

Immuno-oncology Comes of Age: Immunotherapy in the Clinic

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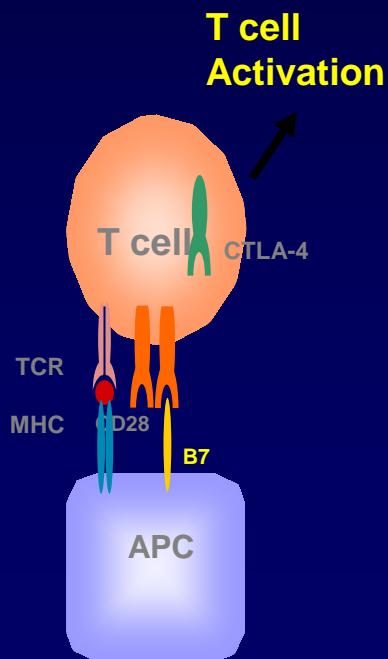
New Haven, Connecticut

Cancer Immune Therapies in the Clinic

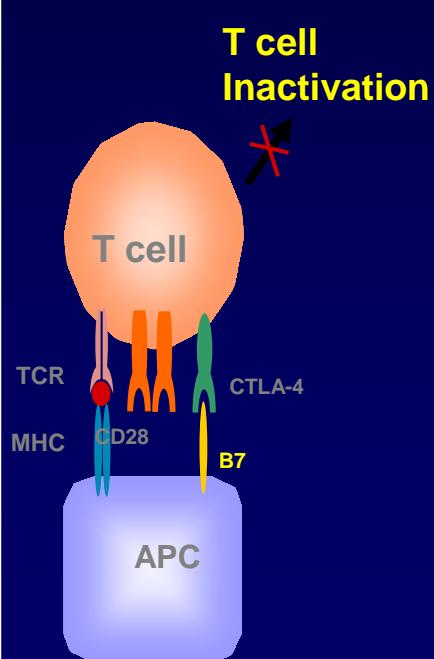
- Cytokines: Interleukin-2 and Interferon-Alfa
- Cell Therapies and Cancer ‘Vaccines’
 - Sipuleucel-T in prostate cancer
 - Allogeneic bone marrow transplant
- Immune Checkpoint Inhibitors
 - Ipilimumab (anti-CTLA-4)
 - *Pembrolizumab (anti-PD-1)*
 - *Nivolumab (anti-PD-1) (pending FDA approval)*

Blocking CTLA-4 Ligation Augments Immune Responses

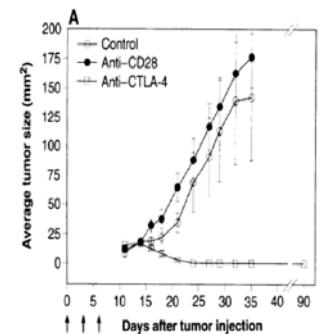
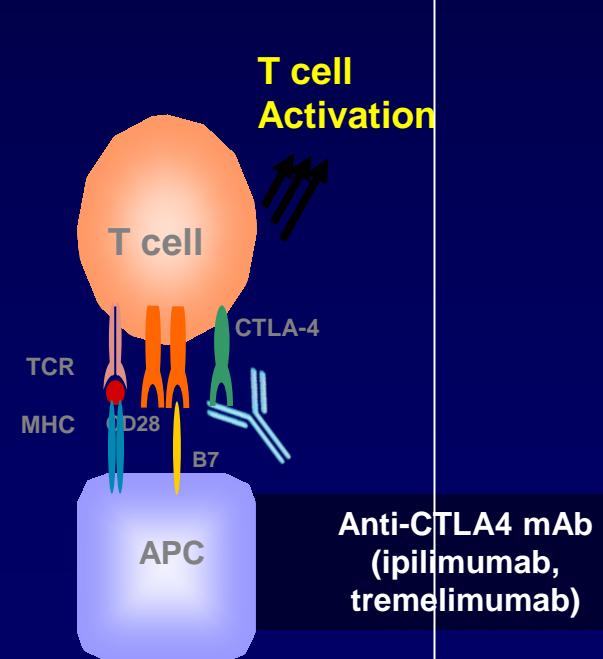
- 1 Co-stimulation via
- CD28 ligation
transduces T cell activating signals



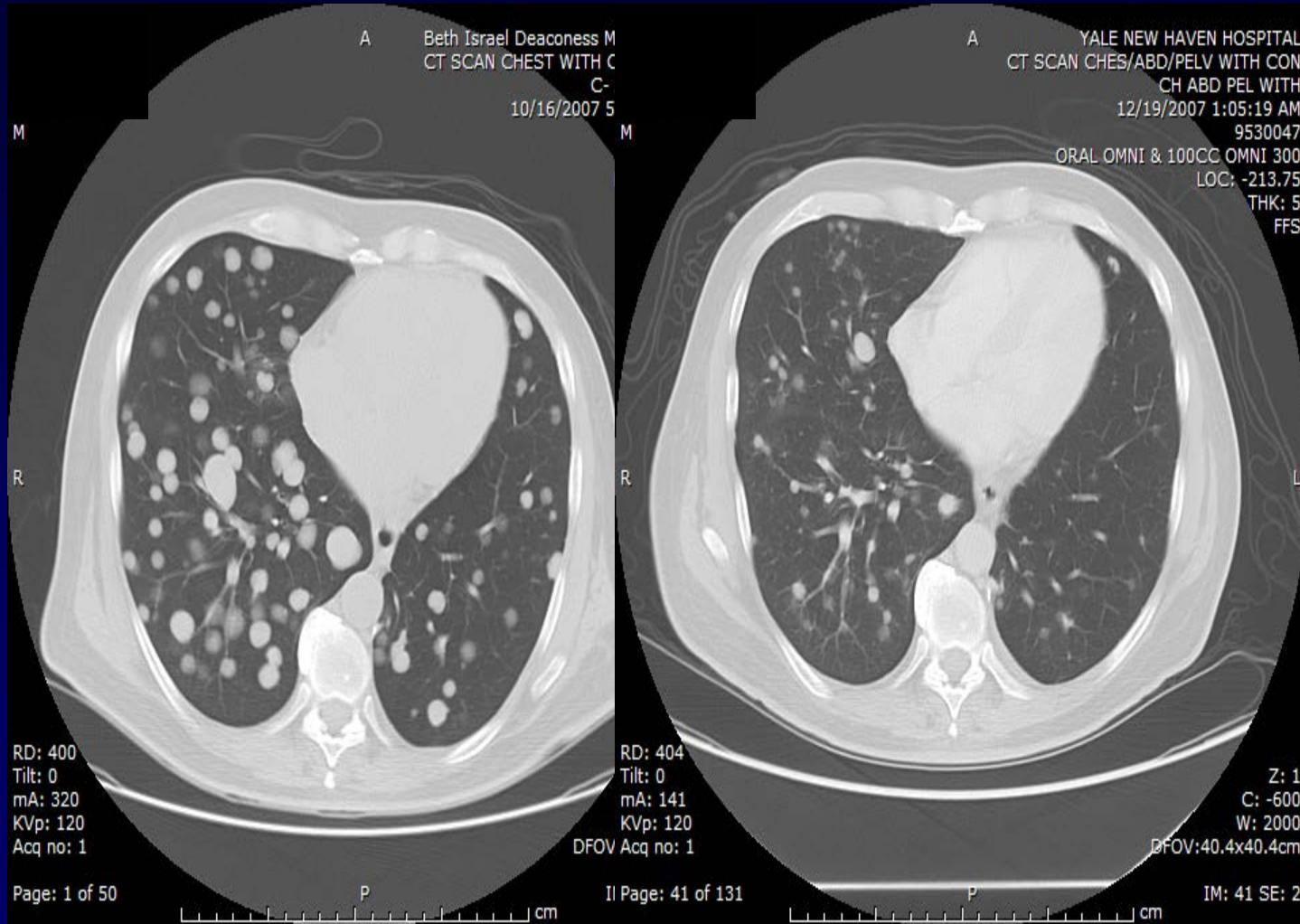
- 2 CTLA-4 ligation on activated T cells
- down-regulates T cell responses



- 3 Blocking CTLA-4
- ligation enhances T cell responses

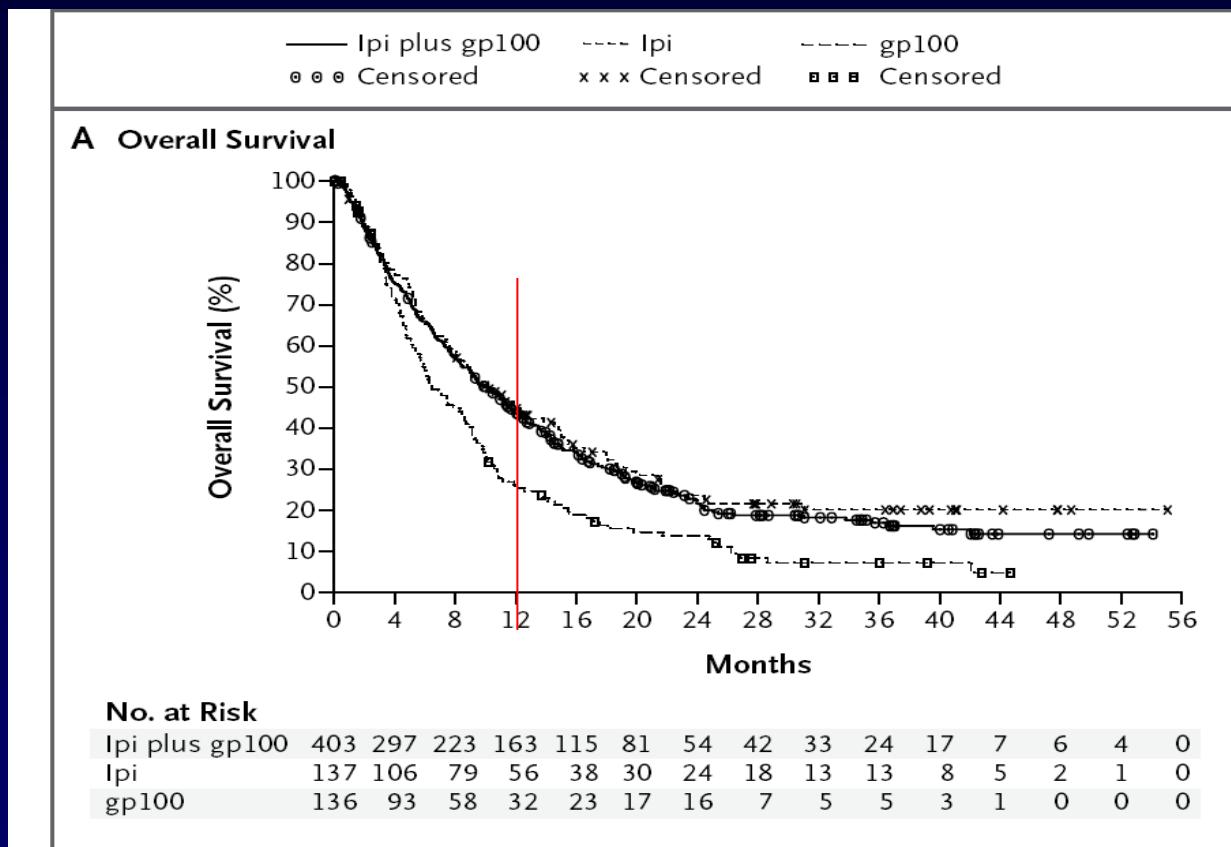


Response to Ipilimumab 10 mg/kg x 2 doses



**2 baseline brain mets regressed also:
No disease progression 5+ years**

Randomized Trial of Ipilimumab +/- gp100 Vaccine Versus Vaccine in Metastatic Melanoma



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

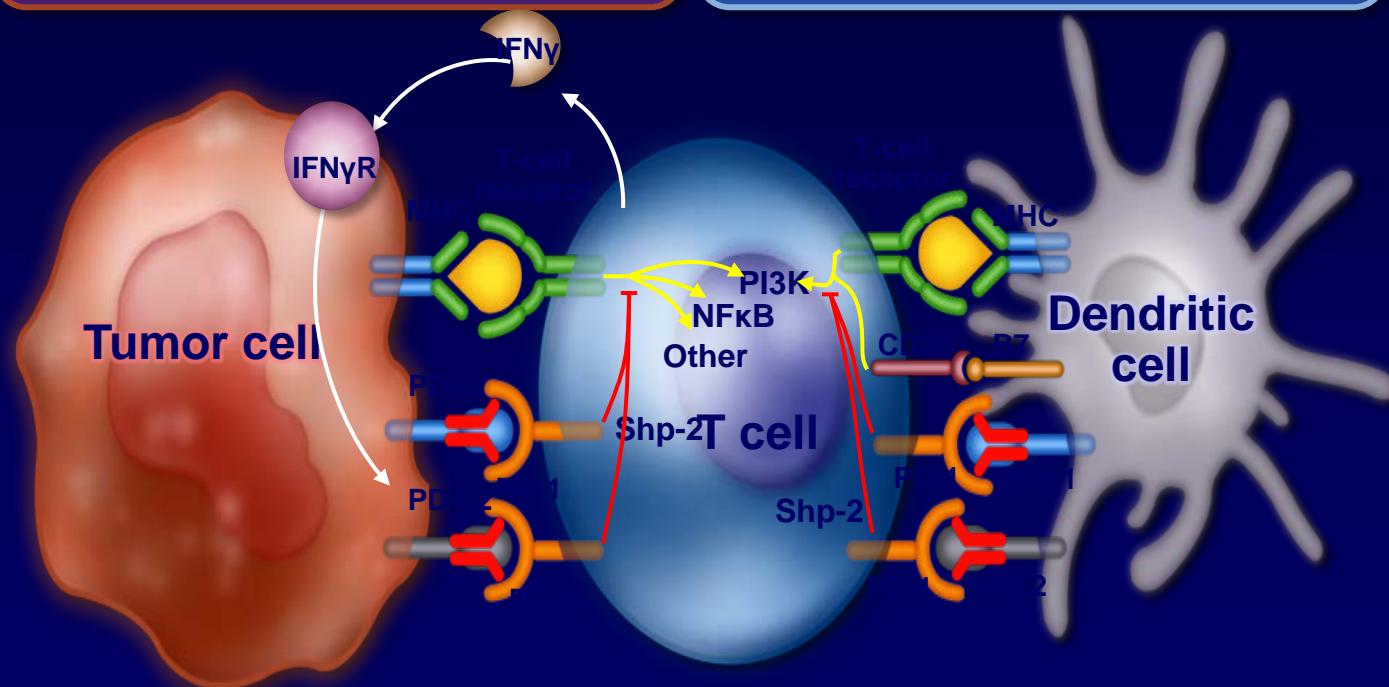
Key Aspects of Immune Checkpoint Therapy

