Immunotherapy for Melanoma

Gregory A Daniels

Disclosures

- None

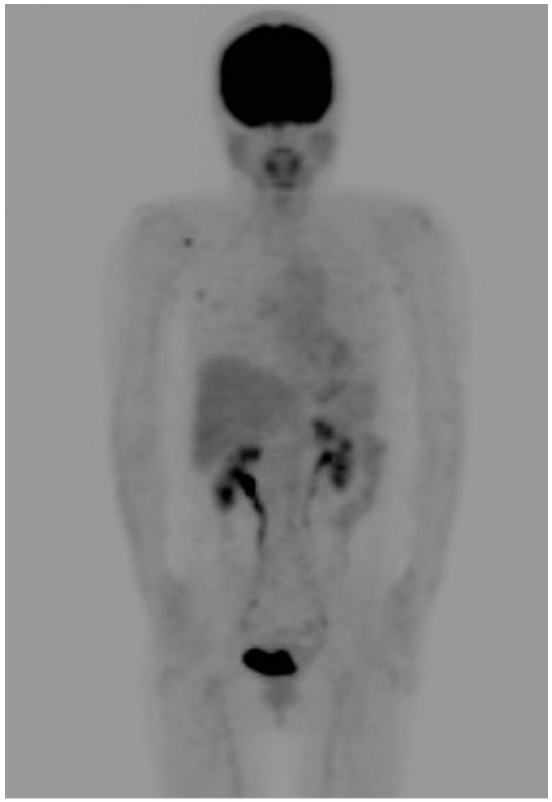
- I will be discussing non-FDA approved treatments. I will indicate this at the time of the slide.

Learning objectives

- Become familiar with the application of approved immune therapies in clinical care
- Appreciate the challenges to develop the “best” treatment plans with respect to outcomes and anticipated adverse events
- Understand the limits of our understanding utilizing case-based discussions and pose future directions for care.

Case

CHIEF COMPLAINT: Resected stage IIIA (pT4aN2aM0) cutaneous melanoma of the RIGHT shoulder with local recurrence.



Foundation : BRAF V600E, CTNNB1, CDKN2A/B, TERT

Pathline: PDL1 tumor cells NEGATIVE

ONCOLOGY HISTORY: 56 y/o woman with a RIGHT shoulder melanoma.

9/14-Increase in size of a long standing mole and darker.

2/26/14-Shave biopsy = 1.77 mm deep nevoid-type melanoma with no ulceration, with 10 mitoses/mm2 and positive deep and peripheral margin

3/26/15-WLE and SLN

*A: Skin, right shoulder, wide local excision **4.5mm nodular** -Malignant melanoma, pT4aN2a, with clear margins.*

*B: Sentinel lymph node, **right supraclavicular**, biopsy-Metastatic melanoma in one of two lymph nodes (1/2).*

*C: Additional sentinel lymph node, **right supraclavicular**, biopsy-Metastatic melanoma in one of one lymph node (1/1).*

6/9/15-LLND RIGHT neck negative

12/4/15-Excisional biopsy of recurrent melanoma at prior site of tumor with 1cm gross margins

A: Right chest wall, mass, excision-Recurrent malignant melanoma, multifocal, see comment.-Tumor present at inferolateral and superior margins.

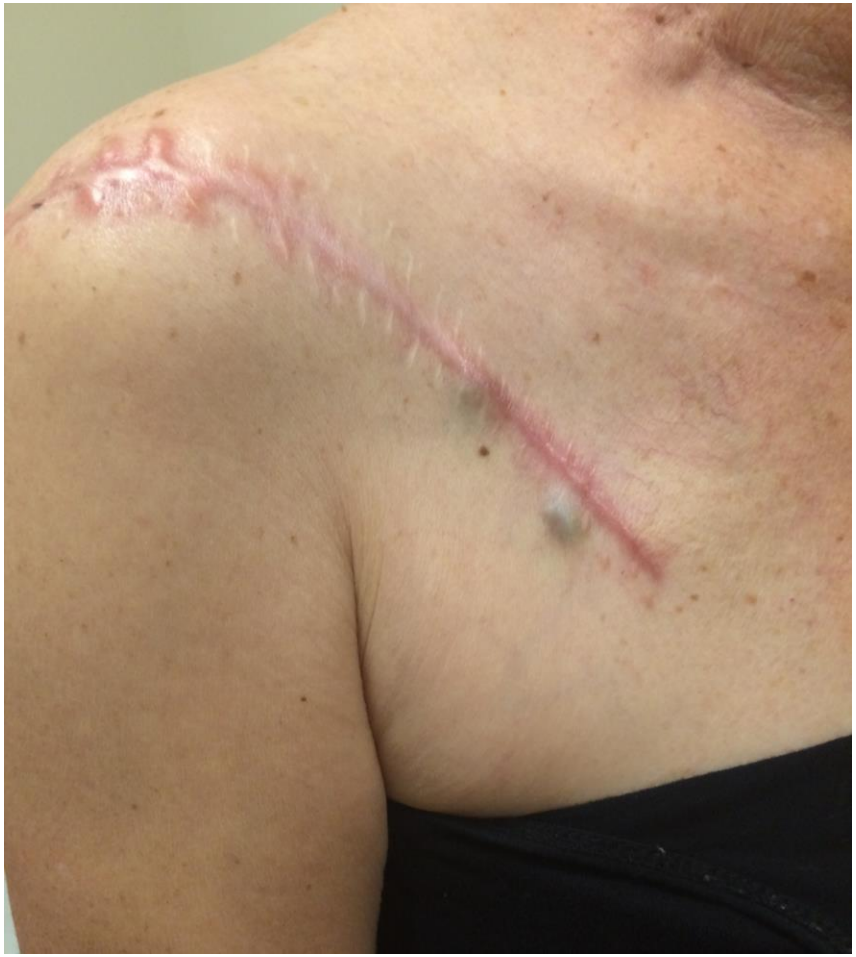
B: Right chest wall, additional medial margin, excision-Benign fibroadipose tissue.

1/15/16-Another firm nodule deep to her RIGHT anterior chest wound, as well as a blue bruise-colored nodule more inferiorly, but also near the wound.

2/12/16-PET

Focal increased activity is present in the right anterior shoulder in the region of previous resection.

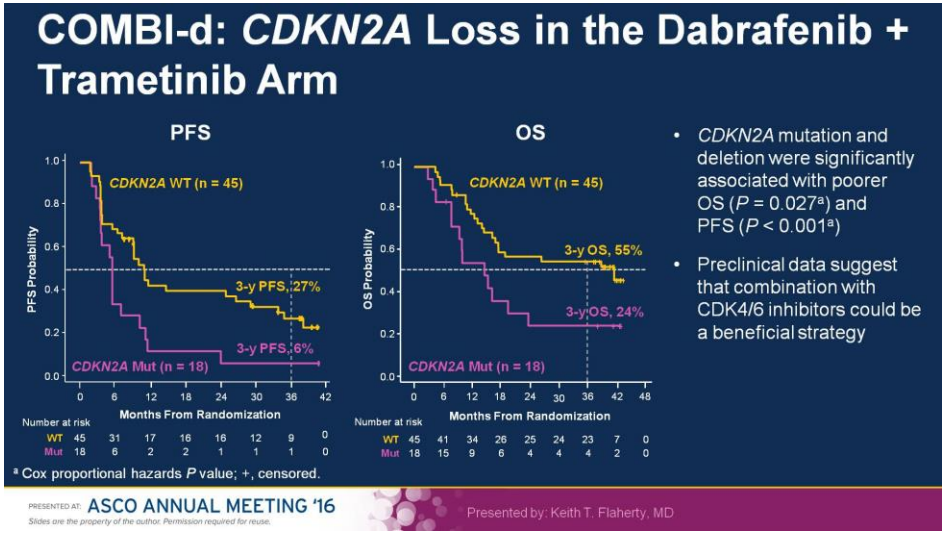
What is the next best treatment option?

