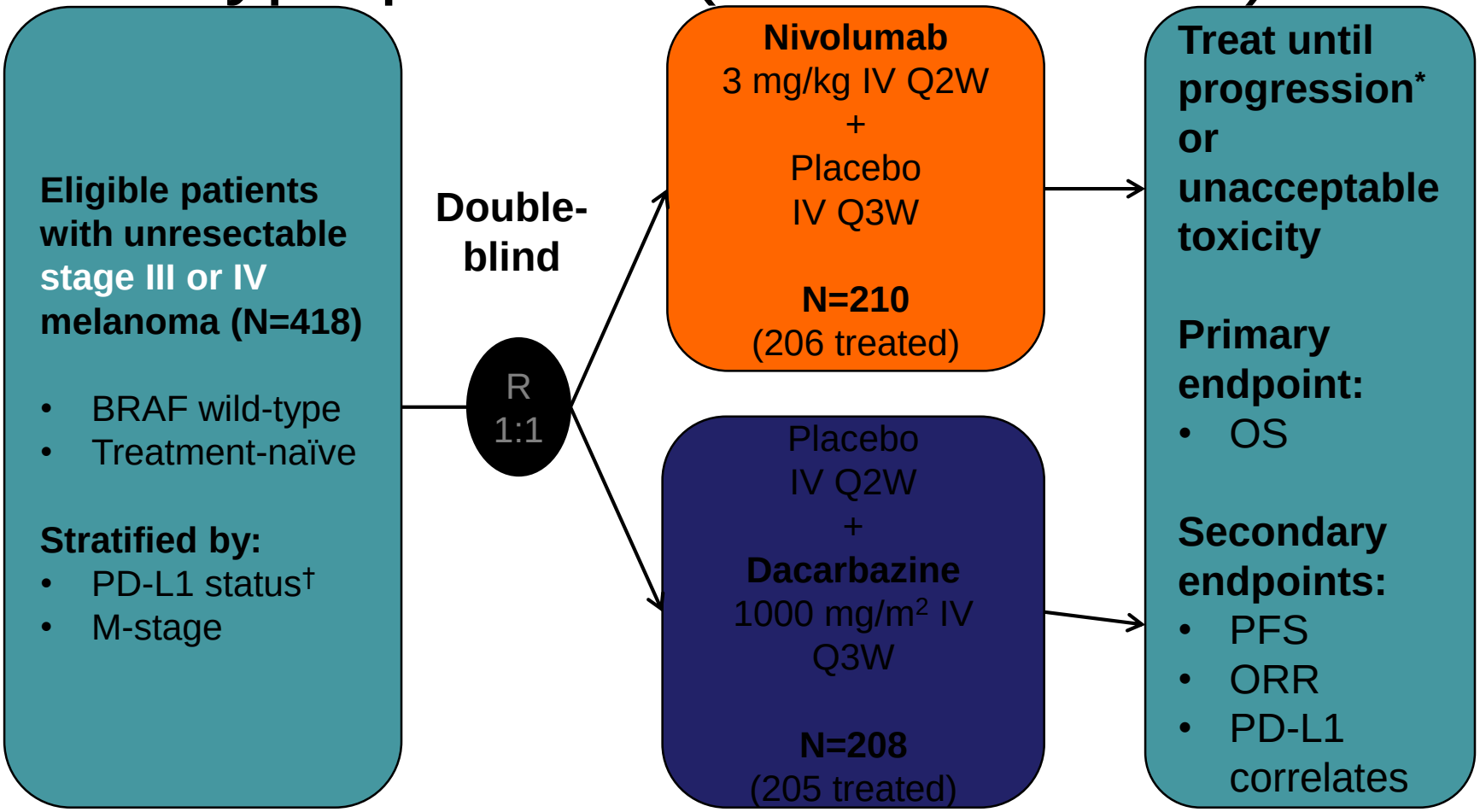




Phase 3 Trial of Nivolumab after Ipilimumab and BRAF Inhibitor Therapy (Checkmate 37)