- Can be associated with autoimmune adverse events
 - Any organ, but rash, colitis, hepatitis and endocrinopathies are most common
 - May require steroids +/- additional immunosuppressive agents
 - Ipilimumab + anti-PD-1 > ipilimumab > anti-PD-1
- Unique kinetics of response in some patients
 - SD with slow, steady decline in total tumor volume
 - Response after initial increase in total tumor volume
 - Response in index plus new lesions at or after the appearance of new lesions
 - Continued benefit after Rx of discordant progressing lesions
- Possibility of second response with re-induction after PD

Role of PD-1 Pathway in Suppressing Anti-tumor Immunity

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNy release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells



Clinical Activity of Nivolumab (Phase 1 Multi-Dose Trial)

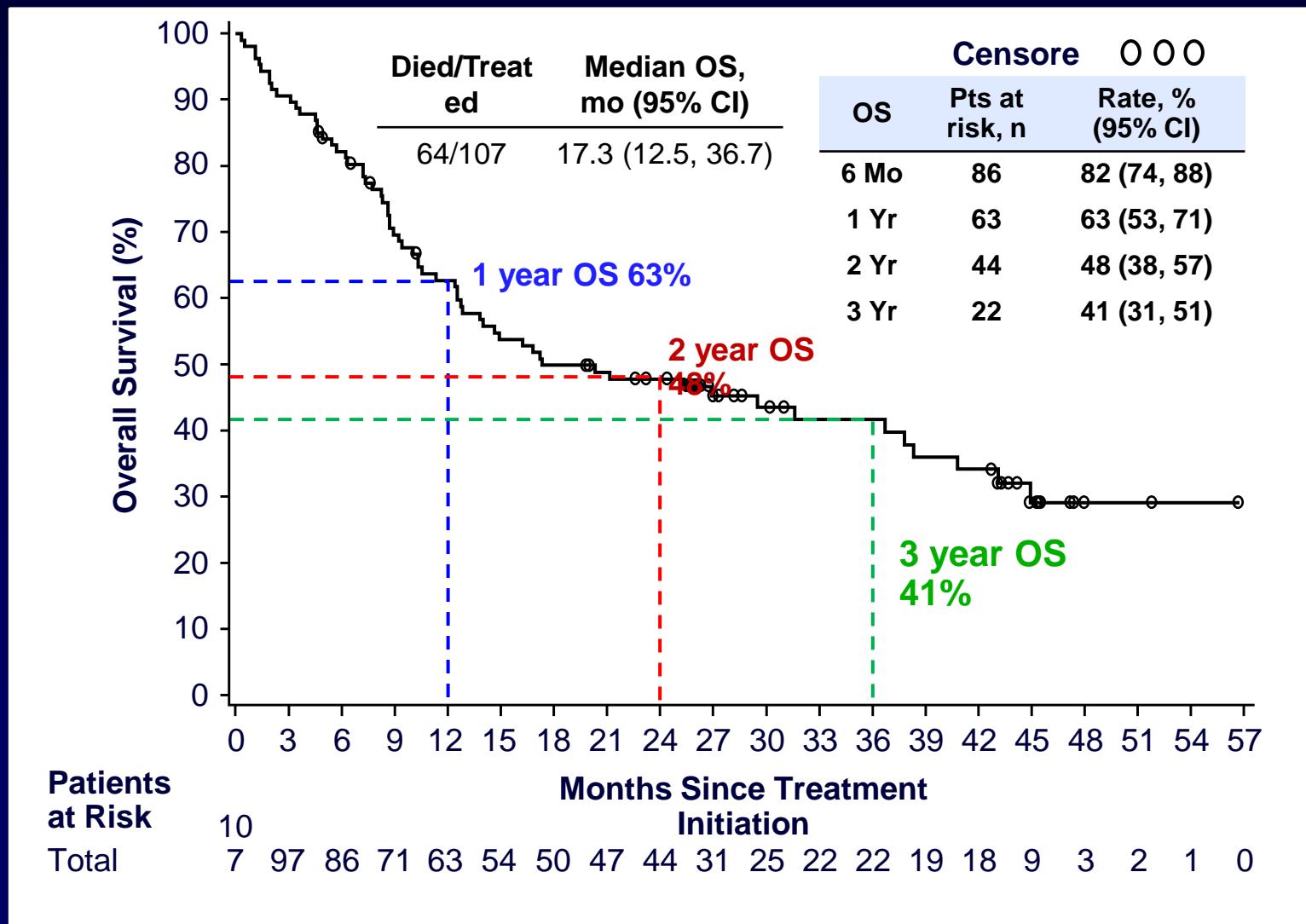
Dose mg/kg	ORR % (n/N)	Estimated Median DOR Weeks (Range)	Stable Disease Rate ≥24 Wks % (n/N)	Median PFS Months (95% CI)
NSCLC	17 (22/129)	74 (6+, 134+)	10 (13/129)	2 (2, 4)
MEL ^a	31 (33/107)	104 (18, 117+)	7 (7/107)	4 (13, 44)
RCC ^a	29 (10/34)	56 (37, 127+)	27 (9/34)	7 (4, 13)

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

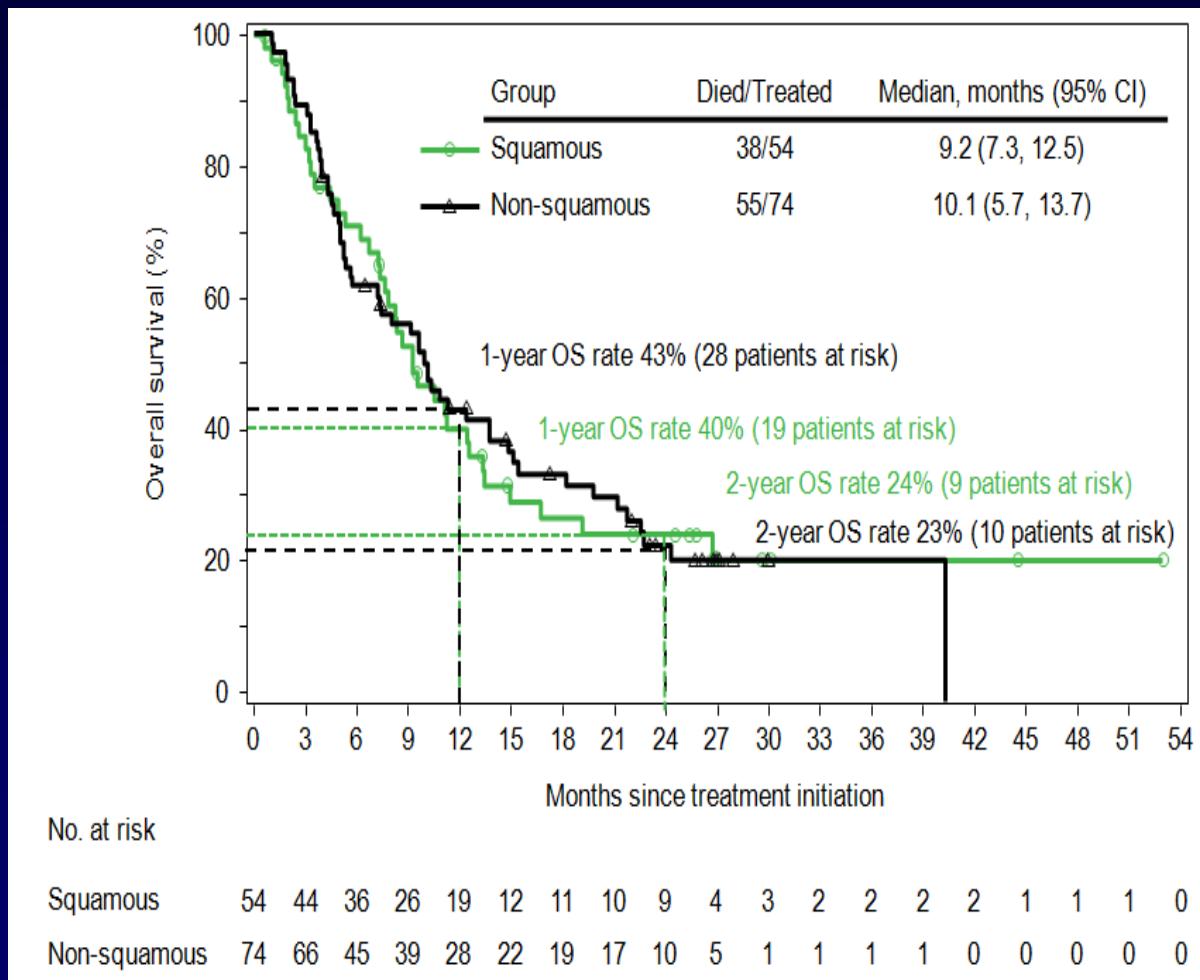
^a1 CR was noted in MEL and 1 CR was noted in RCC.

- 30/65 (46%) responses were evident at first tumor evaluation (8 weeks)
- 42/65 (65%) responses were ongoing >1 year
- No OR in CRPC or CRC

Overall Survival for Patients with Melanoma Treated with Nivolumab



Nivolumab OS by Histology in NSCLC



Nivolumab Multi-Dose: Safety in Total Population CA209-003

- Drug-related AEs: all grades, 75%; grades 3–4, 17%
- Drug-related select AEs: all grades, 46%; grades 3–4, 6%

Select AEs	Any Grade n (%)	Grade 3–4, n (%)
Any select AEs	140 (45.8)	19 (6.2)
Skin	75 (24.5)	1 (0.3)
Rash	45 (14.7)	0
Pruritus	32 (10.5)	1 (0.3)
Rash pruritic	7 (2.3)	0
Urticaria	6 (2.0)	0
Photosensitivity reaction	5 (1.6)	0
Rash macular	4 (1.3)	1 (0.3)
Gastrointestinal	44 (14.1)	3 (1.0)
Diarrhea	41 (13.4)	3 (1.0)
Colitis	6 (2.0)	2 (0.7)
Endocrinopathies	29 (9.5)	3 (1.0)
Blood thyroid-stimulating hormone increased	11 (3.6)	1 (0.3)
Hypothyroidism	11 (3.6)	1 (0.3)
Hyperthyroidism	4 (1.3)	1 (0.3)
Hepatic	18 (5.9)	4 (1.3)
Alanine aminotransferase increased	11 (3.6)	1 (0.3)
Aspartate aminotransferase increased	9 (2.9)	0
Pulmonary	17 (5.6)	6 (2.0)
Pneumonitis	12 (3.9)	4 (1.3)
Infusion reaction	15 (4.9)	2 (0.7)
Infusion-related reaction	12 (3.9)	0
Hypersensitivity	4 (1.3)	2 (0.7)
Renal	6 (2.0)	1 (0.3)
Blood creatinine increased	4 (1.3)	1 (0.3)

Activity of Anti-PD-1 and Anti-PD-L1 in Metastatic Melanoma

Agent	Dose and schedule	N=	ORR (%)	Median response duration, months	Median PFS/ 24 week PFS rate	Median Survival	1 yr/2 yr survival
Nivolumab (Anti-PD1)	0.3-10 mg/kg q2w	107	32%	22.9	3.7 months	<u>17.2 months</u>	<u>63%/48%</u>
Pembrolizumab (Anti-PD1)	2-10 mg/kg q2-3w	411 (168 ipi-N)	34% (40% IPI-N)	NR	5.5 months	NR	<u>69%/ND</u>
MPDL3280 (Anti-PD-L1)	.01-20 mg/kg q3w	44	29%	ND	43%	ND	ND
BMS-936559 (Anti-PD-L1)	0.3-10 mg/kg q2w	52	17%	ND	42%	ND	ND

Activity of Anti-PD1 and Anti-PD-L1 in NSCLC

Agent	Dose mg/kg	N=	ORR % (n/N)	Estimated Median DOR Weeks (Range)	PFS rate at 24 weeks	Median PFS Months (95% CI)	Median OS Months (95% CI)	1 yr/2yr survival rate
Nivolumab Anti-PD-1	1-10 mg/kg q2w	129	17.1%	74.0	ND	2.3	9.9	42%/24%
Pembrolizumab Anti-PD-1	2-10 mg/kg q2-3w	146	19%	ND	ND	Approx 2.5	Approx 8	ND
MPDL3280A Anti-PD-L1	.01-20 mg/kg q3w	53	23%	ND	46%	ND	ND	ND
BMS-936559 Anti-PD-L1	1-10 mg/kg q2w	49	10%	ND	31%	ND	ND	ND
Medi-4736 Anti-PD-L1	0.1 -10 mg/kg q2w	84	~16%	ND	ND	ND	ND	ND

Randomized Phase 2 Trial of Nivolumab in Metastatic Renal Cancer

Overall survival in phase III trials and nivolumab phase II study

	AXIS ^{1,a}	INTORSECT ²	RECORD-1 ³	GOLD ⁴	Nivolumab study
Drug	Axitinib; sorafenib	Temsirolimus; sorafenib	Everolimus; placebo	Dovitinib; sorafenib	Nivolumab; 0.3; 2; 10 mg/kg
Patients, n	389	512	416	570	168
Risk group, % ^b					
Favorable		19	29	20	33
Intermediate	Not stated	69	56	58	42
Poor		12	14	22	25
Prior therapy	Sunitinib	Sunitinib	VEGF	VEGF + mTOR	VEGF ± mTOR
Line of therapy	2nd	2nd	2nd or higher	3rd or higher	2nd to 4th
Median OS, months	15.2; 16.5	12.3; 16.6	14.8; 14.4	11.1; 11.0	18.2; 25.5; 24.7
CI	12.8, 18.3 ^c 13.7, 19.2 ^c	10.1, 14.8 ^c 13.6, 18.7 ^c	Not stated	9.5, 13.4 ^c 8.6, 13.5 ^c	16.2, 24.0 ^d 19.8, 28.8 ^d 15.3, 26.0 ^d

**Nivolumab
ORR ~ 20%**

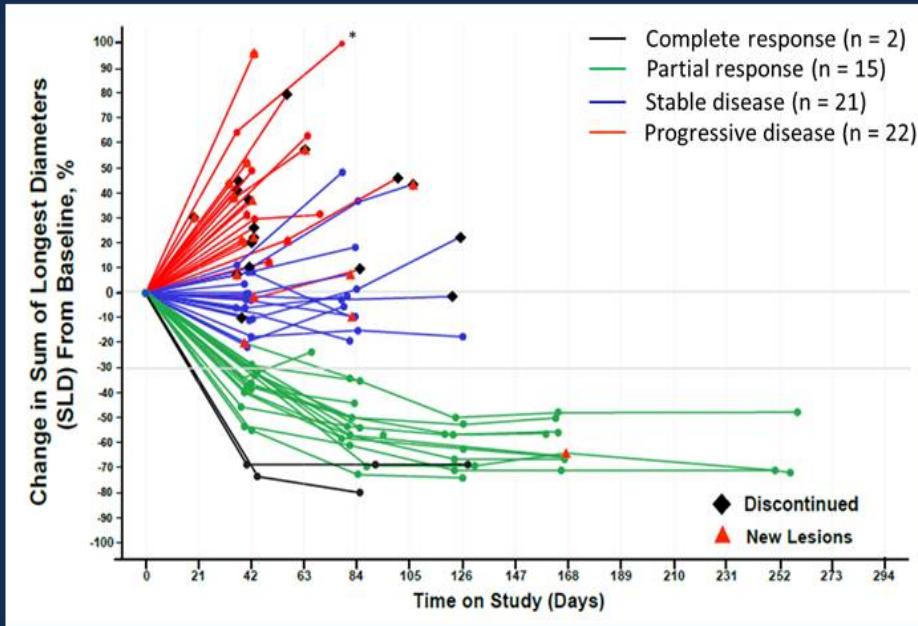
^aPost TKI subset; ^bTotal ≠ 100% due to rounding; ^c95% CI; ^d80% CI.