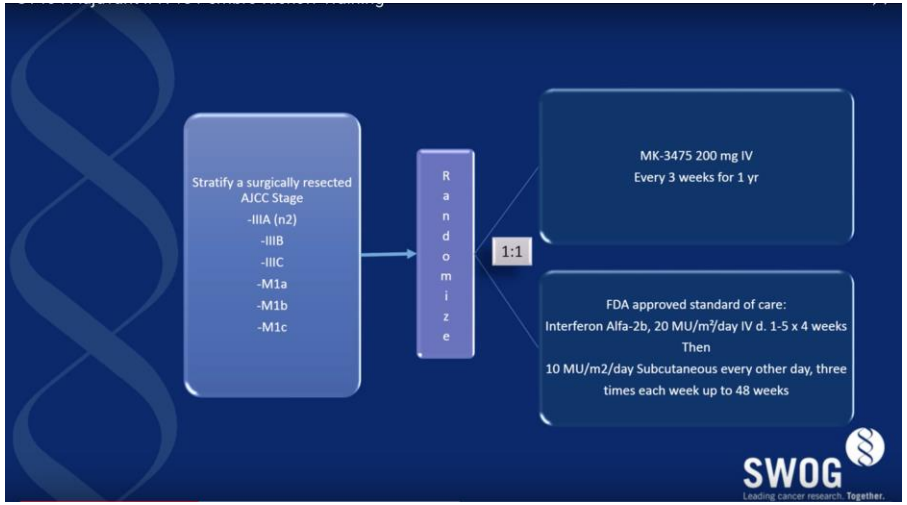


- Re-resection, adjuvant Rx
- BRAF/MEK
- Immune Modulation
  - HD IL2
  - Ipilimumab
  - Pembrolizumab or Nivolumab
  - Ipilimumab and Nivolumab
  - Talimogene laherparepvec

Adjuvant and Targeted Therapy

- HD IFN
- Ipilimumab 10mg/kg
- Clinical trial





Patients with CDKN2A mutations may do worse with targeted agents

Unclear if same mutation influences response to immune modulation

SWOG 1404 amended to offer Ipilimumab as an option for IFN

The “Best” Choice

- Goals of care
  - Symptom relief v long-term treatment free survival
  - Maximize therapy options
- Treatment tolerability
  - AE risk
  - Infusion tschedule v oral med
- Interpretation of data
  - Patient bias (what is important to patient?)
  - Study endpoints and timing of results

Updated Results From a Phase III Trial of Nivolumab Combined With Ipilimumab in Treatment-naïve Patients With Advanced Melanoma (Checkmate 067)

Jedd D. Wolchok,[1] Vanna Chiarion-Sileni,[2] Rene Gonzalez,[3] Piotr Rutkowski,[4] Jean-Jacques Grob,[5] C. Lance Cowey,[6] Christopher D. Lao,[7] Dirk Schadendorf,[8] Pier Francesco Ferrucci,[9] Michael Smylie,[10] Reinhard Dummer,[11] Andrew Hill,[12] John Haanen,[13] Michele Maio,[14] Grant McArthur,[15] Dana Walker,[16] Joel Jiang,[16] Christine Horak,[16] James Larkin,[17*] F. Stephen Hodi[18*]

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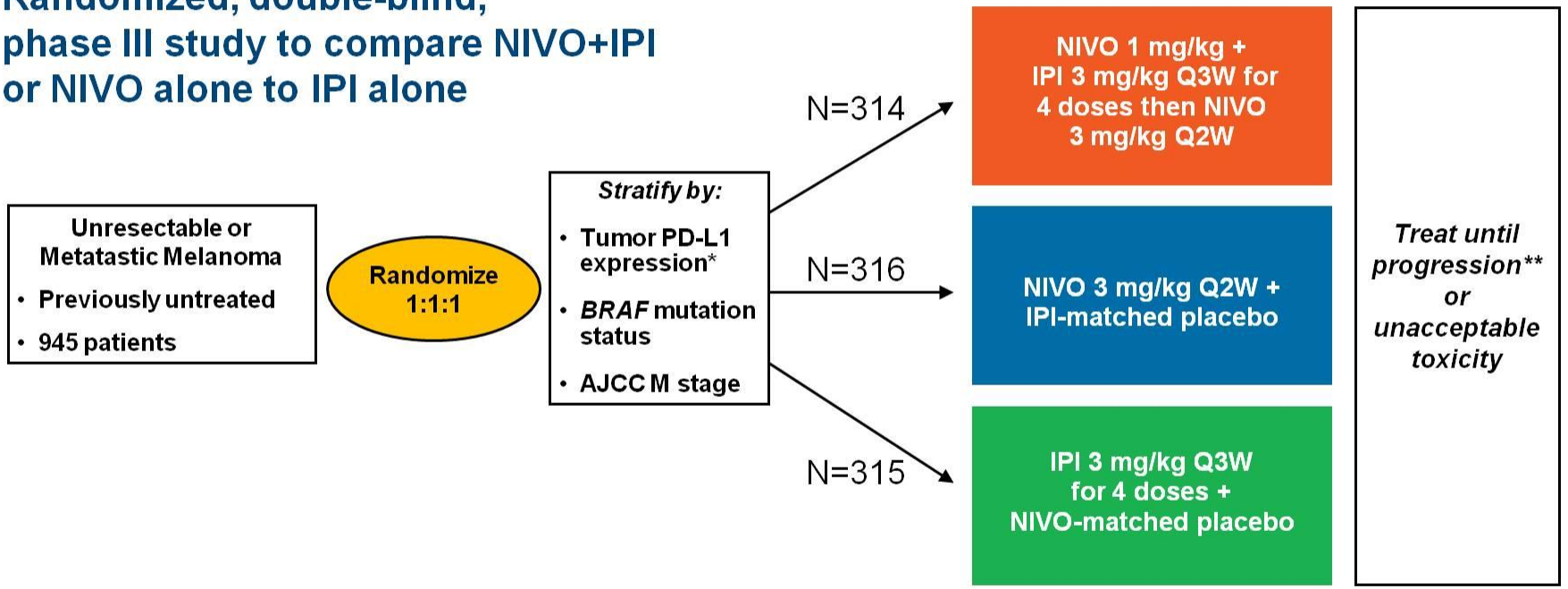
PRESENTED AT: ASCO ANNUAL MEETING '16

CA209-067: Study Design

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone

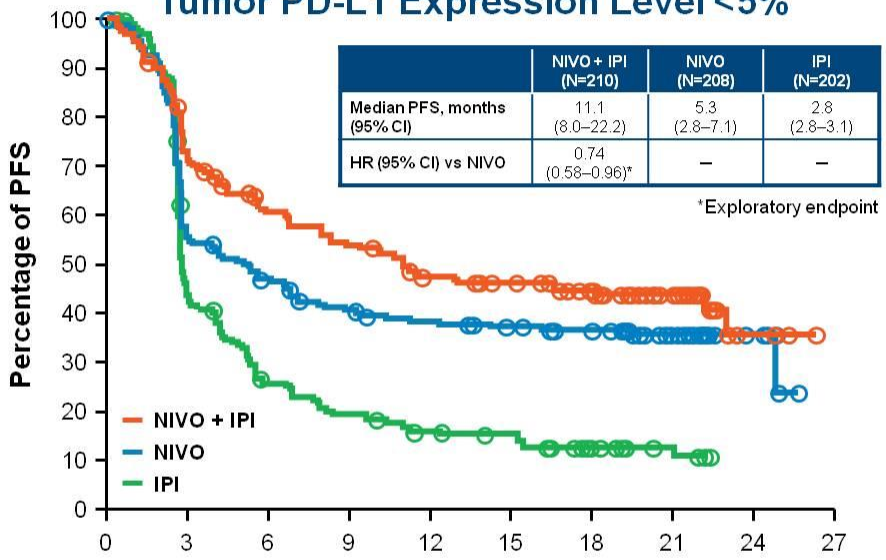


*Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.