- Nivolumab versus chemotherapy
- Prelim results of first 167 reported patients (120 nivo, 47 chemo)
- 32% RR nivolumab versus 10% chemotherapy
- Median duration of response not reached in nivolumab; chemotherapy 3.5 months

Phase 3 CA209-066: Nivo Vs Chemo in first line BRAF-wild type patients (Checkmate 66)



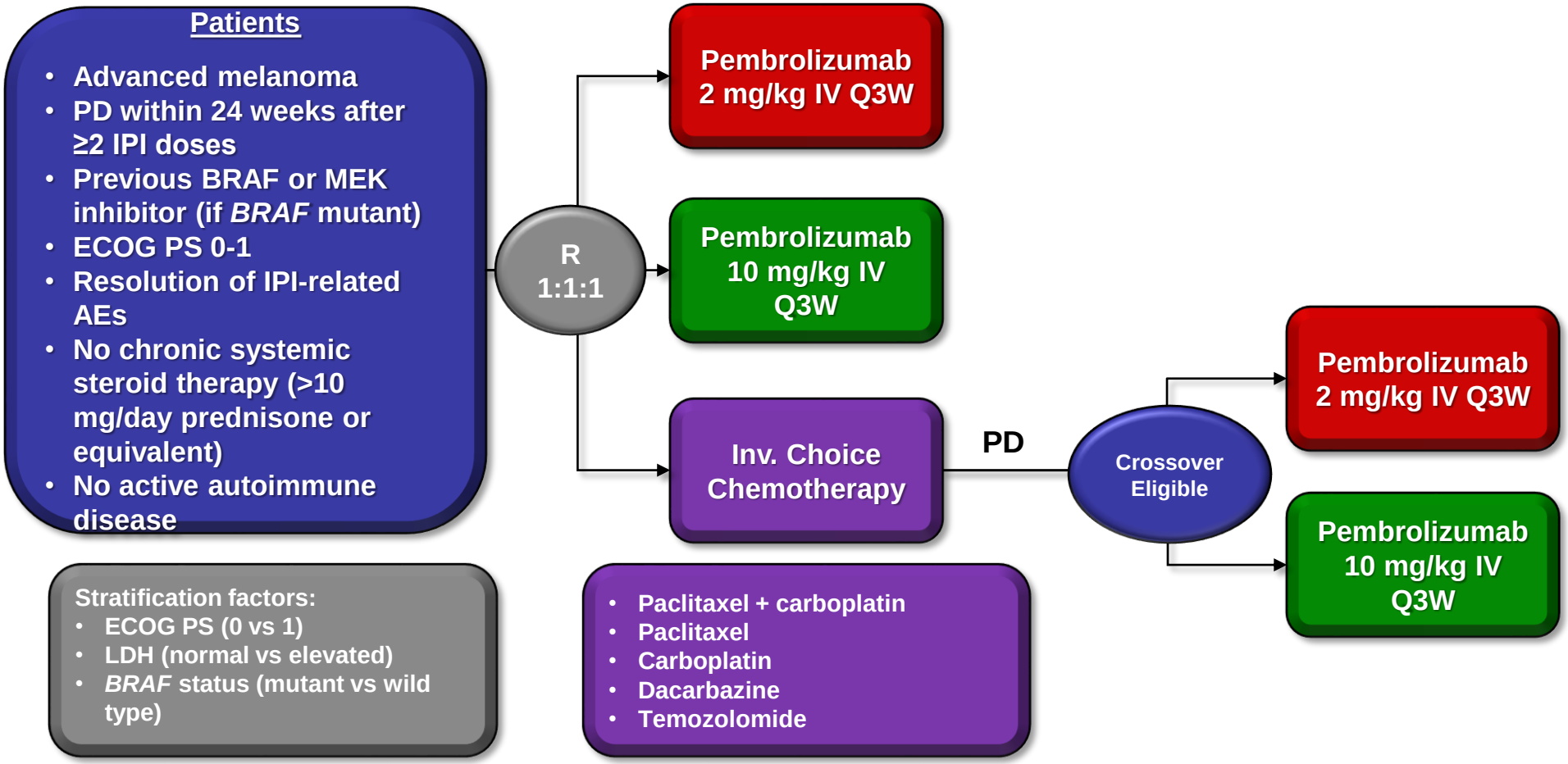
†PD-L1 positive: .