1. Motzer R, et al. *Lancet Oncol*. 2013;14:552-62; 2. Hutson TE, et al. *J Clin Oncol*. 2014;32:760-7; 3. Motzer R, et al. *Cancer*. 2010;116:4256-65;

4. Motzer R, et al. *Lancet Oncol*. 2014;15:286-96.

Promising Activity of Anti-PD-L1 in Advanced Bladder Cancer

MPDL3280A: Tumor Burden Over Time in UBC



- Median time to first response was 42 days (range, 38 to 85 days)
- Median duration of response has not been reached
 - 0.1+ to 30.3+ weeks IHC (IC) 2 or 3 and 0.1+ to 6.0+ weeks for IHC (IC) 0 or 1
- Median follow-up was 4.2 months (1.1+ to 8.5) for Dx+ and 2.7 months (0.7+ to 3.6) for Dx-

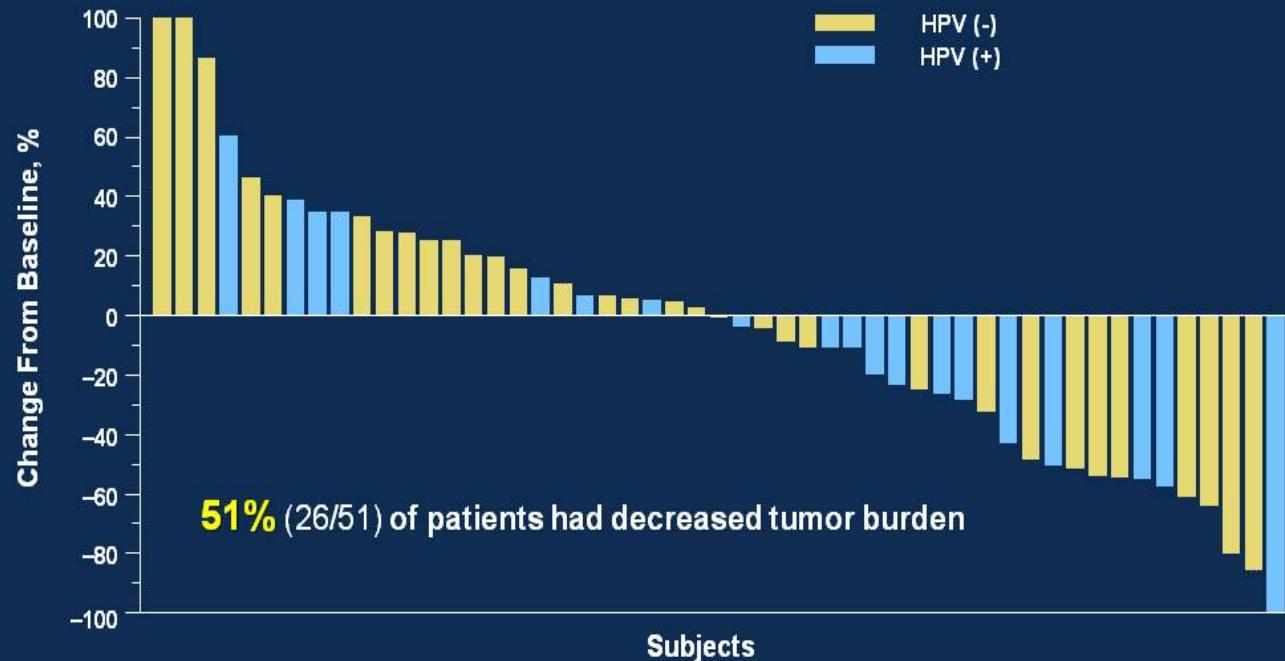
Figure does not include 7 pts without any post-baseline tumor assessment.

Patients closed by Nov 20, 2013 (>6 wk follow-up) with measurable disease at baseline and at least 1 post-baseline measurement.

Clinical data cutoff was Jan 1, 2014.

Activity of Pembrolizumab in PD-L1+ Squamous Cell Cancer of Head and Neck

Efficacy: Waterfall Plot*

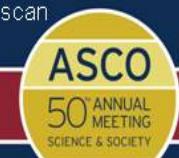


→ Best percent change from baseline in target lesions (site assessment) delineated by HPV status

*as of May 23, 2014; Includes only patients with RECIST measurable lesions at baseline and at least 1 follow-up scan (n=51)

Presented by: Tanguy Seiwert

PRESENTED AT:



Activity of Anti-CTLA-4 and/or Anti-PD1 in Multiple Cancers

- Melanoma
- Renal Cancer
- Non-small cell lung cancer
- Bladder cancer
- Head and neck
- Gastro-esophageal
- Ovarian
- Mesothelioma (anti-CTLA-4)
- Hodgkin's Disease

CA209-004 Ipilimumab/Nivolumab Combination Phase I Study: Dose Cohorts

Regimen Cohort No.	N	Dose (mg/kg),		Treatment Schedule	
		Nivolumab	Ipilimumab	Induction	Maintenance
Concurrent					
1	14	0.3	3	Nivo Q3W x 8	Nivo + IPI Q12W
2	17	1	3	+ IPI Q3W x 4	x 8
2a	16	3	1		
3	6	3	3		
8*	41	1	3	Nivo Q3W x 4 + IPI Q3W x 4	Nivo 3 mg/kg Q2W (Max. 48 doses)
Sequenced					
6	17	1	Prior		
7	16	3	Prior		Nivo Q2W (Max of 48 doses)

*Insufficient follow-up at this data collection to report survival endpoints

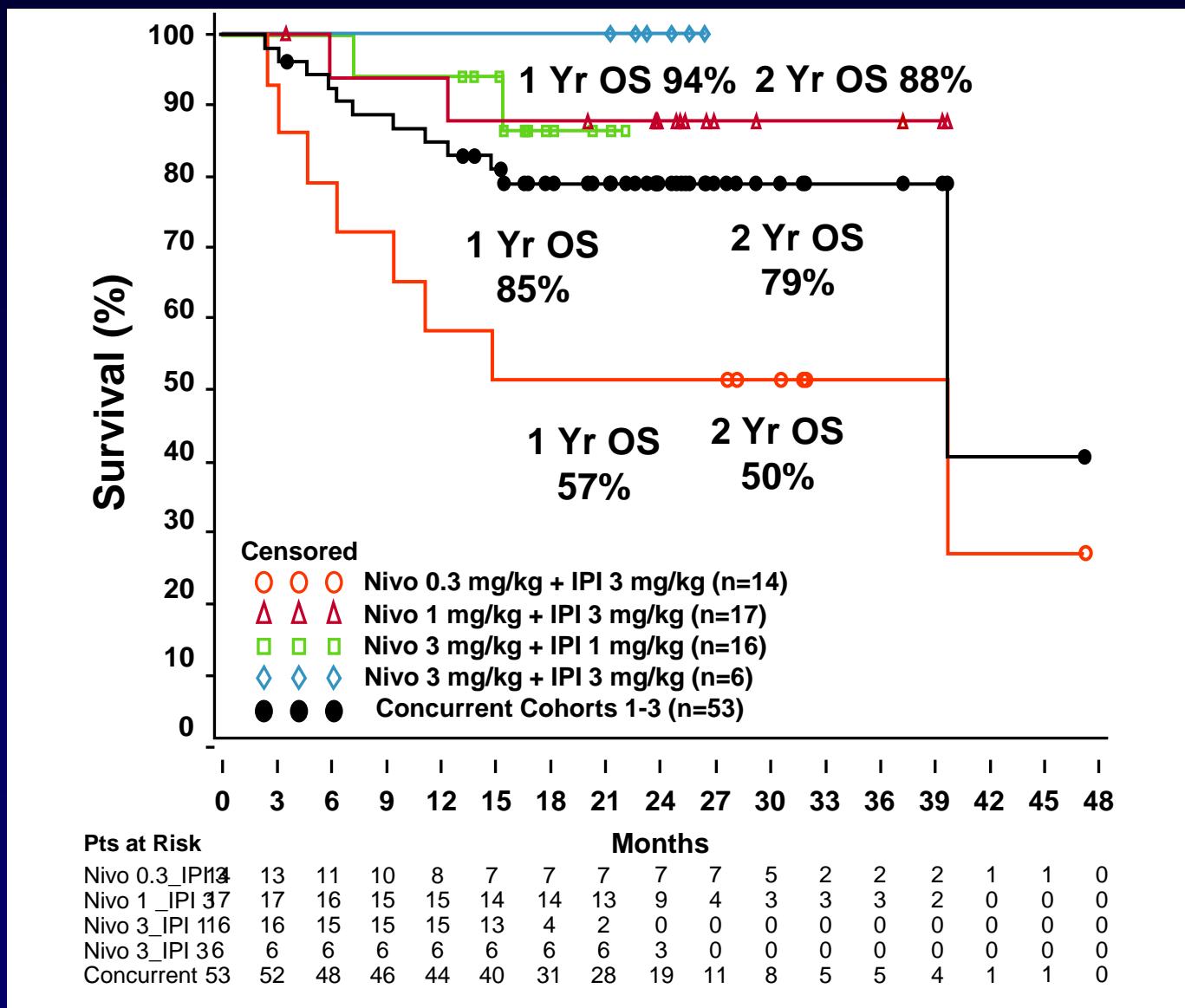
Activity Summary: Concurrent and Sequenced Cohorts from 004

Nivolumab (mg/kg) + IPI (mg/kg)	N	ORR ^a , %	CR, %	Aggregate Clinical Activity Rate	$\geq 80\%$ tumor burden reduction at 36 wks ^b , %
Concurrent Cohorts 1-3	53	42	17	<u>70</u>	<u>42</u>
0.3 + 3	14	21	14	57	36
1 + 3	17	53	18	65	53
3 + 1	16	44	25	81	31
3 + 3	6	50	0	83	50
1 + 3 [Cohort 8] ^c	40	43	10 ^d	53	28
Sequenced	33	31	3	44	31

^aper RECIST, [CR+PR]/N x 100; ^b Best overall response; ^cCohort 8: Phase 2/3 trial; last patient, first dose Nov 2013. ^d2 confirmed and 2 unconfirmed responses

n: no. response-evaluable pts.

Overall Survival for Concurrent Therapy by Dose Cohort



Ipilimumab + Nivolumab Safety Overview

AE, %	Concurrent Cohorts 1-3 n=53		Cohort 8 n = 41		All Concurrent n=94	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4
All Related AEs	96	62	95	61	96	62
Select AEs						
Gastrointestinal	43	9	34	20	39	14
Hepatic	30	15	12	12	22	14
Skin	79	4	73	15	77	9
Endocrine	17	4	22	2	19	3
Renal	6	6	0	0	3	3
Other						
Uveitis	6	4	2	2	4	3
Pneumonitis	6	2	2	2	4	2
Lipase increased	26	19	15	10	21	15
Amylase increased	21	6	12	7	17	6

- No new safety signals with 22 months of follow-up for the initial concurrent cohorts
- 22/94 (23%) patients discontinued treatment due to treatment-related adverse events
- 1/94 drug-related death in trial; fatal multi-organ failure (as a result of colitis) in cohort 8

Nivolumab + Ipilimumab in Metastatic Renal Cancer

ASCO 2014

Antitumor activity

	N3 + I1 (n=21)	N1 + I3 (n=23)
Confirmed ORR, n (%) 95% CI	9 (43) 21.8-66.0	11 (48) 26.8-69.4
Median duration of response, weeks (range) ^a	31.1 (4.1+42.1+) ^b	NR (12.1+35.1+) ^c
Ongoing responses, % (n/N)	78 (7/9)	82 (9/11)
Best objective response, n (%)		
Complete response	0	1 (4)
Partial response	9 (43)	10 (43)
Stable disease	5 (24)	8 (35)
Progressive disease	5 (24)	3 (13)
Unable to determine	1 (5)	1 (4)
24-week PFS, % (95% CI)	65 (40-82)	64 (41-80)

^aDue to the high percentage of ongoing responses, median duration of response may be misleading; ^bMedian follow-up 36.1 weeks; ^cMedian follow-up 40.1 weeks

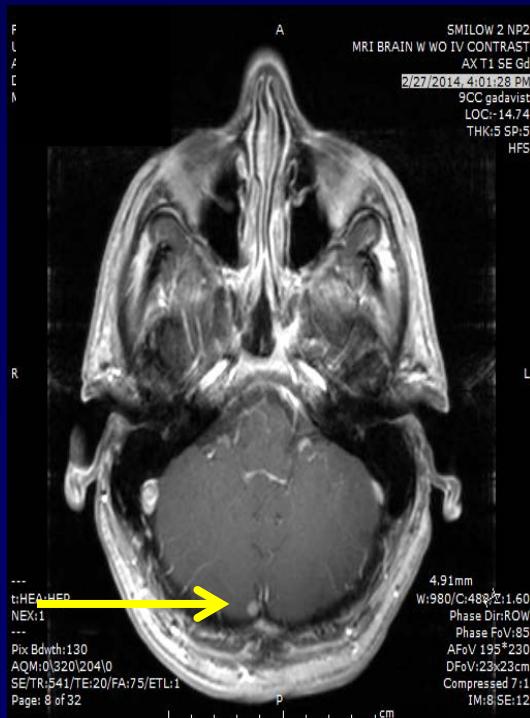
Duration of response defined as time between date of first response and date of disease progression or death (whichever occurs first).