**Patients could have been treated beyond progression under protocol-defined circumstances.

Progression-free Survival by Tumor PD-L1 Expression

Tumor PD-L1 Expression Level <5%

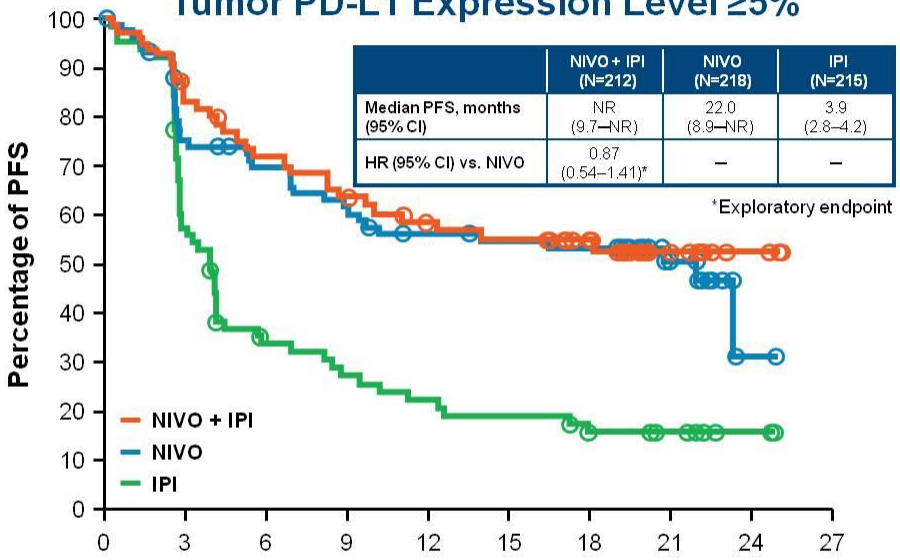


	NIVO + IPI (N=210)	NIVO (N=208)	IPI (N=202)
Median PFS, months (95% CI)	11.1 (8.0–22.2)	5.3 (2.8–7.1)	2.8 (2.8–3.1)
HR (95% CI) vs NIVO	0.74 (0.58–0.96)*	–	–

*Exploratory endpoint

Number of patients at risk:										
NIVO + IPI	210	142	113	101	86	81	69	31	5	0
NIVO	208	108	89	75	69	62	55	29	7	0
IPI	202	82	45	34	26	22	12	7	0	0

Tumor PD-L1 Expression Level ≥5%



	NIVO + IPI (N=212)	NIVO (N=218)	IPI (N=215)
Median PFS, months (95% CI)	NR (9.7–NR)	22.0 (8.9–NR)	3.9 (2.8–4.2)
HR (95% CI) vs. NIVO	0.87 (0.54–1.41)*	–	–

*Exploratory endpoint

Number of patients at risk:										
NIVO + IPI	68	53	44	39	33	31	22	13	3	0
NIVO	80	57	51	45	39	37	36	16	1	0
IPI	75	40	21	17	14	12	8	6	2	0

- For the original PD-L1 PFS analysis, the descriptive hazard ratio comparing NIVO+IPI vs NIVO was 0.96, with a similar median PFS in both groups (14 months)

Database lock Nov 2015

Glass Half Full or Half Empty

Figure 4B. Progression-free survival at 2 years of follow-up

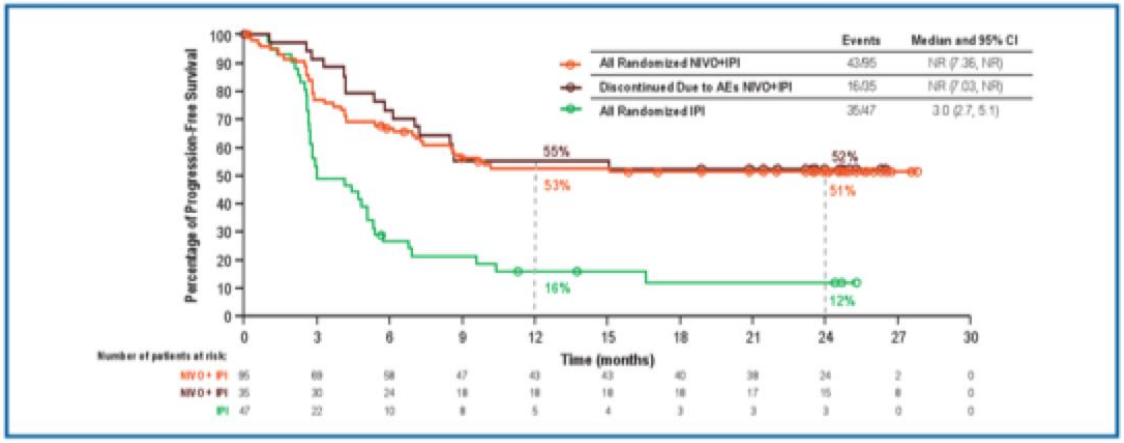
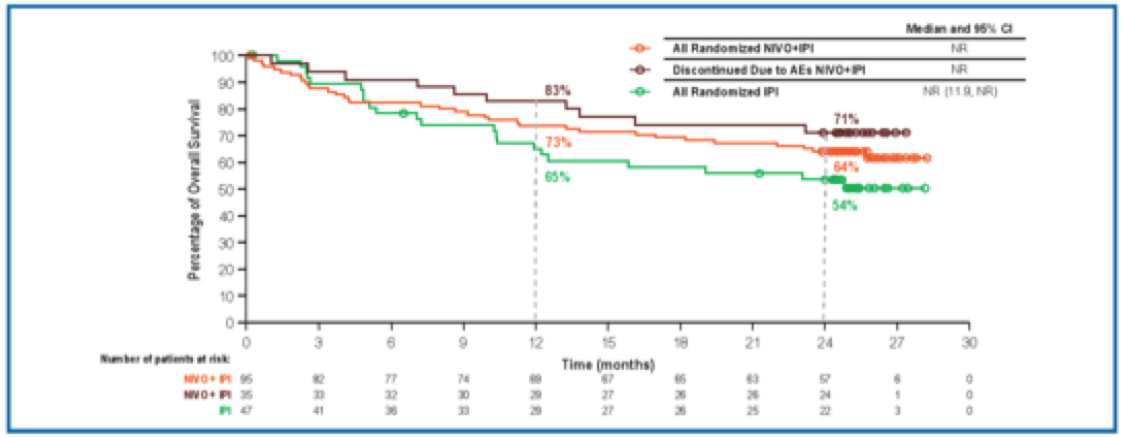