*Patients may be treated beyond initial RECIST v1.1-defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug.

Phase 3 CA209-066:

- 1 yr OS rate 73 % nivolumab versus 42% dacarbazine
- 6 months PFS rate 48% nivolumab versus 19% dacarbazine
- ORR 40% nivolumab versus 14% dacarbazine
- 86% treated with nivolumab had ongoing response, median duration not reached; versus 52% with dacarbazine, median duration 6 months
- Activity irrespective of PD-L1 status

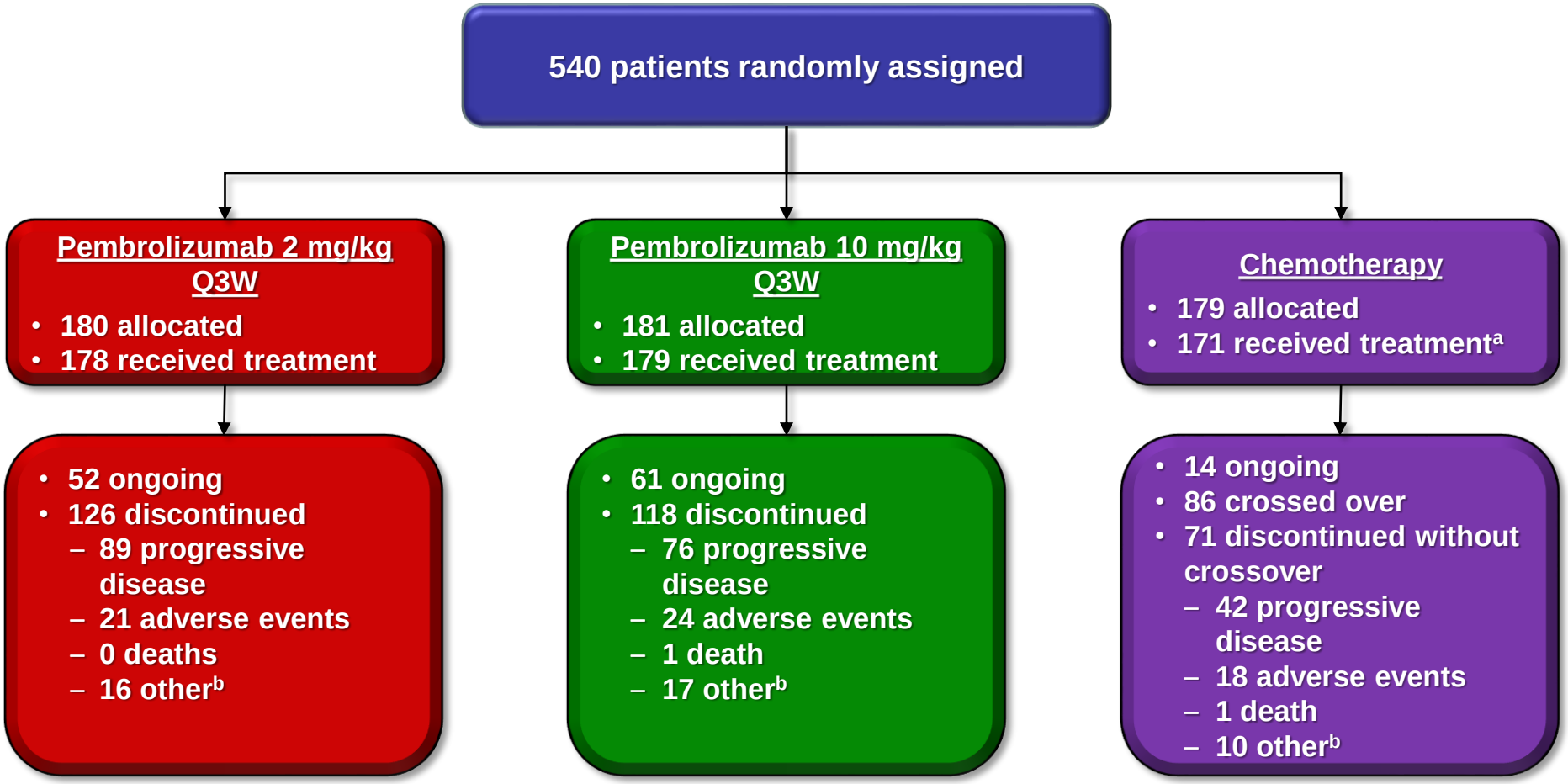
KEYNOTE-002 (NCT01704287): International, Randomized, Pivotal Study n= 540