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Patient Case 1

A patient with BRAF wild-type metastatic melanoma received checkpoint inhibitors as first-line therapy as part of CA209-067.

At week 12 there was marked regression of lung metastases and 2 new brain lesions



Week 13

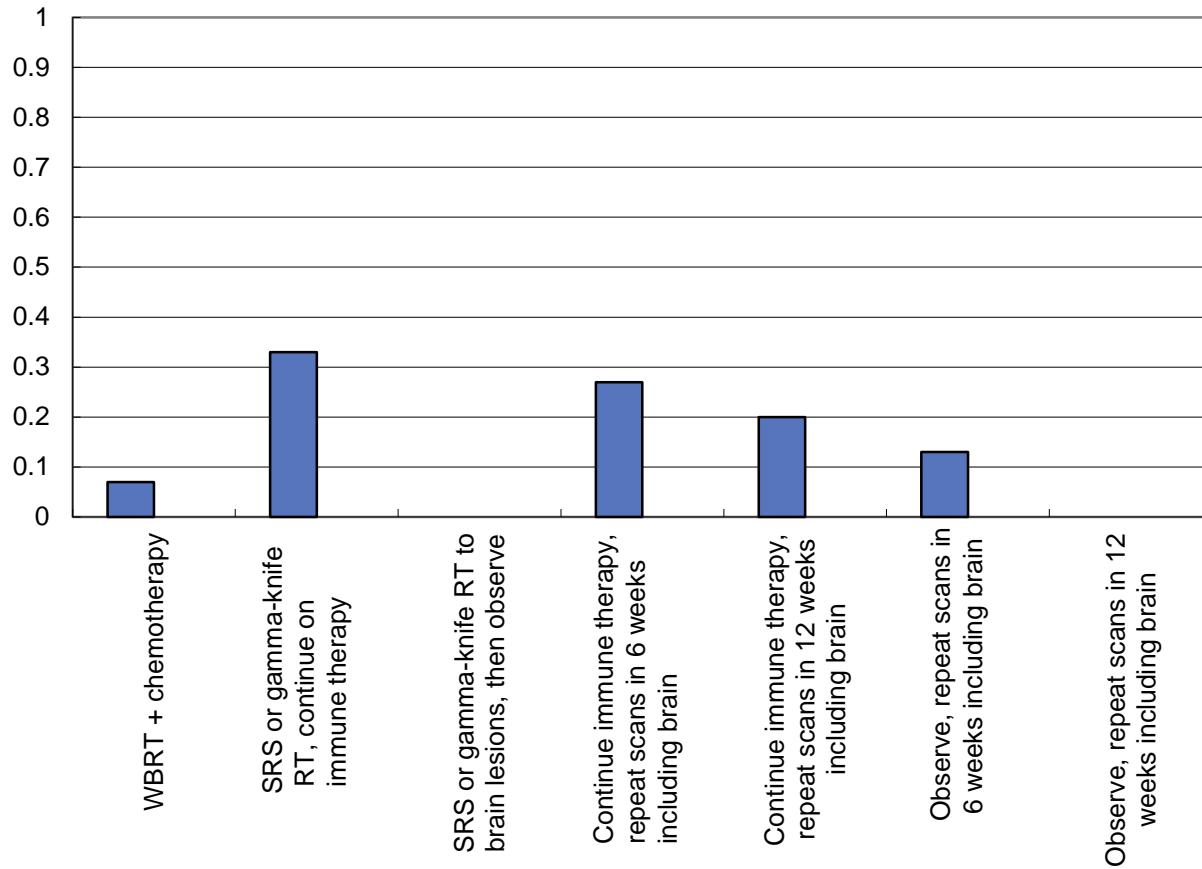


Case 1: What would you do next?

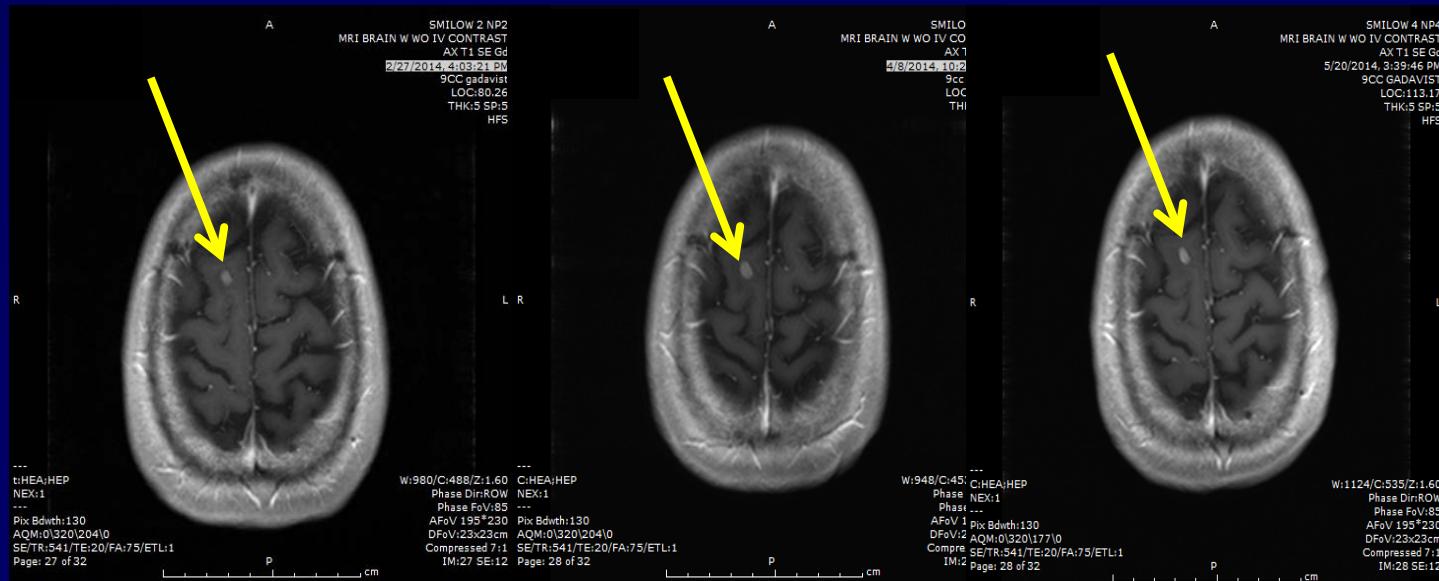
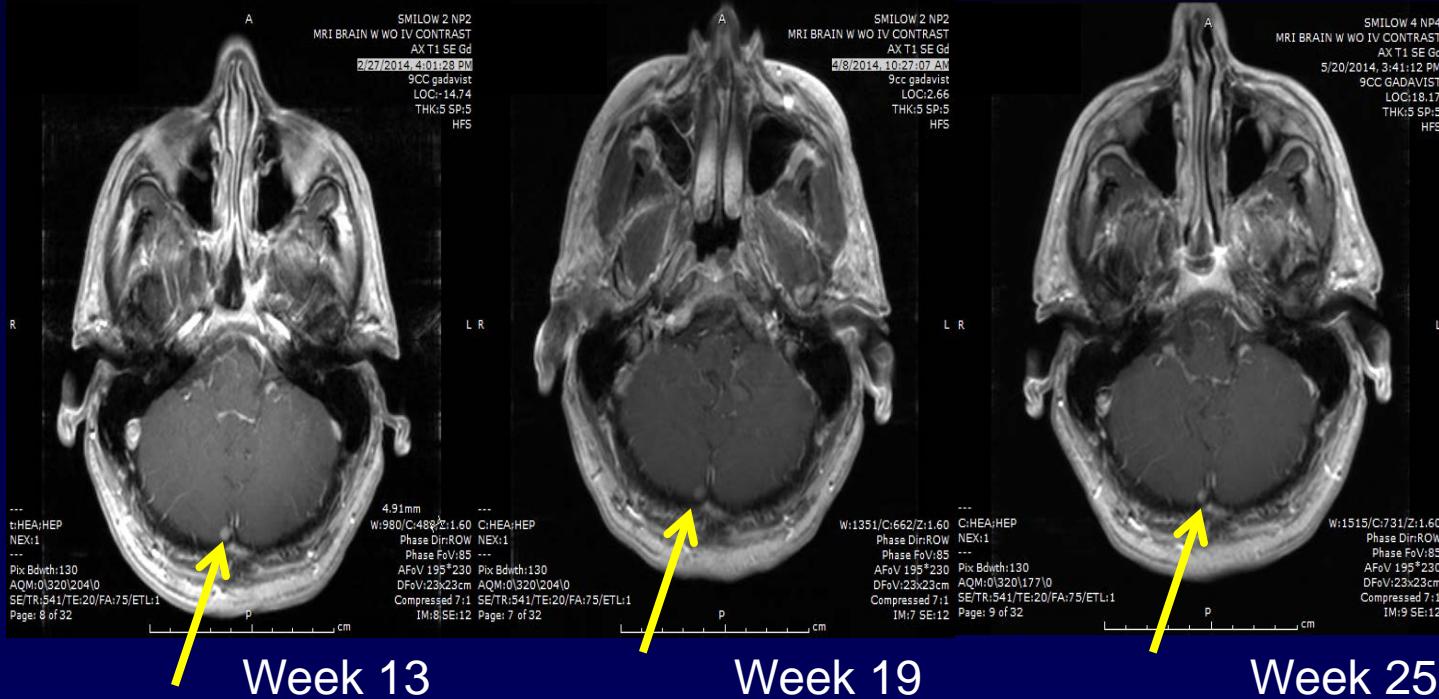
- 1. WBRT + chemotherapy**
- 2. SRS or gamma-knife RT to brain lesions, continue on immune therapy**
- 3. SRS or gamma-knife RT to brain lesions, then observe**
- 4. Continue immune therapy, repeat scans in 6 weeks including brain**
- 5. Continue immune therapy, repeat scans in 12 weeks including brain**
- 6. Observe, repeat scans in 6 weeks including brain**
- 7. Observe, repeat scans in 12 weeks including brain**

Results

What would you do next?

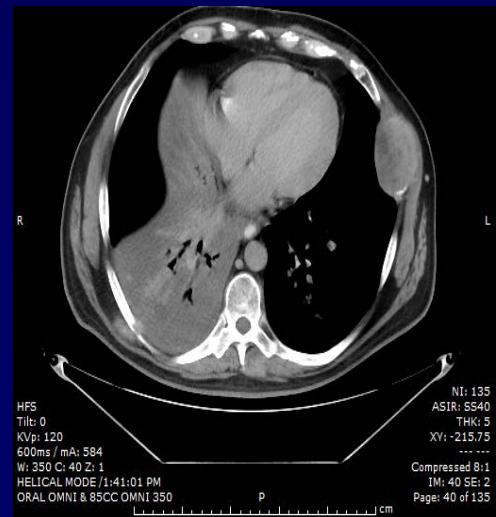
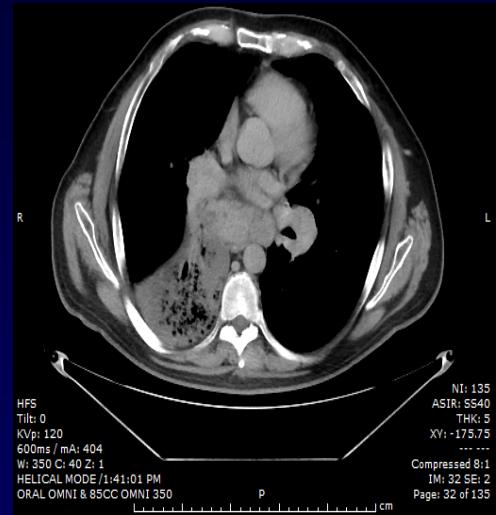


Left untreated, brain lesions grew slightly at week 19 and began to regress at week 25



Case 2

- Treatment-refractory mRCC
- Prior RX: anti-PD1, HD IL-2, sunitinib, everolimus, axitinib, gemcitabine, RT
- Primary in place; Mets to: brain, bone, LN, lung, adrenal, SQ, muscle
- Received 4 doses of ipilimumab; week 12 scans showed mostly PD, slight reduction in adrenal met and primary tumor

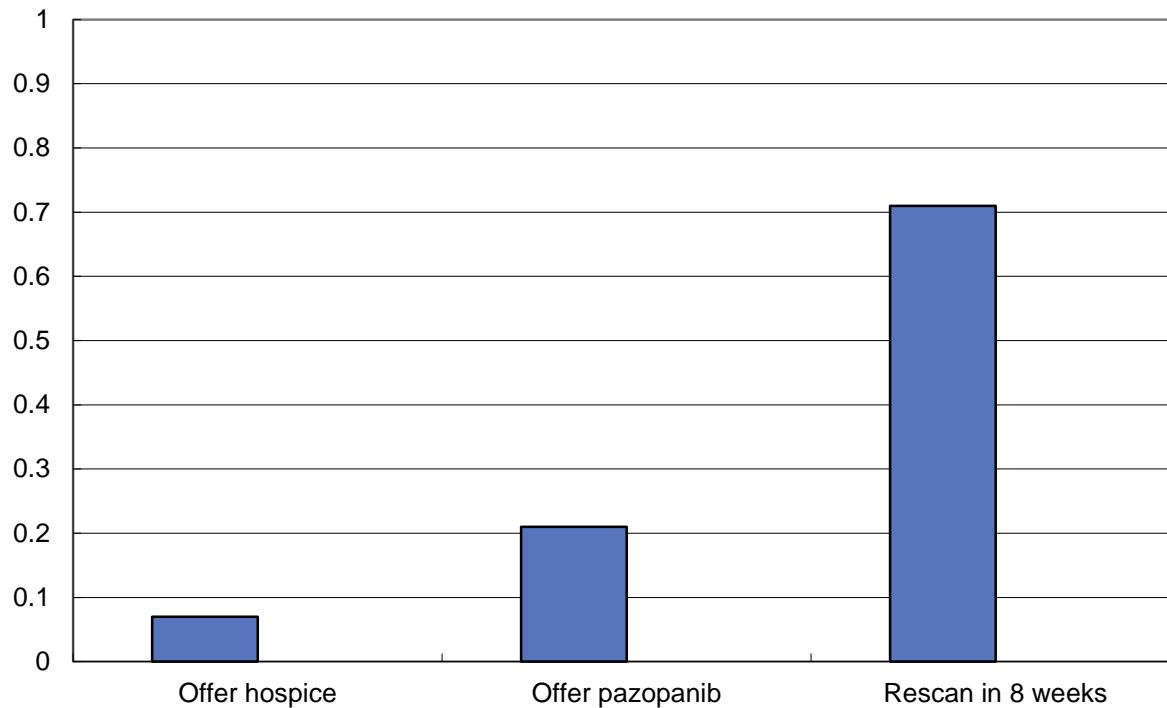


Case 2: What would you do next?