Figure 4A. Overall survival at 2 years of follow-up



Hodi ASCO 2016

Checkmate 069-Phase 2 trial
2:1 Ipi/Nivo v Ipi

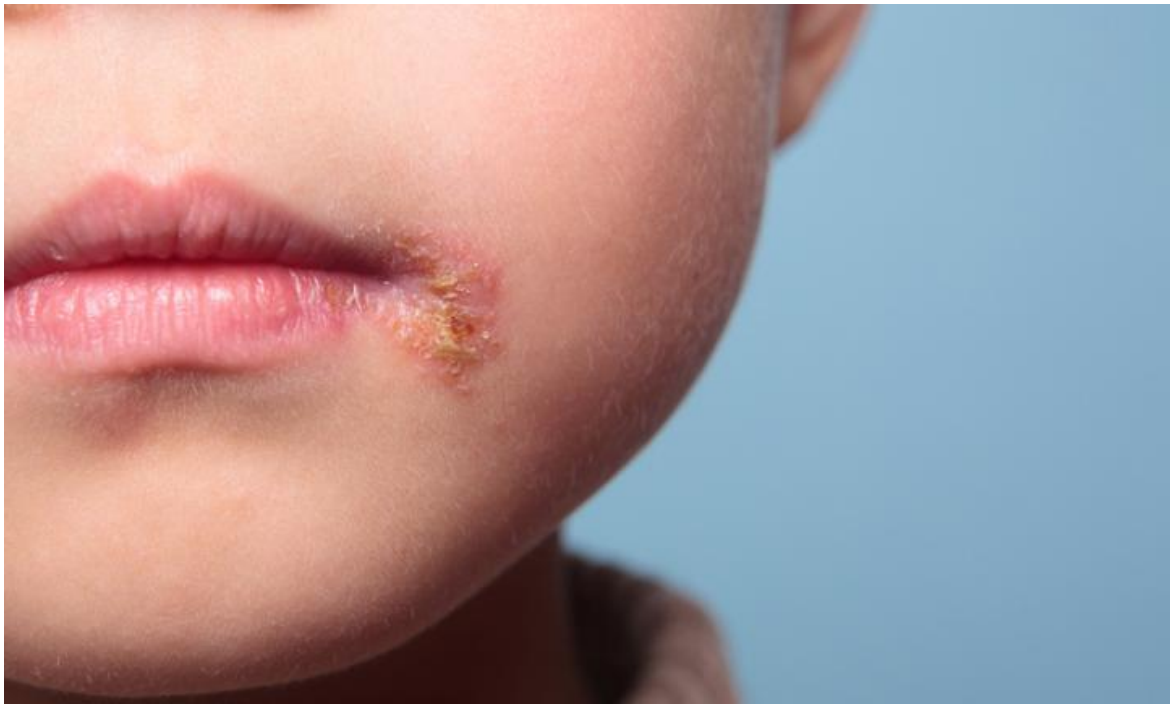
PFS and OS similar in patients who continued compared to discontinued.

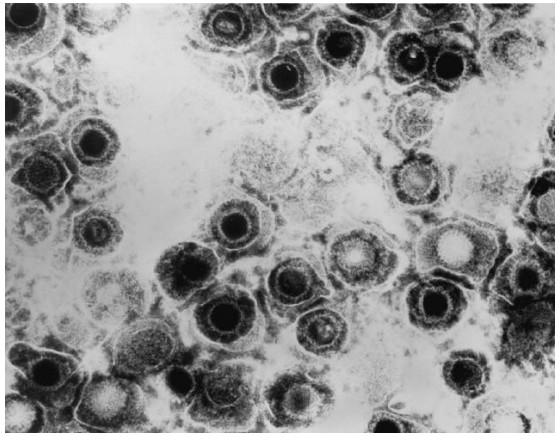
Table 5. Most common treatment-related select AEs (NIVO+IPI patients)

	All randomized (N = 94)		Discontinued due to AEs (n = 35)	
Patients reporting event, %[a]	Any grade	Grade 3/4	Any grade	Grade 3/4
Drug-related select AE	88	45	86	71
Gastrointestinal AEs	49	20	63	46
Diarrhea	45	10	51	23
Colitis	18	13	34	29
Hepatic AEs	32	13	40	20
Elevated ALT	26	11	31	17
Elevated AST	28	7	31	14
Skin AEs	73	9	74	11
Rash	43	4	31	6
Pruritus	40	1	37	0
Endocrine AEs	31	5	29	6
Hypothyroidism	17	0	17	6
Hypophysitis	13	2	9	0
Pulmonary AEs	11	2	9	6
Pneumonitis	10	2	9	6
Renal AEs	3	1	3	3
Creatinine increased	2	1	3	3

[a]Safety was evaluated in all patients who received at least one dose of study treatment, up to 30 days after the last dose

Talimogene laherparepvec

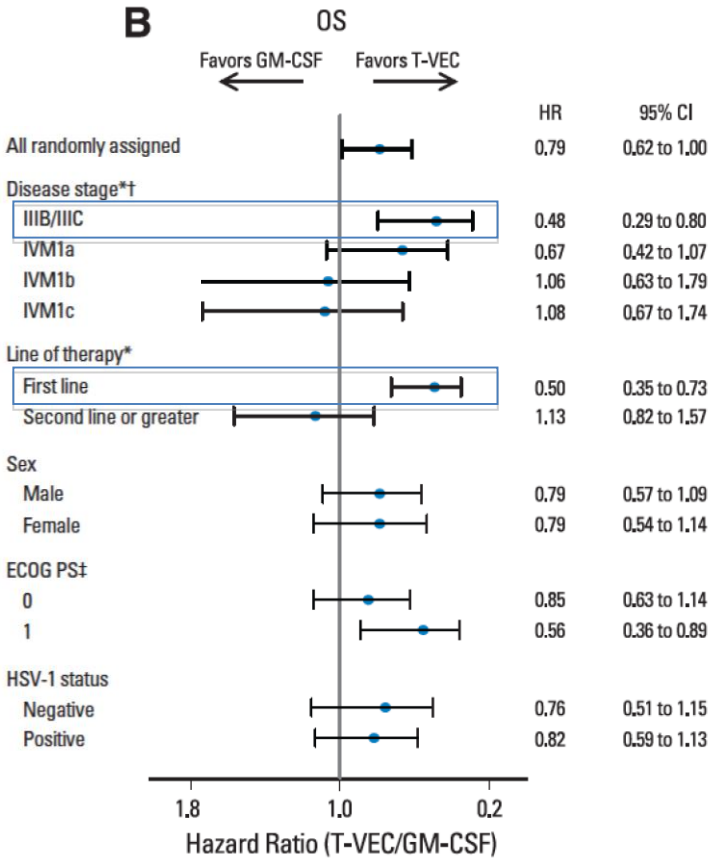


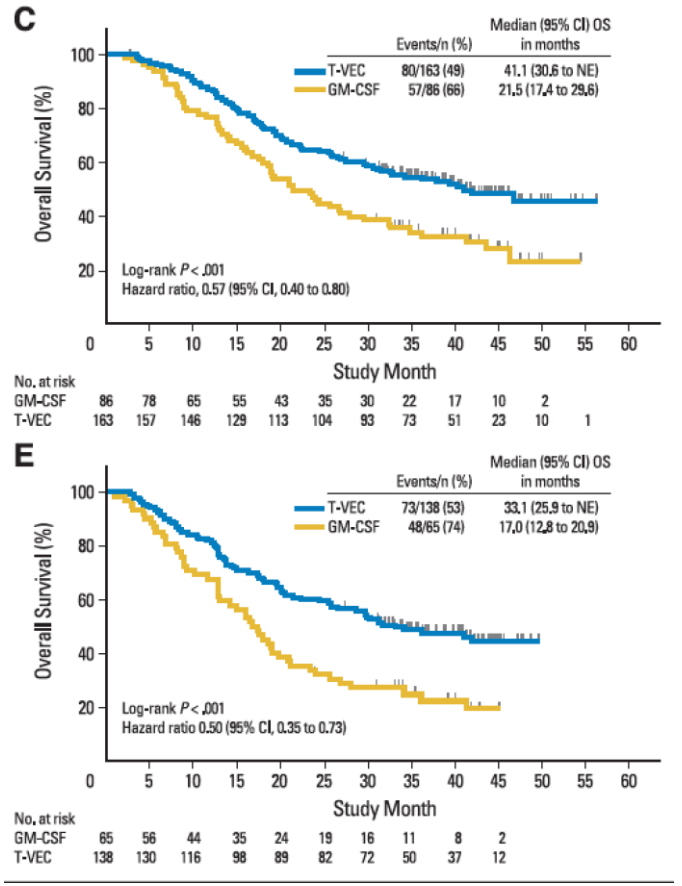


HSV-1 (JS1 strain)

- Deleted for ICP34.5=more selective tumor replication
- Deleted for ICP47=more antigen presentation better growth
- Insertion of GM-CSF=?enhance immune response

Who is the correct patient for Talimogene laherparepvec?