- Primary end points: PFS and OS
- Secondary end points: ORR, duration of response, safety
- Prespecified exploratory end point: health-related quality of life at week 12 (HRQoL)

Acknowledgment, A. Ribas

Patient Disposition



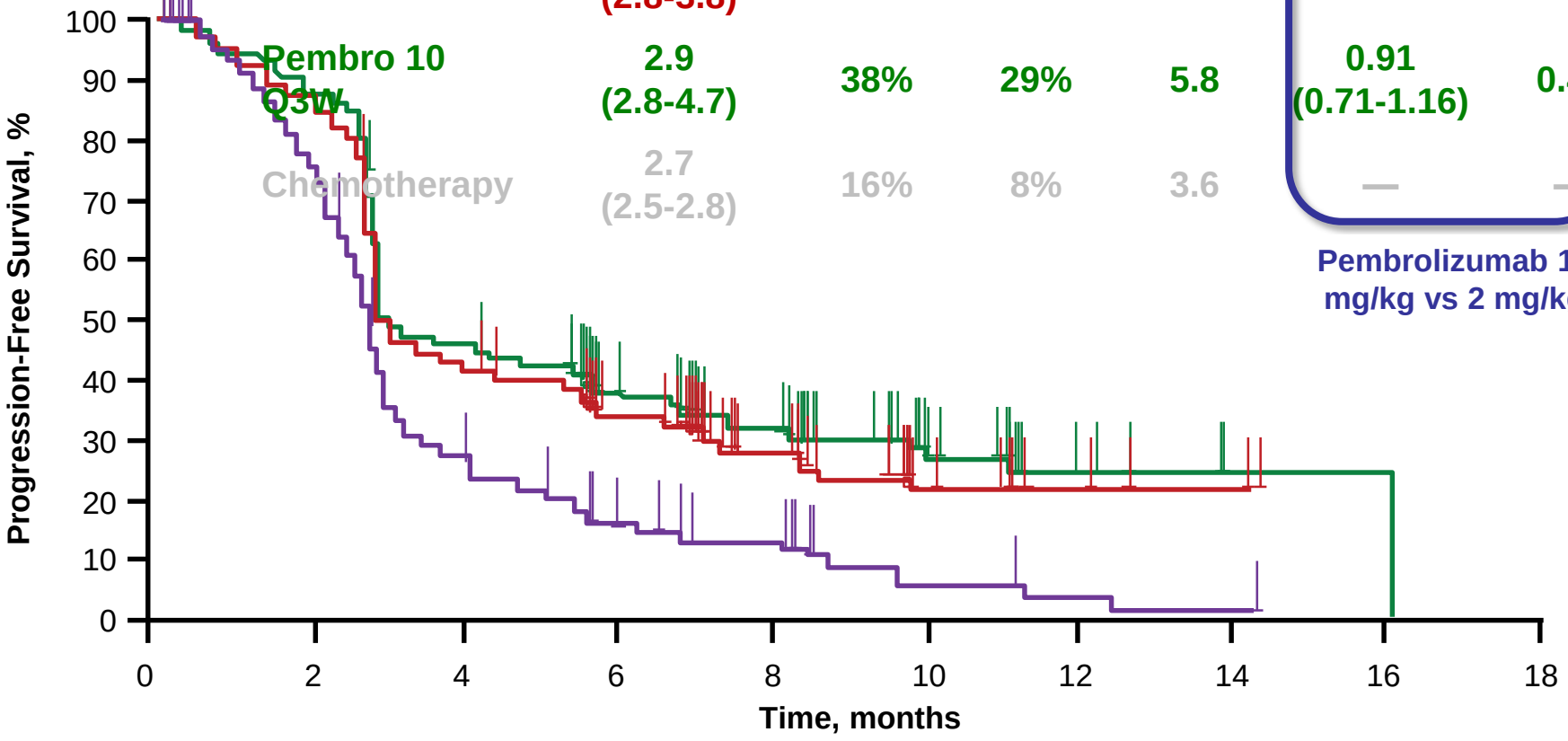
- **Enrollment period: November 2012 to November 2013**
- **Analysis cutoff date: May 12, 2014**
- **Median follow-up duration: 10 months**