- 1. Offer hospice**
- 2. Offer pazopanib**
- 3. Rescan in 8 weeks**

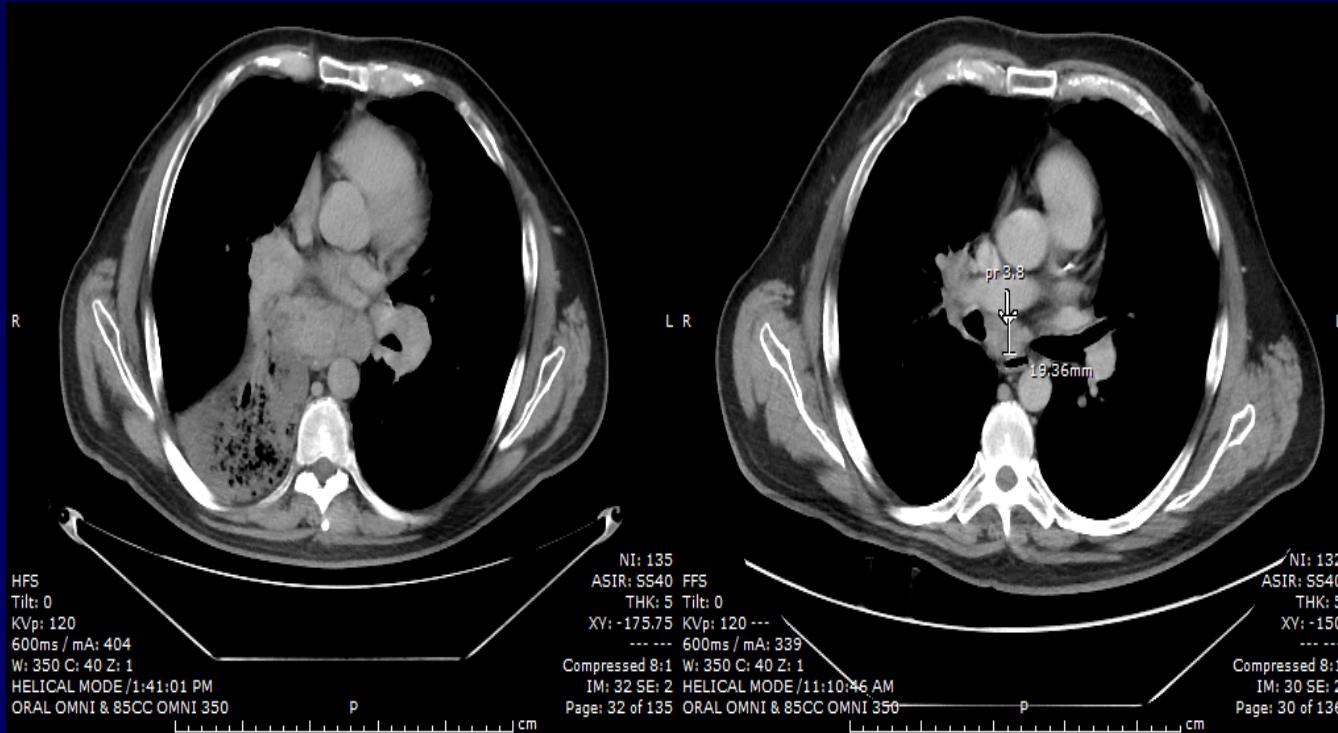
Results

What would you do next?



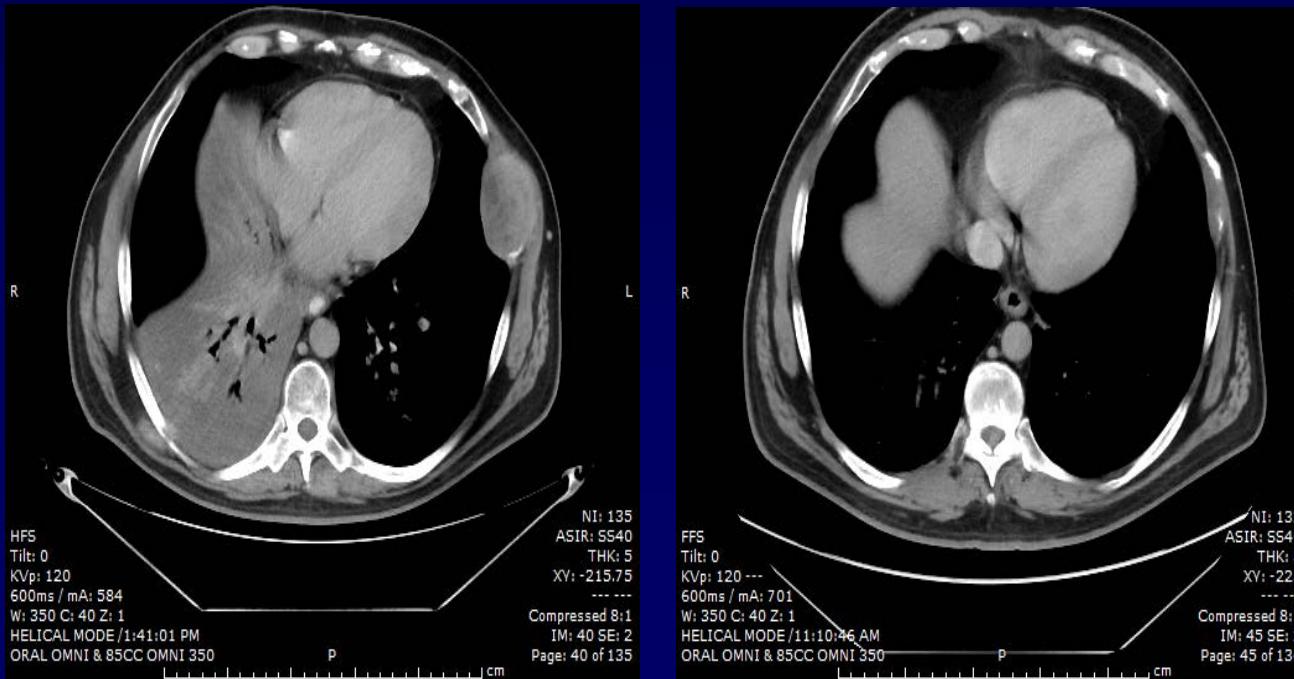
Response to Ipilimumab at Week 20 in Treatment-Refractory mRCC

- Primary in place
- Mets to: brain, bone, LN, lung, adrenal, SQ, muscle
- Prior RX: anti-PD1, HD IL-2, sunitinib, everolimus, axitinib, gemcitabine, RT



Response to Ipilimumab in Treatment-Refractory mRCC

Prior RX: anti-PD1, HD IL-2, sunitinib, everolimus, axitinib, gemcitabine, RT



Case 3

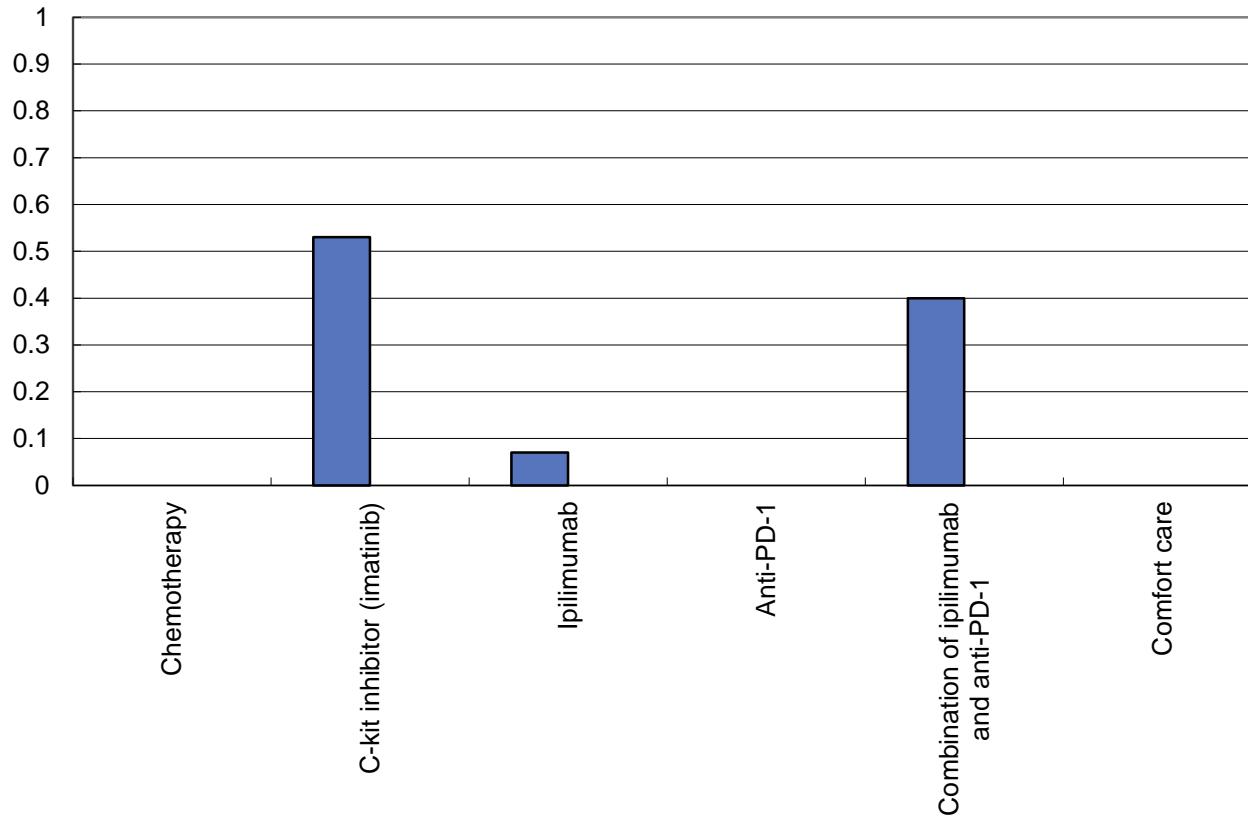
- 45 yo, ECOG PS = 0
- Anal-mucosal melanoma, metastatic to multiple sites
- Tumor contains mutation in c-kit (L576P)
- Hx of hypothyroidism

Case 3: What would you offer as first-line therapy?

1. Chemotherapy
2. C-kit inhibitor (imatinib)
3. Ipilimumab
4. Anti-PD-1
5. Combination of ipilimumab and anti-PD-1
6. Comfort care

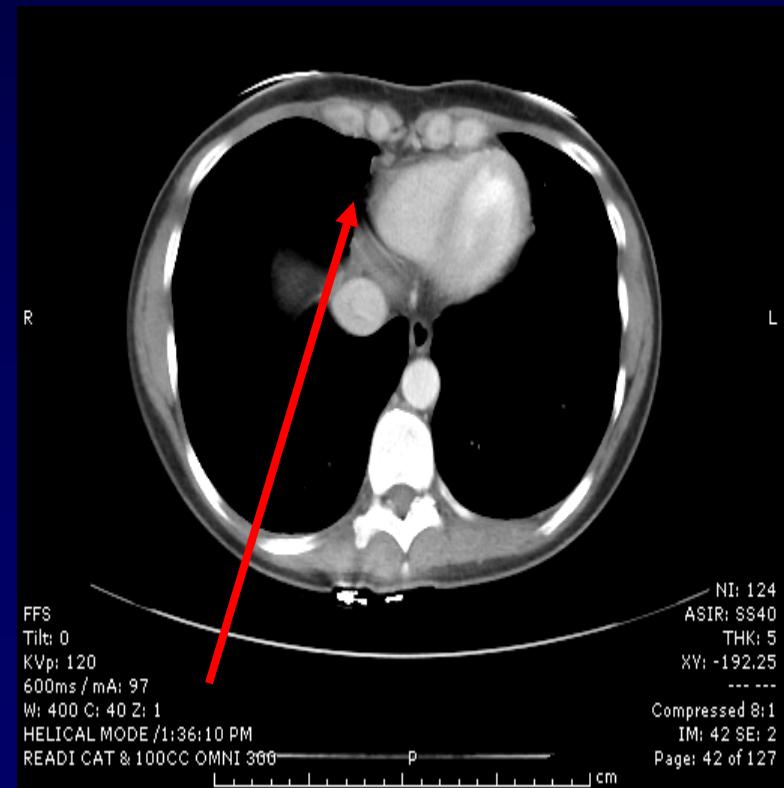
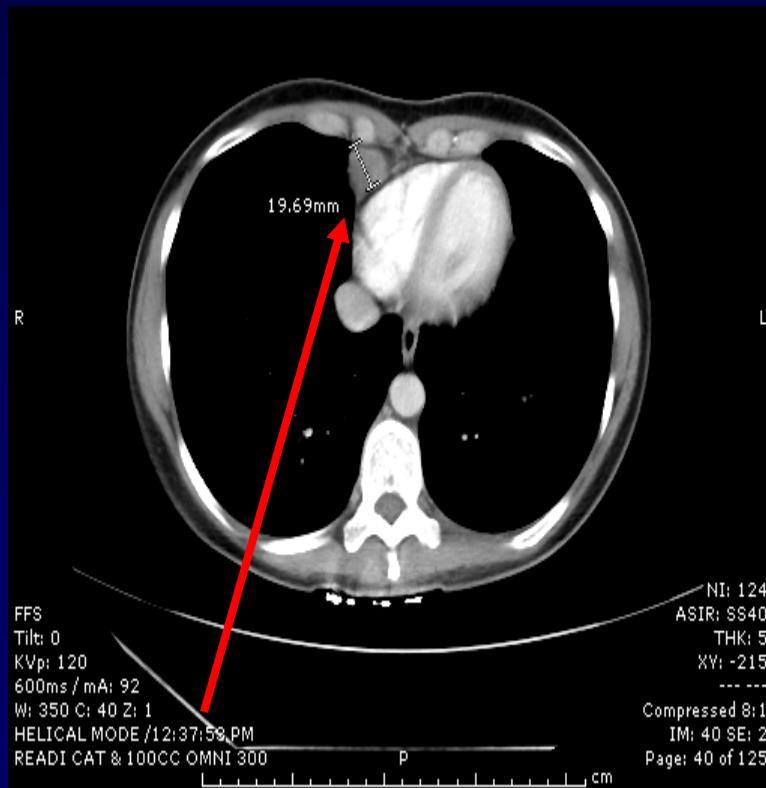
Results

What would you offer as first-line therapy?