Stage IIIB, IIIC, or IVM1a

First line

Appears that front line and minimal disease are best candidates

Case

Table 3. Patient Incidence of AEs

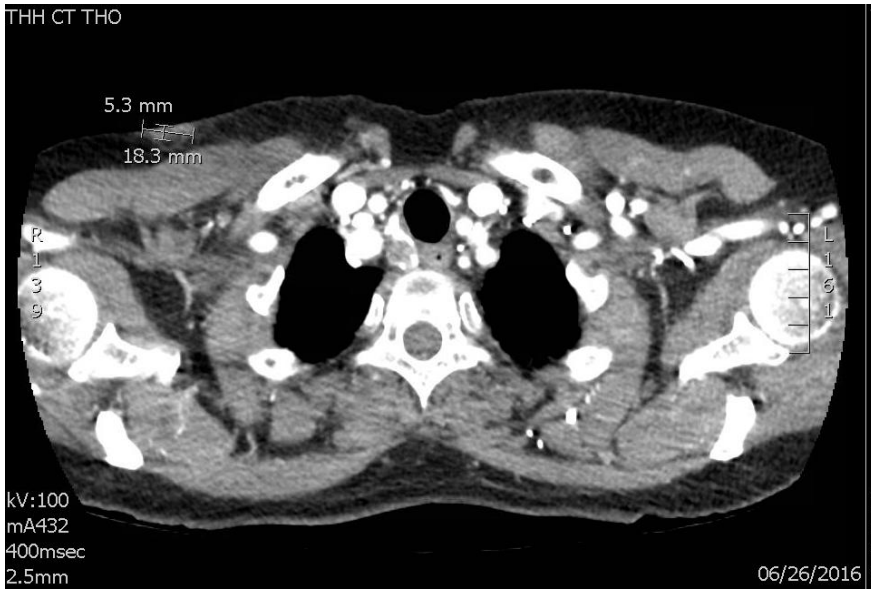
	T-VEC (n = 292)				GM-CSF (n = 127)			
	Any Grade		Grade 3 or 4		Any Grade		Grade 3 or 4	
AE*	No.	%	No.	%	No.	%	No.	%
Fatigue	147	50.3	5	1.7	46	36.2	1	0.8
Chills	142	48.6	0	0	11	8.7	0	0
Pyrexia	125	42.8	0	0	11	8.7	0	0
Nausea	104	35.6	1	0.3	25	19.7	0	0
Influenza-like illness	89	30.5	2	0.7	19	15.0	0	0
Injection-site pain	81	27.7	3	1.0	8	6.3	0	0
Vomiting	62	21.2	5	1.7	12	9.4	0	0
Diarrhea	55	18.8	1	0.3	14	11.0	0	0
Headache	55	18.8	2	0.7	12	9.4	0	0
Myalgia	51	17.5	1	0.3	7	5.5	0	0
Arthralgia	50	17.1	2	0.7	11	8.7	0	0
Pain in extremity	48	16.4	4	1.4	12	9.4	1	0.8
Pain	47	16.1	2	0.7	13	10.2	1	0.8
Peripheral edema	35	12.0	2	0.7	12	9.4	2	1.6
Constipation	34	11.6	0	0	8	6.3	1	0.8
Cough	31	10.6	0	0	10	7.9	0	0
Decreased appetite	30	10.3	0	0	14	11.0	0	0
Pruritus	28	9.6	0	0	19	15.0	0	0
Cellulitis	17	5.8	6	2.1	2	1.6	1	0.8
Injection-site erythema	15	5.1	0	0	33	26.0	0	0
Dyspnea	13	4.5	3	1.0	13	10.2	2	1.6
Injection-site pruritus	5	1.7	0	0	21	16.5	0	0

Abbreviations: AE, adverse event; GM-CSF, granulocyte macrophage colony-stimulating factor; T-VEC, talimogene laherparepvec.
*Treatment-emergent AEs of any grade with incidence ≥ 10% in either arm and/or grade 3 to 4 AEs with incidence of ≥ 2% in either arm.

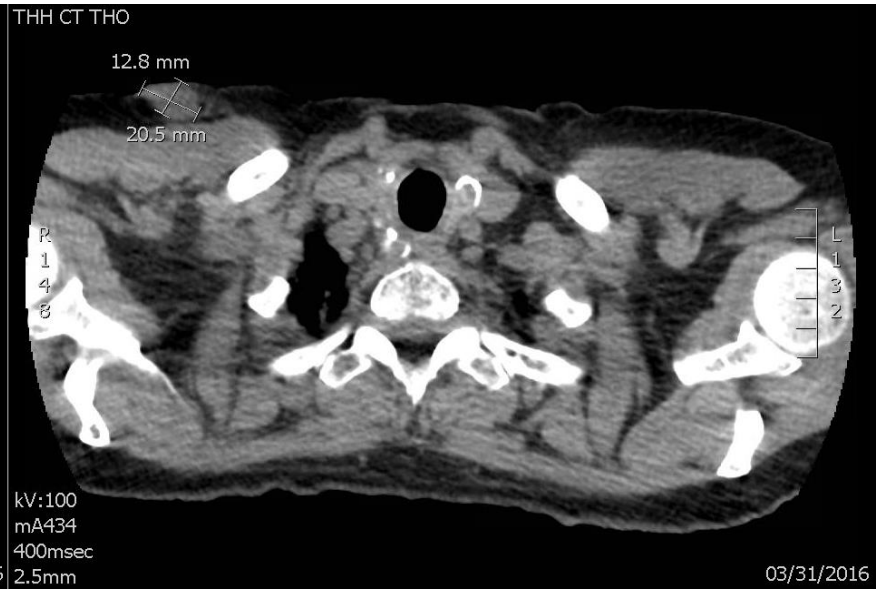
Biosafety level 2

Case

- 1cc LD TVEC followed 3 weeks later by 1cc HD TVEC every two weeks
- Mild fever 1 to 2 days after injections