[a]Paclitaxel + carboplatin, n = 42; paclitaxel, n = 28; carboplatin, n = 13; dacarbazine, n = 45; temozolomide, n = 43.
[b]Includes physician decision, withdrawal by patient, and noncompliance with study drug.

Primary End Point: PFS (RECIST v1.1, Central Review)

Arm	Median (95% CI), mo	Rate at 6 mo	Rate at 9 mo	Mean,[a] mo	HR (95% CI)	*P*
Pembro 2 Q3W	2.9 (2.8-3.8)	34%	24%	5.4	—	—
Pembro 10 Q3W	2.9 (2.8-4.7)	38%	29%	5.8	0.91 (0.71-1.16)	0.44
Chemotherapy	2.7 (2.5-2.8)	16%	8%	3.6	—	—

Pembrolizumab 10 mg/kg vs 2 mg/kg



[a]Restricted mean PFS time based on 12 months of follow-up.
Analysis cut-off date: May 12, 2014.

Overall Response Rate (RECIST v1.1, Independent Central Review)

	Pembrolizumab 2 Q3W n = 180	Pembrolizumab 10 Q3W n = 181	Chemotherapy n = 179
Best overall response			
Complete response	2%	3%	0%
Partial response	19%	23%	4%
Stable disease	18%	17%	18%
Progressive disease	47%	48%	62%
Not evaluable	14%[a]	10%	15%
Median	NR	NR	37
Range	6+ to 50+	5+ to 48+	7+ to 41
Ongoing responses	92%	87%	63%

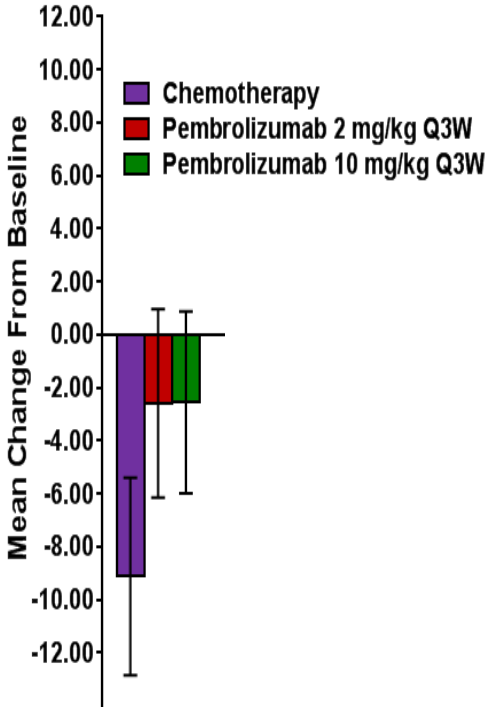
- *P* < 0.0001 each for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W vs chemotherapy
- *P* = 0.21 for pembrolizumab 10 mg/kg Q3W vs 2 mg/kg Q3W

[a]Includes 1 patient each with no disease and no assessment.
Analysis cut-off date: May 12, 2014.

Change From Baseline to Week 12 In HRQoL (EORTC QLQ-C30)

- Difference in least squares mean change from baseline at week 12
  - Pembrolizumab 2 mg/kg vs chemotherapy: 6.52, *P* = 0.011
  - Pembrolizumab 10 mg/kg vs chemotherapy: 6.57, *P* = 0.009
  - Pembrolizumab 10 mg/kg vs 2 mg/kg: 0.04, *P* = 0.986

Global Health Status/Quality of Life Scale[a]



[a]A higher score denotes better HRQoL or function, and a higher negative score denotes worse HRQoL or functions.
Analysis cut-off date: May 12, 2014.