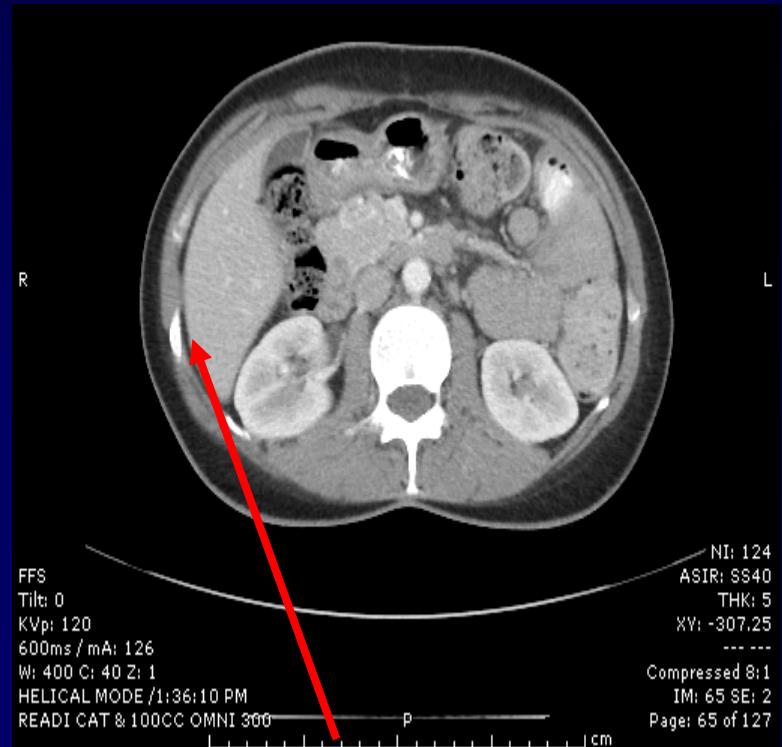
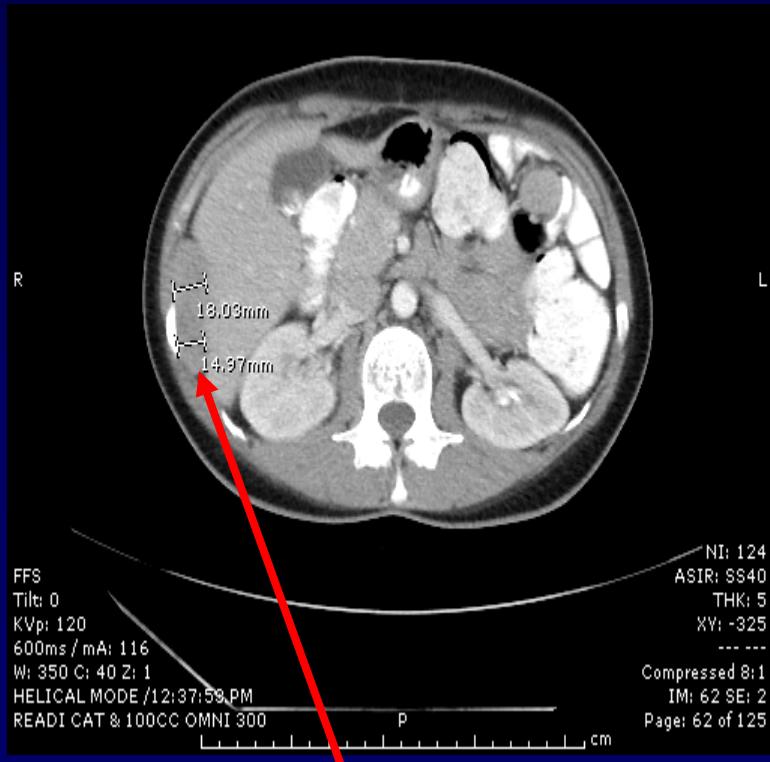
Case 3, cont

Metastatic melanoma from anal mucosal primary,
response to ipilimumab 3 mg/kg + nivolumab 1 mg/kg



Case 3, cont

Metastatic melanoma from anal mucosal primary,
response to ipilimumab 3 mg/kg + nivolumab 1 mg/kg



Case 3, cont

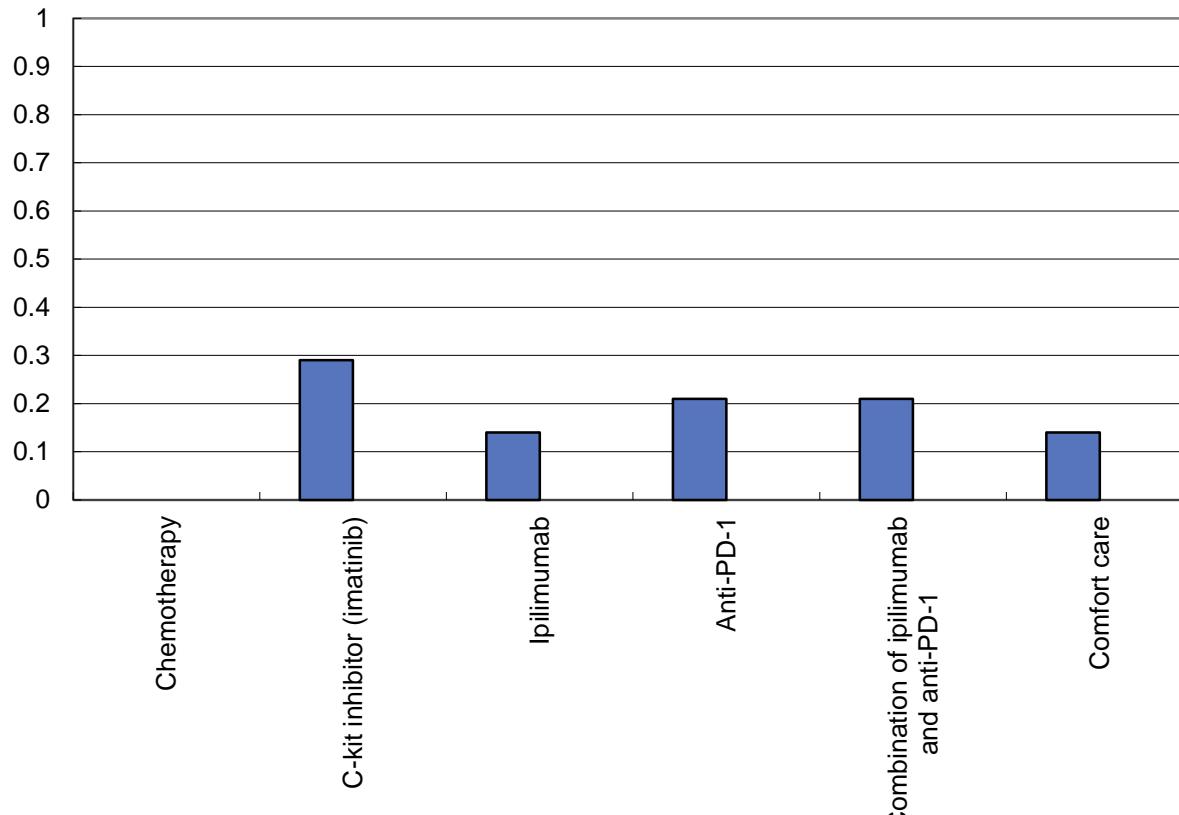
- She received one dose of ipi+ nivo, complicated by posterior uveitis, and treated with high dose steroids
- Treatment was stopped
- Achieved complete response (developed extensive vitiligo)
- After 2.5 years, developed mild anemia
- At 3 years, scan showed large mass in gastric wall, otherwise NED – not resectable, Bx + for recurrent melanoma

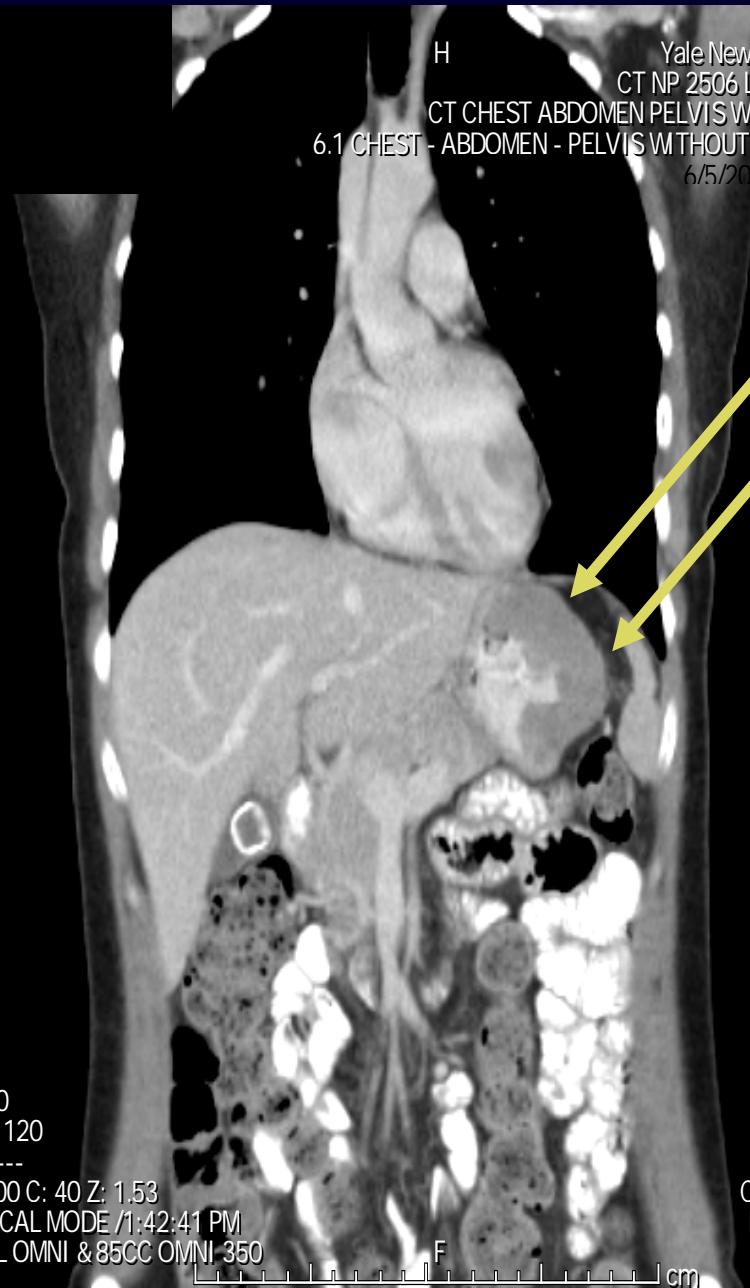
Case 3: What would you offer next?

- 1. Chemotherapy**
- 2. C-kit inhibitor (imatinib)**
- 3. Ipilimumab**
- 4. Anti-PD-1**
- 5. Combination of ipilimumab and anti-PD-1**
- 6. Comfort care**

Results

What would you offer next?