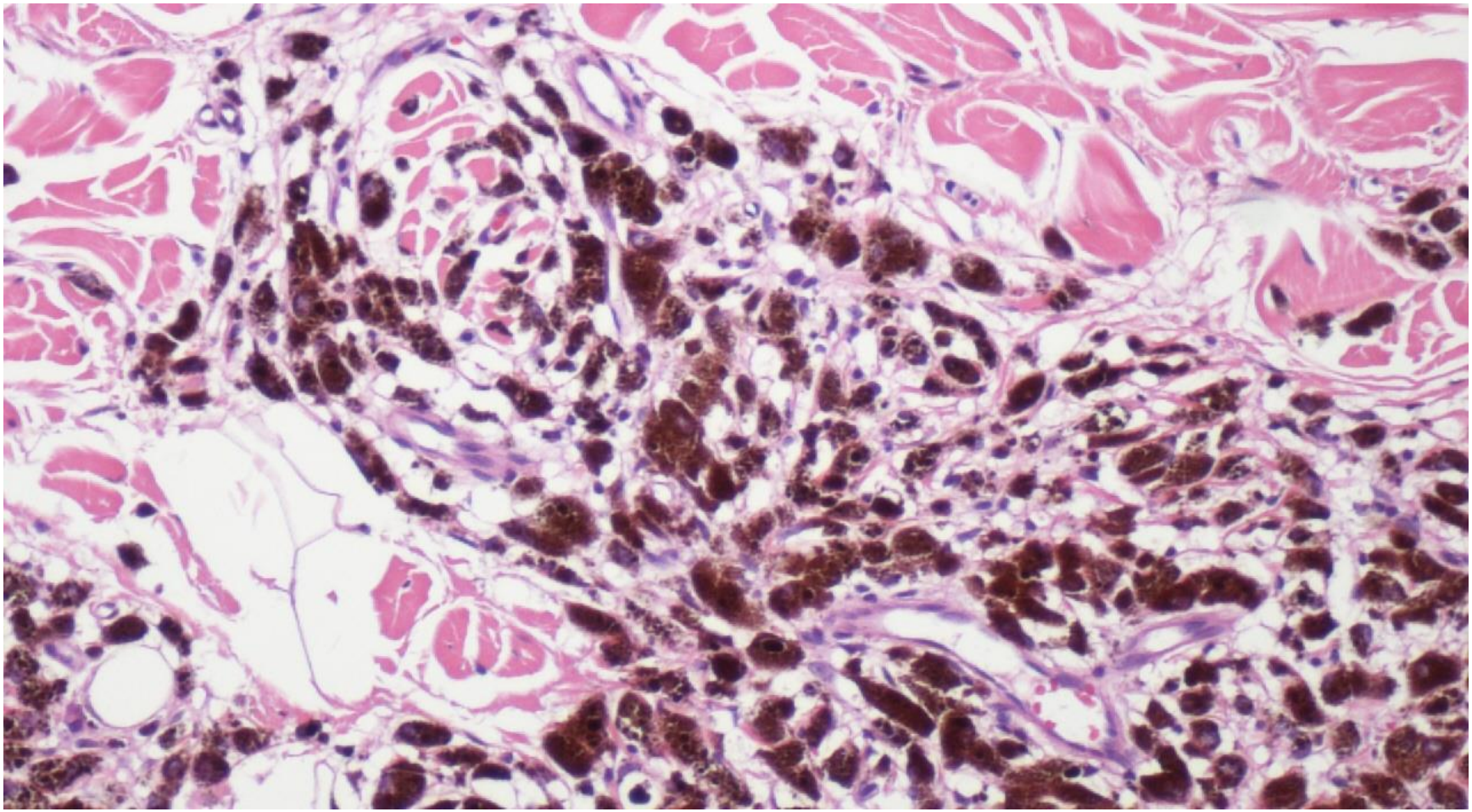


3 month restaging



Baseline

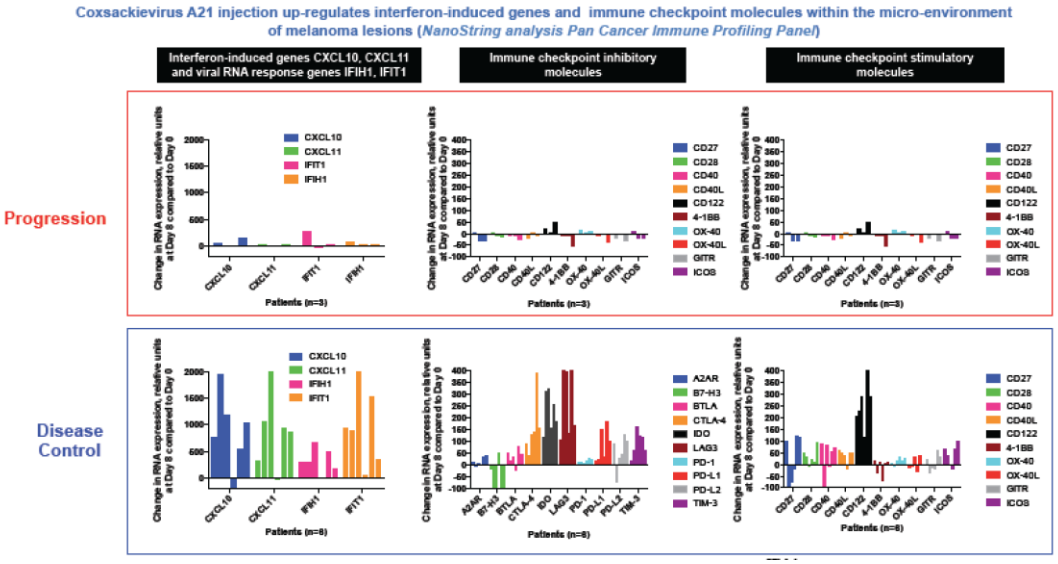
Endpoint for Response?



Daniels unpublished

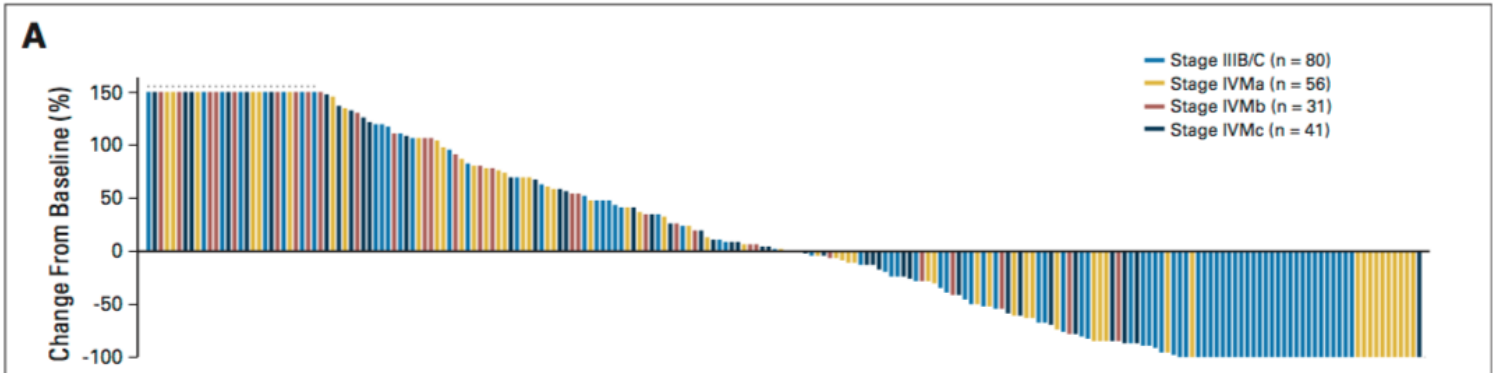
Intralesional Therapy (Future)

- Single agents
  - TLR (SD101), Viral (Herpes. Coxsackie)
  - Intralesional v systemic
- Combination therapy
- Mechanism
  - Neoadjuvant studies
  - Turning “cold” to “hot” tumor?