KEYNOTE-002 (NCT01704287) highlights:

- Mostly M1C disease
- Pretreated population
- Brain metastases stable for four weeks
- Primary Endpoint of PFS

KEYNOTE-002 (NCT01704287):

- **Doubling** of 6 month PFS ($P < 0.0001$) with 34% and 38% pembrolizumab versus 16% chemotherapy
- Responses increased **5-6 fold** over chemotherapy ($P < 0.0001$)
- Lower incidence of treatment related AE's in pembrolizumab arm
- OS data immature

- **Anti-PD-1 antibodies induce durable clinical responses that are superior to chemotherapy**
- **The role of combination with other existing immunotherapies in sequencing or combination is a subject of current investigation**

- **ARE YOU REALLY GOING TO TREAT TEN PATIENTS FOR THE ONE WHO RESPONDS?**
- **NOW THAT WE HAVE STANDARDS, WHO WILL GO ON A TRIAL?**

What is a biomarker?

NCI Website: “biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule”

What are the properties of a useful biomarker?

- Accurate measurement
- Feasible
- Valid
- Reproducible
- Cost effective

Preliminary Candidate Biomarkers of Ipilimumab and IL-2 Efficacy

IL-2:

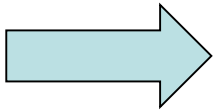
- Performance status
- Development of autoimmunity
  - Thyroiditis
  - Vitiligo
- Amount of IL-2 given during first course
- Height of the rebound lymphocytosis
- CA IX (in renal cell carcinoma)
- VEGF

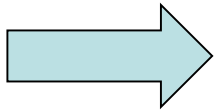
Ipilimumab:

- Increase ALC and eosinophils correlate with improved survival? (Delyon J 2013 Annals Oncology)
- Low frequencies of monocytic myeloid-derived suppressor cells (MDSC) predicts better outcome? (Meyer C 2014 Cancer Immunology and Immunotherapy)
- Baseline FoxP3 infiltrates; increased TILs post-therapy (Hamid 2011)
- NY-ESO-1 antigen-specific CD4(+) T cell responses (Kitano 2013 Cancer Immunol Research)
- Ipilimumab increases frequency of CD4 cell with inducible costimulator (ICOS) Ng Tang 2013, *Cancer Immunology Research*

An Ideal Paradigm for Biomarker Development

Trastuzumab:

mechanism of tumor aggression determined for a subset of patients 

development of a specific drug 

clinical trials with patients whose tumors express the target

Assay Methodology

- Antibody and staining conditions (proteins)
- Automated or manual read
- Multiple assays in development, how to compare?
- **Defining a positive result (cut-offs):**
  - Cell type expressing the biomarker (immune cell versus tumor or both)
  - Presence or absence of immune cell infiltrate
  - Location of expression – cell surface versus intracellular
  - intensity
  - Distribution - patchy versus diffuse, intratumoral versus peripheral
  - percent of cells ‘positive’

TISSUE IS THE ISSUE: CHALLENGES

- Bx type - Excisional versus core versus FNA
- **Addressing heterogeneity** – multiple tumors and multiple passes within a tumor
- Interval between biopsy and treatment – effect of other therapies
- Primary versus metastatic disease
- Practical applications of tumor retrieval