Selection of Patients

- Predictive biomarkers
- Clinical features associated with response or resistance
- Tumor burden and rate of disease progression
 - Kinetics of tumor response for immune therapy versus alternate therapies
- Clinical contraindications (autoimmunity, drug interactions)
- Potential for durable response with immune therapy versus alternate therapies (requirement for ongoing treatment)
- Availability and toxicity/effectiveness of alternate therapies

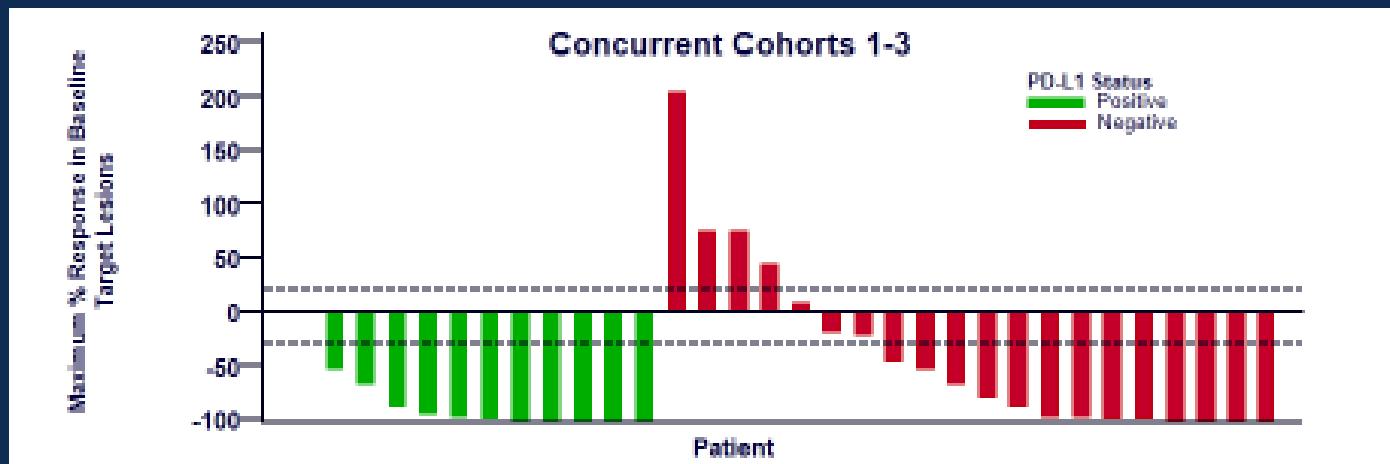
Intra-tumoral PD-L1 Expression and Response to PD-1/PD-L1 Blockade

	Nivolumab Solid Tumors (Topalian et al. NEJM 2012)	Nivolumab Melanoma (Weber ASCO 2013)	Nivolumab Melanoma (Grosso et al. ASCO 2013)	MPDL3280a Solid Tumors (Herbst et al ASCO 2013)	MPDL3280a Melanoma (Hamid et al ASCO 2013)	MPDL3280a NSCLC (Soriaj et al ECC 2013)	Pembrolizumab Melanoma (Daud et al AACR 2014)	Pembrolizumab NSCLC (Gandhi et al AACR 2014)	MPDL3280a Bladder (Powles et al ASCO 2014)	Pembrolizumab Head & Neck (Selwert et al ASCO 2014)	Pembrolizumab Melanoma (Ribas et al ASCO 2014)
n=	42	44	34	94	30	53	113	129	65	55	411
Response Rates											
Unselected	21%	32%	29%	22%	23%	23%	40%	19%	26%	18%	40%
PD-L1 +	36%	67%	44%	39%	27%	46%	49%	37%	43%	46%	49%
PD-L1 -	0%	19%	17%	13%	20%	15%*	13%	11%	11%	11%	13%

No Correlation of PD-L1 Tumor Expression with Response to Ipilimumab + Nivolumab

ORR by PD-L1 Status (5% cutoff)

Cohort [n]	Evaluable Samples	ORR, n (%)	
		PD-L1+	PD-L1-
Concurrent Cohorts 1-3 [53]	36	8/14 (57)	9/22 (35)
Cohort 8 [41; Nivo1 + IPI3]	20	0/0	8/20 (40)
Sequenced [33]	23	5/8 (63)	3/15 (20)



Presented by:

PRESENTED AT:

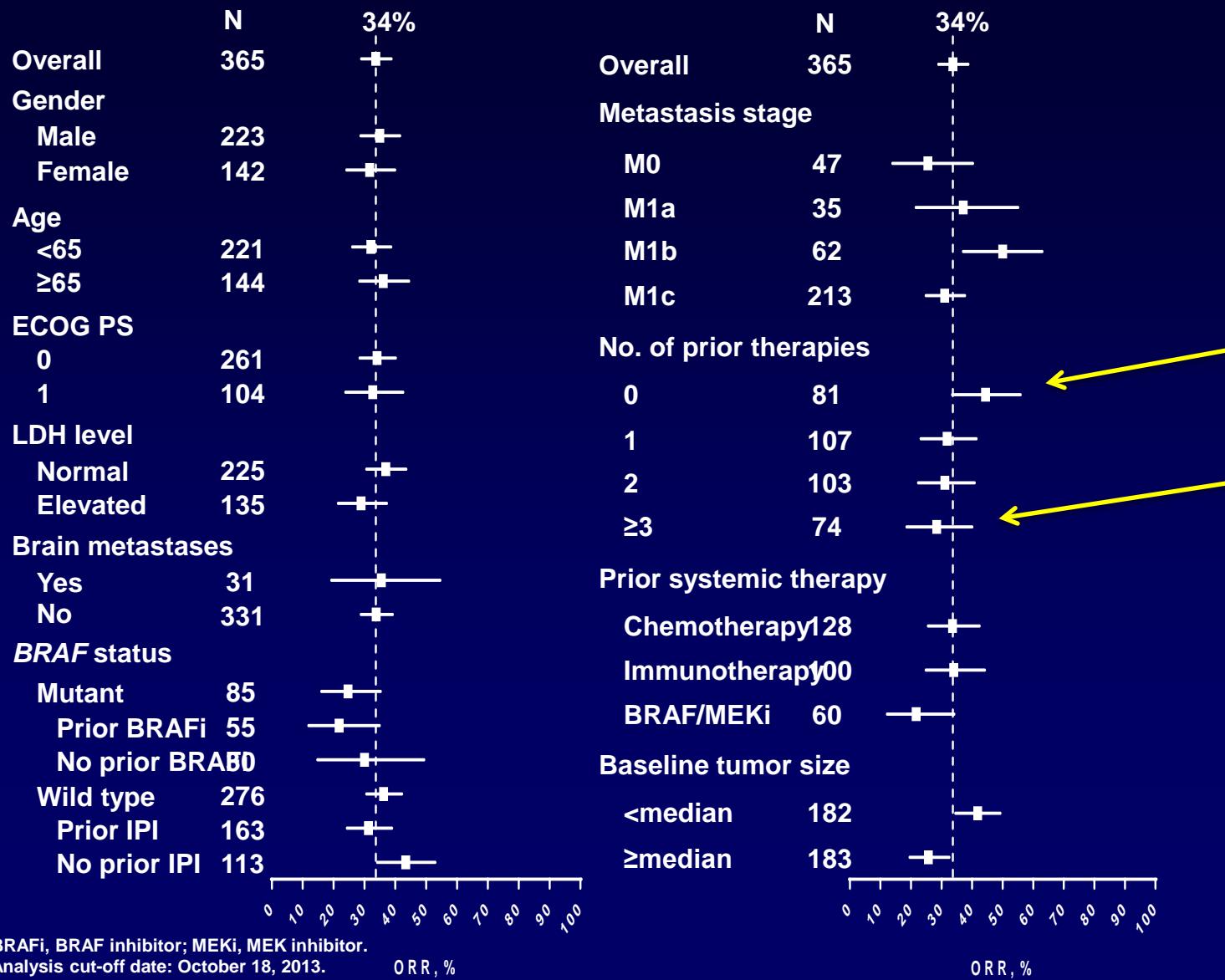


Clinical Features Possibly Associated with Lower Immune Therapy Clinical Response

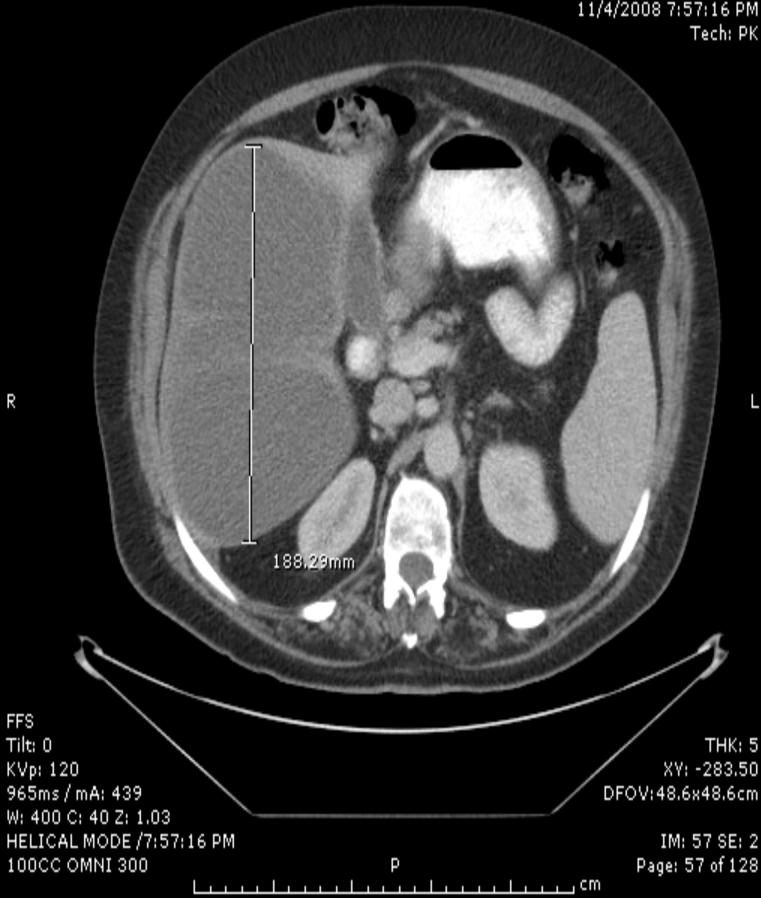
- ‘High’ tumor burden (melanoma, pembrolizumab)
- CRP > 1.5x ULN (tremelimumab, melanoma)
- High LDH
- Baseline abs lymphocyte count < 1000 (ipilimumab, melanoma)

Pembrolizumab Confirmed ORR in Subgroups

(Central Review, RECIST v1.1)



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CT 2115 LightSpeed16
CT SCAN CHES/ABD/PELV WITH CON
6.1 CHEST - ABDOMEN - PELVIS WITHOUT AND/OR WITH
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- Metastatic Melanoma, Prior HD II-2
- Anti-PD1 1 mg/kg every other week x 2 years
- Negative PET CT at 6 months
- Improving PR at 5.5 years

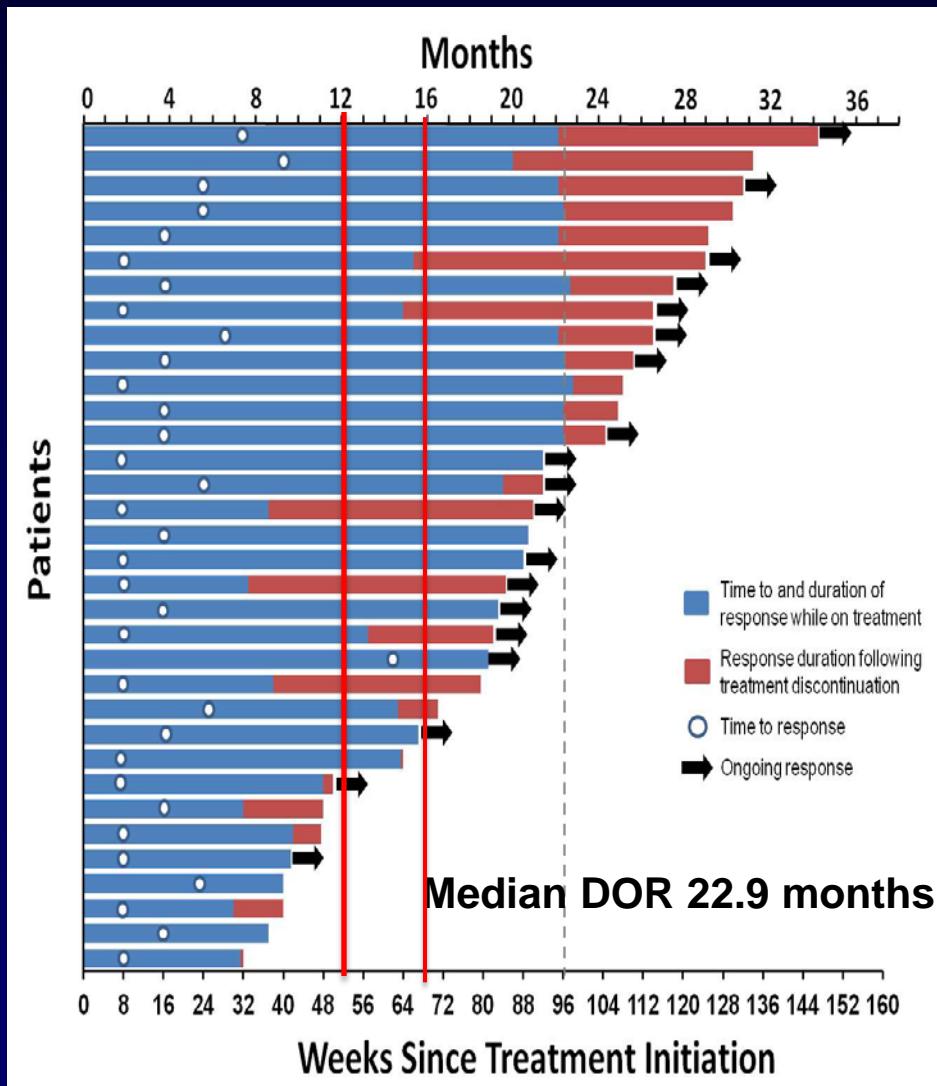
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Clear cell renal carcinoma, histologic grade 4, PD-L1 tumor expression+:
Prior excellent mixed response to HD IL-2, began anti-PD-L1 20 mg/kg
q3w on 12/9/12,
No AEs (liver lesion also regressed, not shown) – slide 1