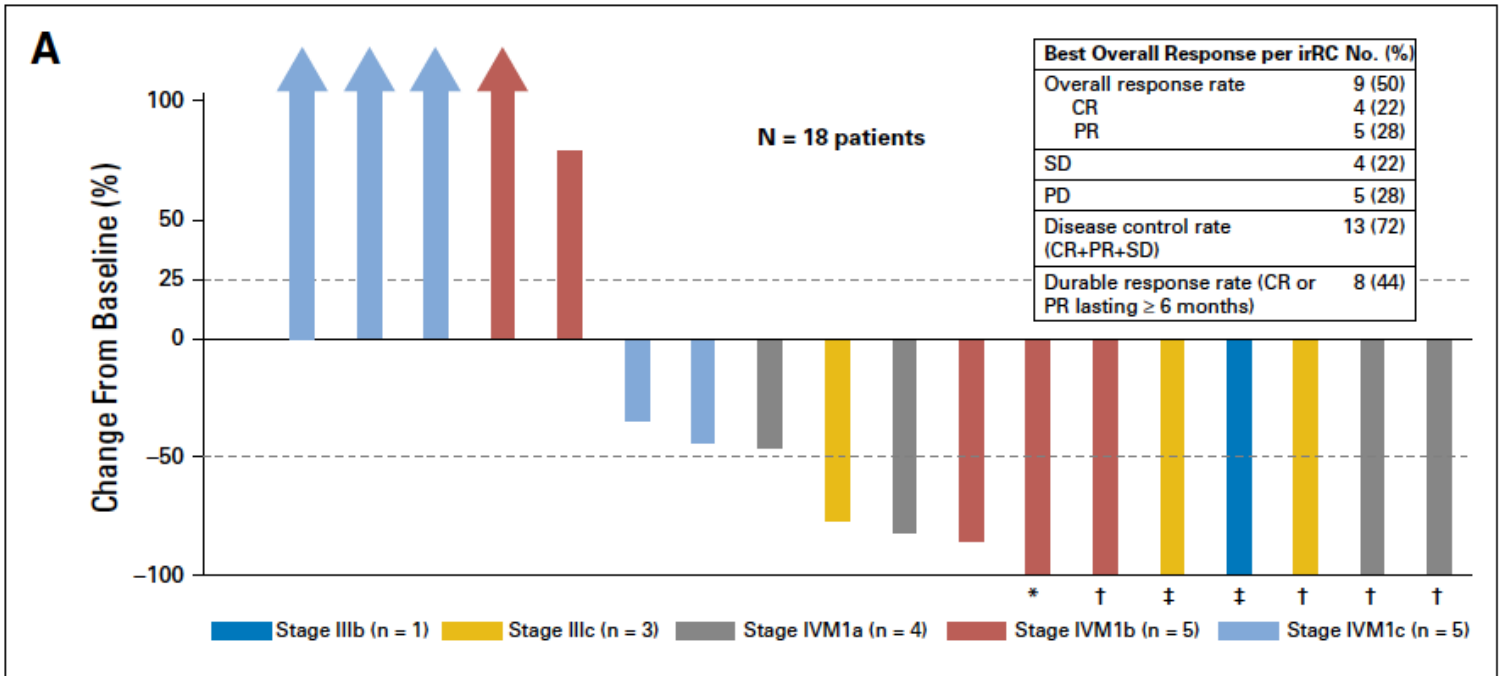
Andtbacka ASCO 2016
Dynamics of tumor response in advanced melanoma patients treated with Coxsackievirus A21

Intralesional Therapy (Future)



TVEC

Antebacka JCO 2015



TVEC and Ipilimumab

Puzanov JCO 2016

Case

Chief complaint: Remote history of RIGHT ocular melanoma 2007 with subsequent melanoma resected from the LEFT axilla 2011 now with progressive disease in the pancreas and lung.

Foundation testing: GNA11 and myc amp (7/19/11 sample LEFT axilla)
Low positive PDL1 on tumor cells

Oncology History: 58 y/o woman with a history of RIGHT ocular melanoma. Briefly,
2006-Right eye "heavy feeling"
2/07-15x13x6mm choroidal melanoma.
4/07-Plaque therapy to RIGHT eye

6/2/11-Discovered lump under left axilla. Mammo normal, ultrasound with mass in the left axilla.
6/8/11-BIopsy=melanoma

Melanoma RF: NO melanomas in family, NO other related cancers. She is fair skinned and a personal history of ocular melanoma

7/19/11-CLND LEFT axilla **1/36** nodes positive. NO adjuvant therapy.

12/28/11-PET/CT-OK

Case

8/16/14-PET/CT **RIGHT lung nodule** 4mm

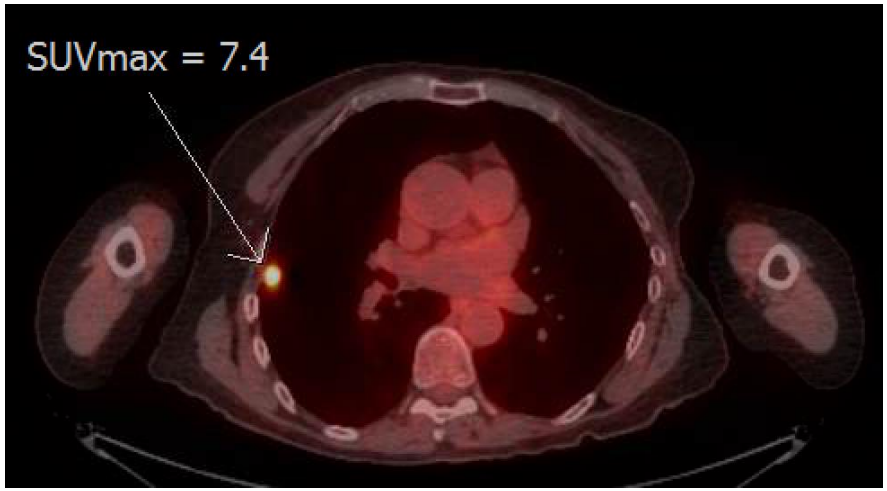
12/3/14-CT chest progression of RIGHT lung nodule 7mm RML

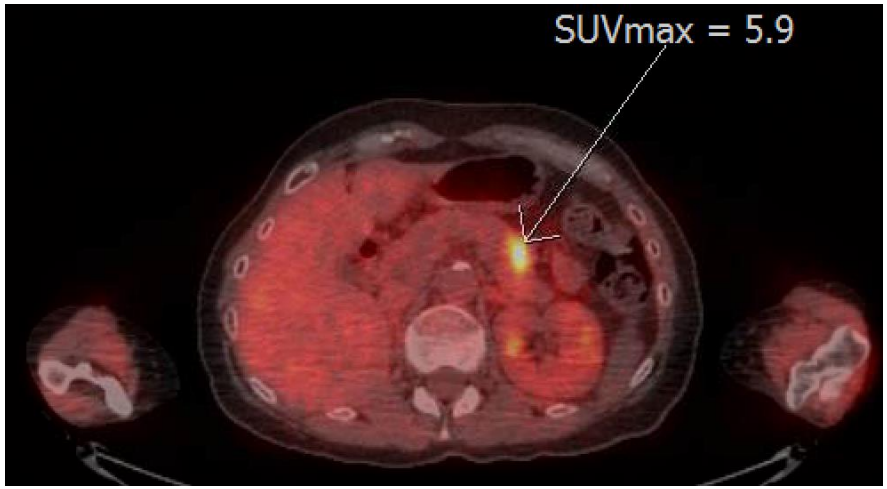
2/10/16-Feeling well except RIGHT sided back pain--pinching, intermittent. Some sweating on the neck at night. Weight stable. NO headaches. ECOG=1

2/25/16-PET/CT lung and pancreatic lesions

3/3/16-NO changes in health. Mild, intermittent RIGHT abdominal discomfort. NO radiation. Bowels normal, NO nausea. Weight stable. NO cough. NO fevers. ECOG=1