  -“YOUR TUMOR, YOUR LIFE”
- Frozen versus FFPE

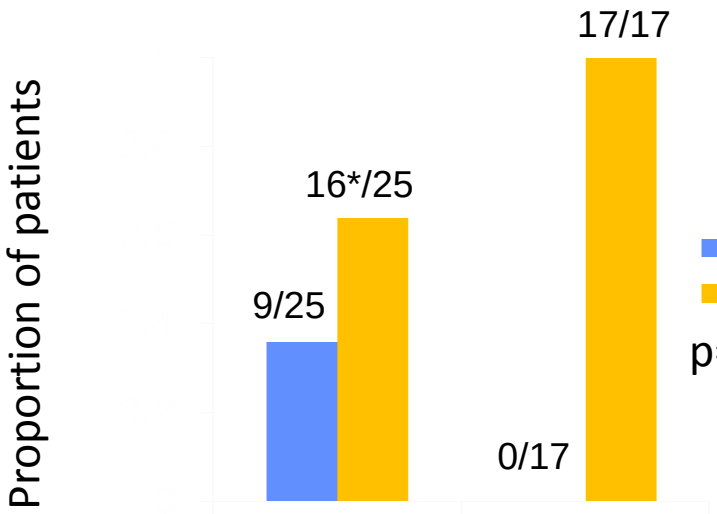
  - Does everyone get a fresh biopsy?

  - Insurance reimbursement

  - Patient willingness

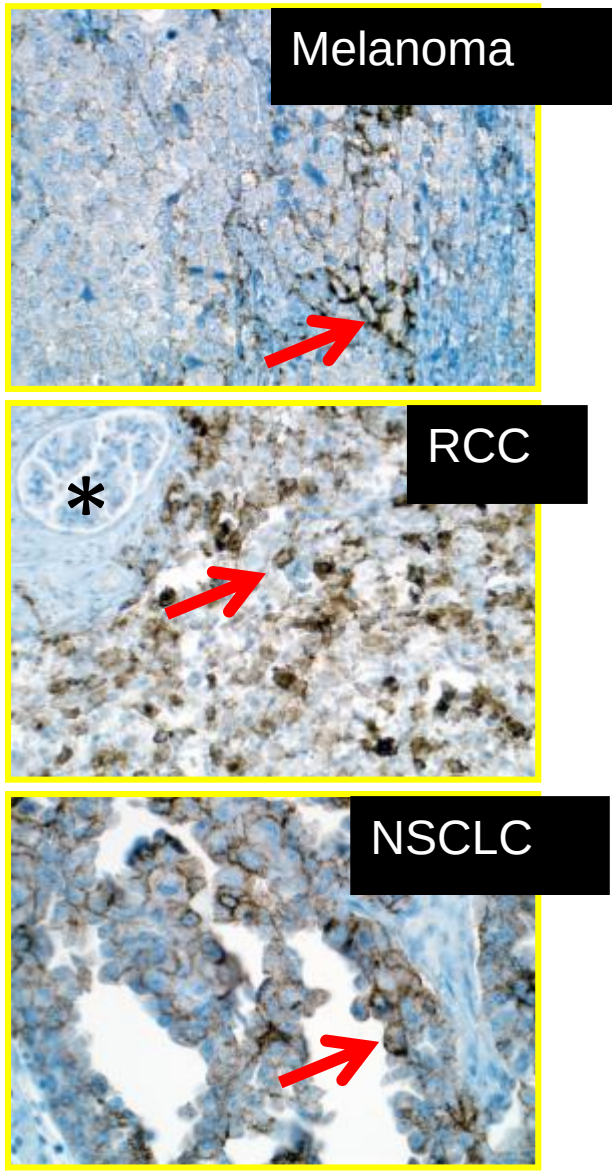
Correlation of PD-L1 expression in pretreatment tumor biopsies with clinical outcomes

42 pts include 18 MEL, 10 NSCLC, 7 CRC, 5 RCC, and 2 CRPC.