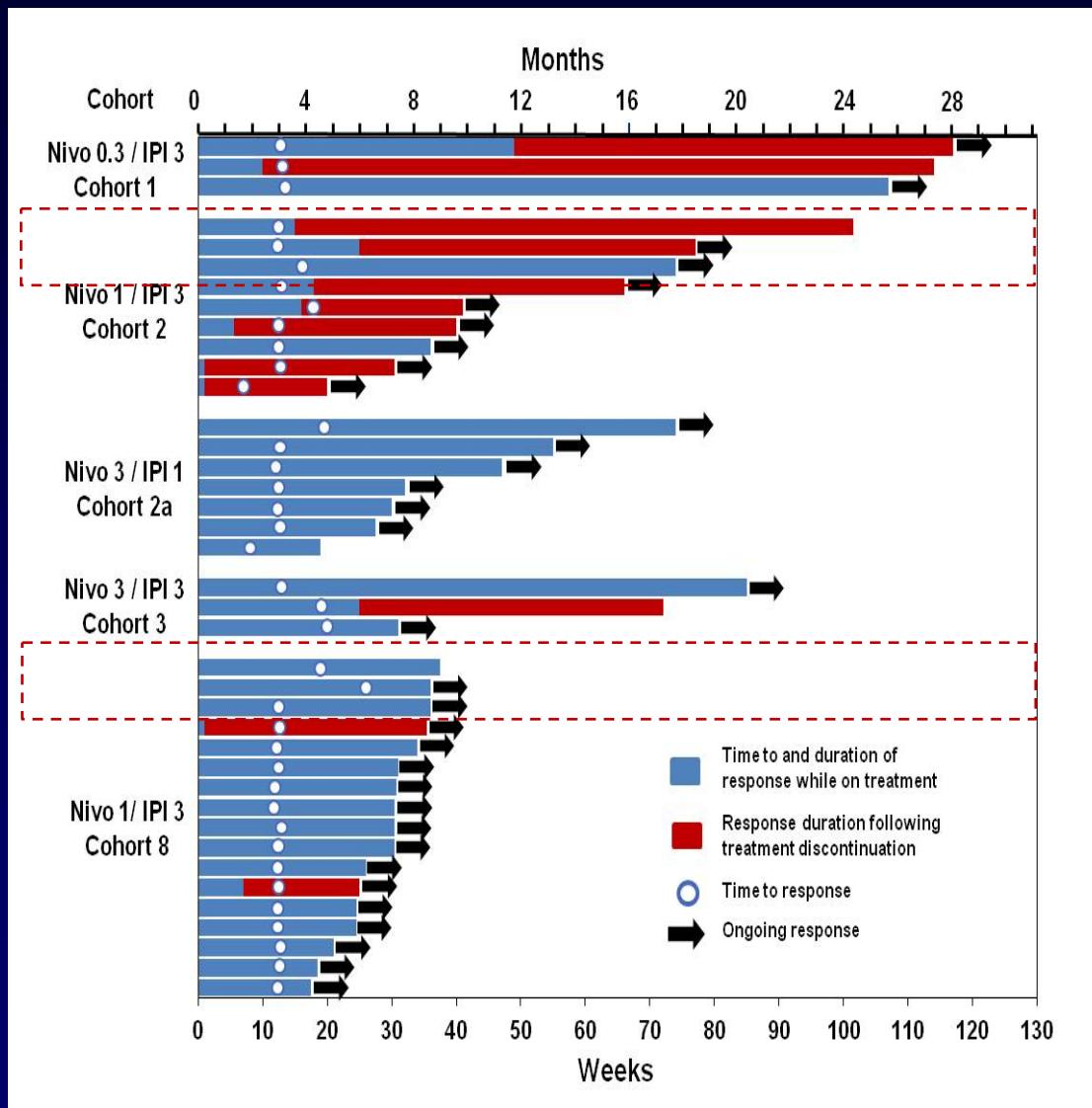


Response Characteristics in Patients with Melanoma Receiving Nivolumab



- Longest follow-up of any PD-1 pathway inhibitor; MEL pt enrollment: November 2008 through January 2012
- Responses ongoing in 19/34 (56%) responders at time of analysis
- 52% (11/21) of responding pts who discontinued therapy for reasons other than PD responded for ≥ 24 weeks
- 64% (7/11) remained in response from 24-56 weeks
- 44% (15/34) of responding patients showed a response at first tumor assessment (8 weeks)

Ipilimumab+Nivolumab Characteristics of Response



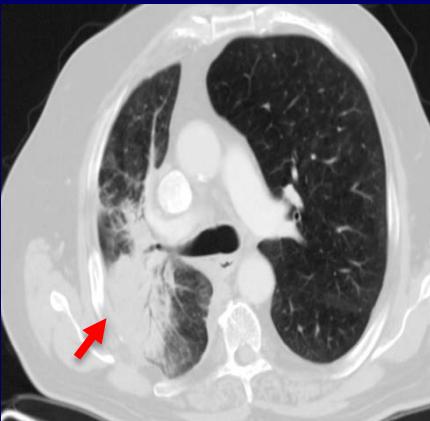
- Median duration of response in Cohorts 1-3 and cohort 8 not reached
- 18/22 responses ongoing

Rapid Response in an NSCLC Patient Treated With MPDL3280A Monotherapy

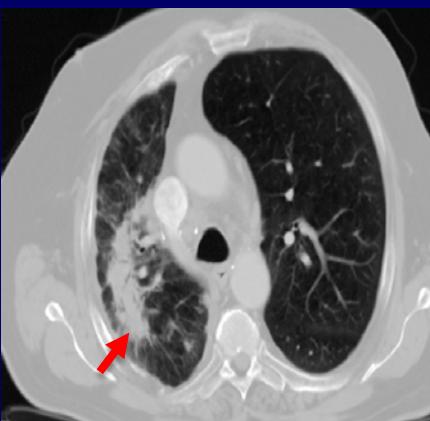
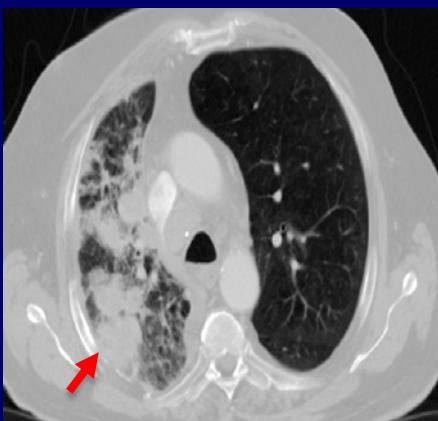
Baseline



Post C2 (Week 6)

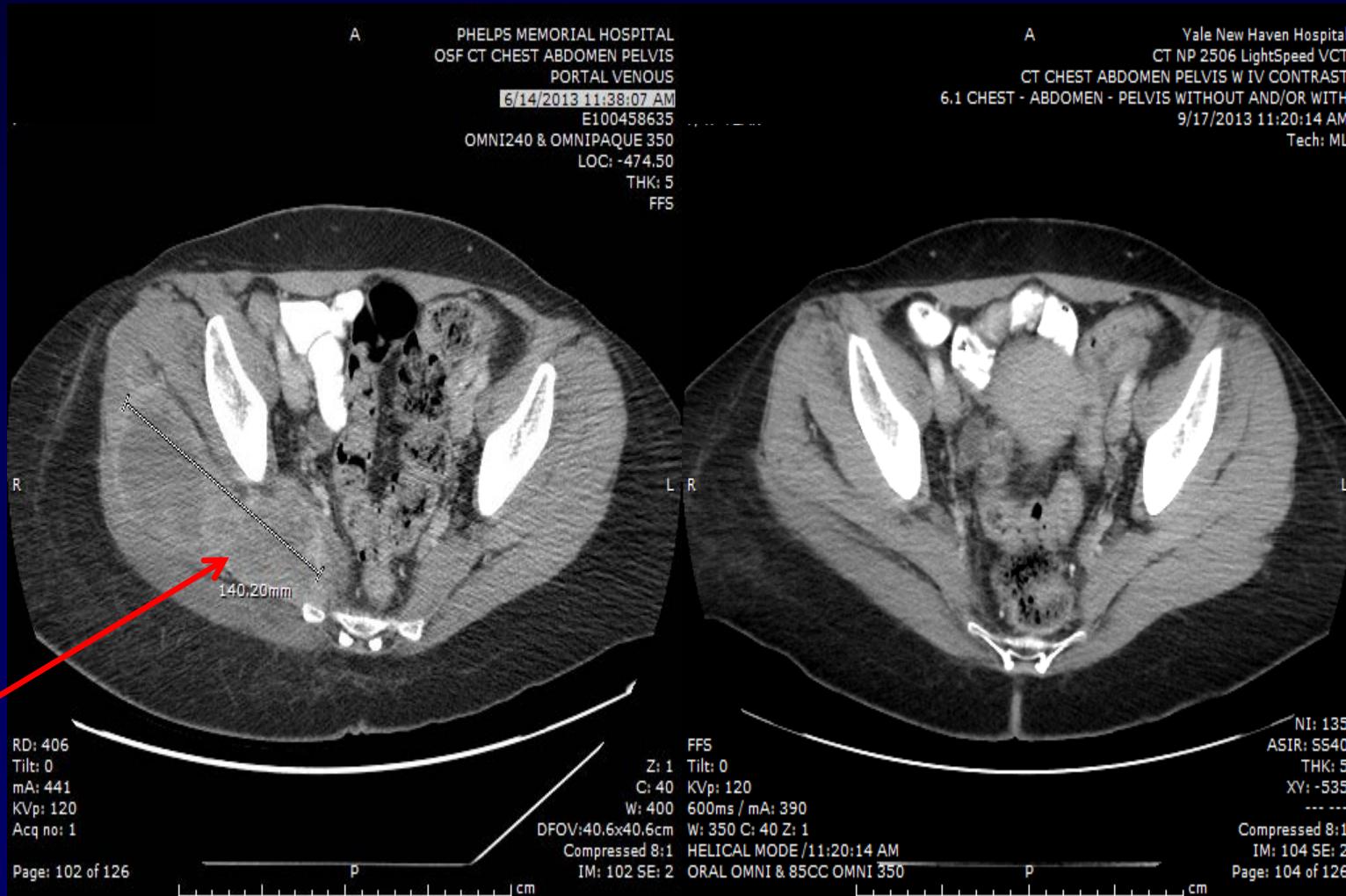


Post C4 (Week 12)

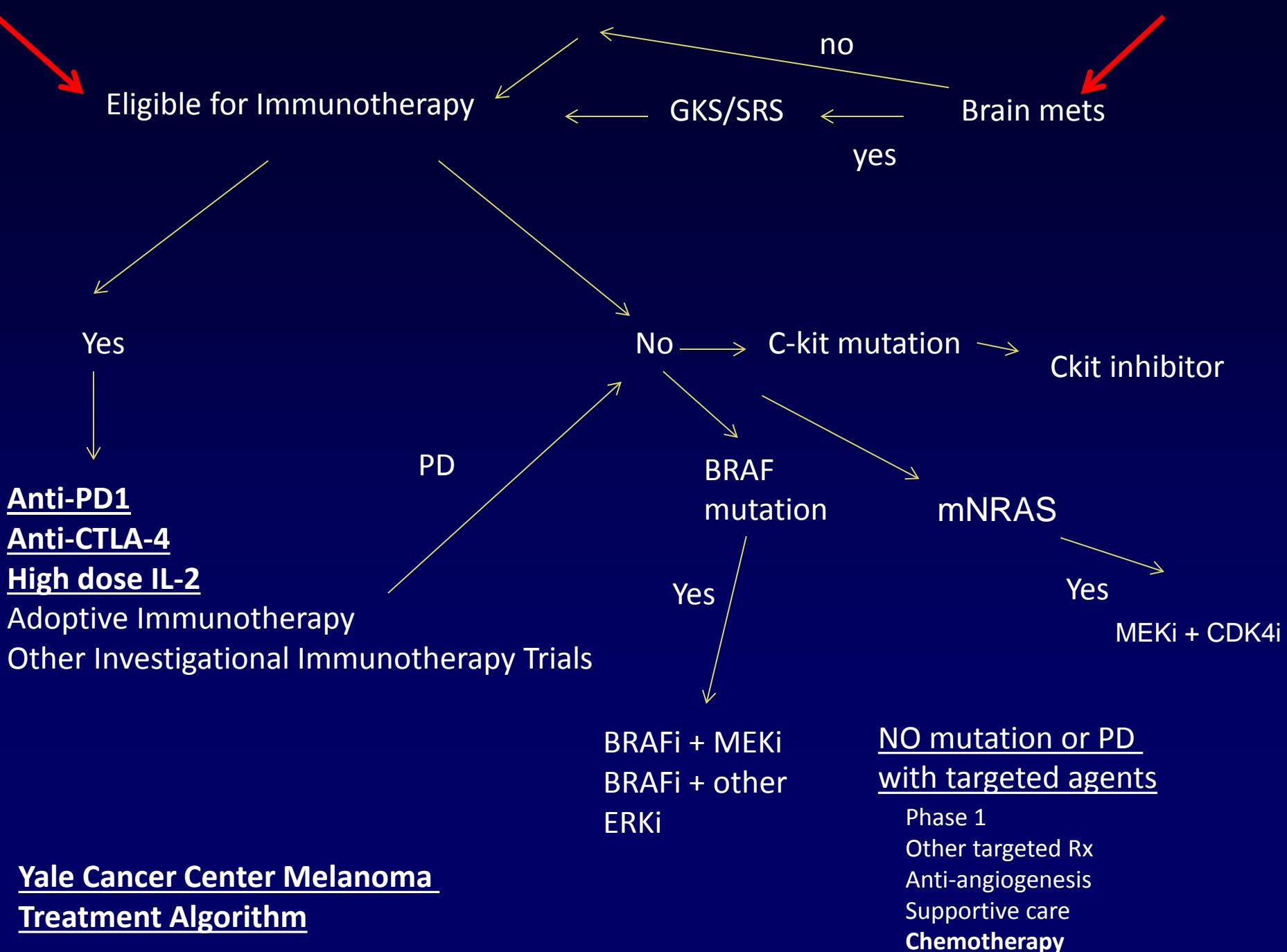


64-year-old male with squamous NSCLC s/p R lobectomy, cisplatin + gemcitabine, docetaxel, erlotinib, PD-L1 positive

Cohort 8, Ipilimumab + Nivolumab Response at 12 weeks



Prior therapy with HD-IL2, multiple resections, Vemurafenib, and RT;
LDH > 2000 at baseline; LDH nearly normal within 3 weeks



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Management of Adverse Events

- **Never use prophylactic immune suppression**
- **Adverse events can involve any organ system**
- Most common: skin, GI (colitis/enteritis), liver, endocrine (thyroid, pituitary)
- Education of patient and staff is critical
- Steroids are cornerstone of management, but when to start, how much ,and for how long depend on the event
- Algorithms are available to guide management

Potential Mistakes

- Start steroids too soon
- Start steroids too late
- Underdose steroids
- Stop steroids too soon
- Don't recognize severe colitis or more diffuse GI involvement
- Don't recognize hypophysitis
- Don't monitor labs (for LFT abnormalities)
- Don't recognize unusual iRAEs (pneumonitis)
- Don't monitor for serial iRAEs
- Don't monitor after initial response to steroids
- Don't consider use of anti-TNF agent or mycophenolate for adverse events unresponsive to steroids

Conclusions

- Immune therapies, particularly checkpoint inhibitors, demonstrate activity in various malignancies
- Responses to immune therapy can be durable and may not require continued therapy
- Clinical features and biomarkers may enrich for response but do not identify all responders
 - Weigh relative risk/benefit in any individual patient
 - Value of specific biomarkers may diminish in combinations
- Optimal sequence with other therapies for optimal outcome not known
- Immune related adverse events are ‘different’ but are manageable
 - Appropriate use of steroids and other immune suppressive agents
 - Require education of both patient and staff