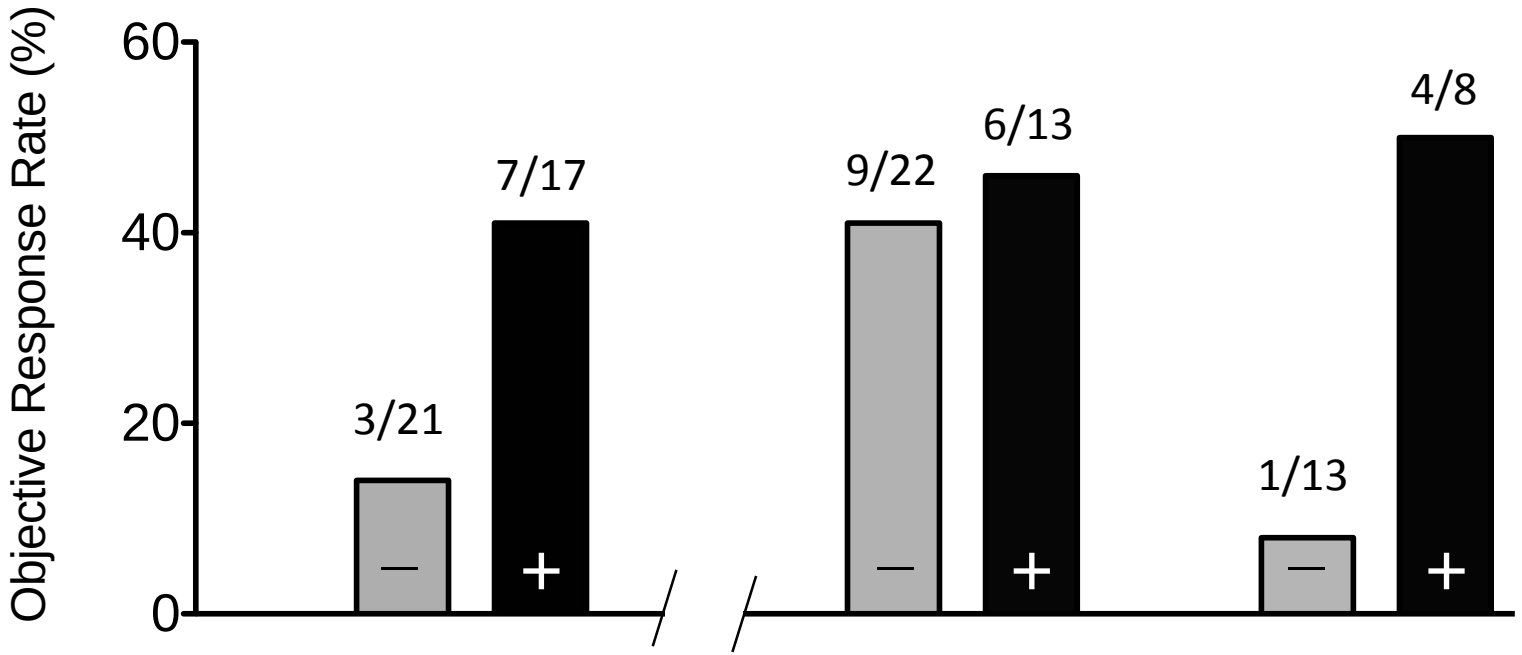
Association Between Pretreatment Tumor PD-L1 Expression and Clinical Response

Response Status	PD-L1 Positive no. (%)	PD-L1 Negative no. (%)	Total no. (%)
CR/PR	9 (36)	0	9 (21)
Nonresponder	16* (64)	17 (100)	33 (79)
All Patients	25	17	42



Topalian S, et al. NEJM 2012;366:2443-2454; Acknowledgement, M. Sznol.

Evaluating PD-L1 status as a candidate biomarker



Positivity rate = 45% (17/38, monotherapy), 37% (13/35, combination therapy), and 38% (8/21, sequenced therapy) =

Expression appears to enrich for responses in single agent therapy

Acknowledgement, M. Sznol

Biomarkers: Summary

- Relatively small sample sizes studied to date
- Valid, reliable, assays necessary to move biomarker development forward
- Without a certain target that can be feasibly and reliably measured, patients who might benefit from these agents will be excluded
- Without a clear integral biomarker…treat an ask questions later?
- Tumor microenvironment analysis of other factors in blood and tumor that affect induction/effectiveness of immune interventions will likely be necessary to optimize biomarker development

Society for Immunotherapy of Cancer (SITC)

Lessons and Take Home Messages

Key Points:

-Immunotherapy induces meaningful, durable responses and often is tolerable, though side effects can be serious and unpredictable

-Immunotherapy is an important weapon in the battle against melanoma, but strategies to maximize response rates must be considered, particularly as part of clinical trials.

-Expert consultation in melanoma cases is often useful and available.

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Skin and Soft Tissue Oncology