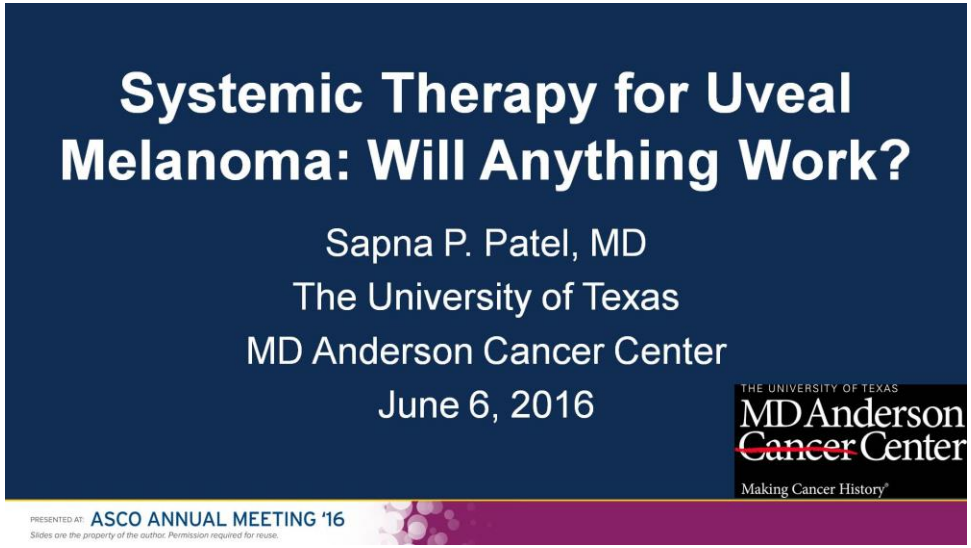
3/22/16-FNA of pancreatic mass=**melanoma**





What is the next “best” treatment option?

- MEK inhibitor
- Ipilimumab
- Pembrolizumab or Nivolumab
- Ipilimimab+Nivolumab
- Clinical trial



Ipilimumab (Melanoma)

Cutaneous

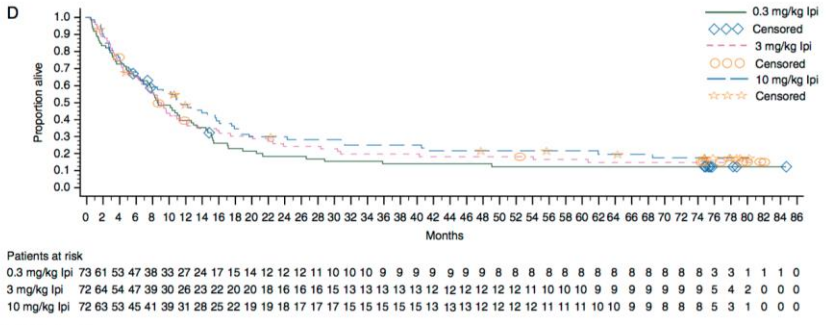


Fig. 2 *Continued*

Table 3. Adverse events and irAEs during ipilimumab retreatment at 10 mg/kg

AEs and irAEs, *n* (%)	Ipilimumab dose in parent study with retreatment at 10 mg/kg (*N* = 111)					
	0.3 mg/kg (*n* = 24)		3 mg/kg (*n* = 34)		10 mg/kg (*n* = 53)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any AE	24 (100.0)	10 (41.7)	33 (97.1)	10 (29.4)	51 (96.2)	18 (34.0)
Any irAE	18 (75.0)	6 (25.0)	23 (67.6)	2 (5.9)	30 (56.6)	7 (13.2)
Gastrointestinal	14 (58.3)	3 (12.5)	7 (20.6)	1 (2.9)	11 (20.8)	2 (3.8)
Dermatologic	10 (41.7)	1 (4.2)	18 (52.9)	1 (2.9)	18 (34.0)	2 (3.8)
Hepatic	1 (4.2)	1 (4.2)	0 (0.0)	0 (0.0)	3 (5.7)	2 (3.8)
Endocrine	1 (4.2)	1 (4.2)	2 (5.9)	0 (0.0)	3 (5.7)	1 (1.9)
Other[a]	1 (4.2)	0 (0.0)	3 (8.8)	0 (0.0)	2 (3.8)	0 (0.0)

[a]Most common (>1%) grade 3/4 "other" irAEs were hypersensitivity and interstitial lung disease; none were grade 5.
AE, adverse event; irAE, immune-related adverse event.

Wolchok JD Lancet Oncol 2010

Ocular

Phase 2
53 patients from May 2011 to Sept 2012

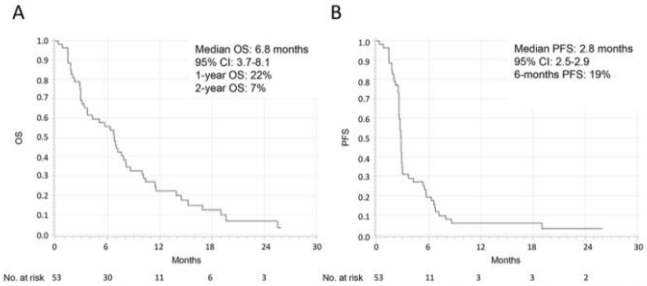
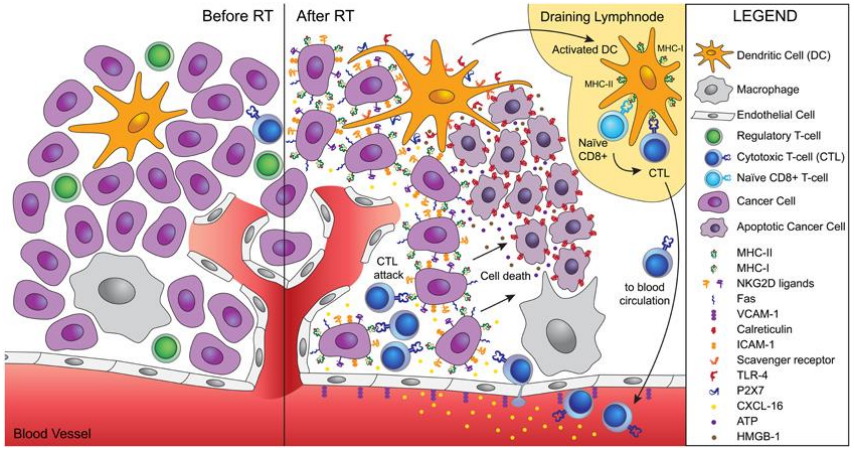


Fig 2. Kaplan-Meier curves for overall survival (A) and progression-free survival (B) of treatment-naïve and pretreated patients with metastatic ocular melanoma who received ipilimumab 3 mg/kg.

"Ipilimumab has very limited clinical activity in patients with metastatic UM. Toxicity was manageable when treated as per protocol-specific guidelines."

Zimmer PLOS ONE 2015

Radiation as Immune Adjuvant



- Abscopal Effect
  - Effect of XRT on non-XRT lesions
- Combination?
  - Ipililimumab
  - IL2
  - PD1
- Dosing? Tumor type? Site of XRT?

IL2 and Radiation

- Radiation
  - SBRT 20Gyx1, x2, x3
  - 3,5,7 days prior to IL2
- HDIL2
  - 600,000IU/kg/8hours
  - Up to 6 cycles
- Response
  - CR= 6/12 per PET
  - ORR= 8/12

Seung SciTransMed 4(137) 2012

Patient	Sex	Age (years)	Performance status	Baseline LDH	Cohort	Histology	SBRT site (max diameter, cm)	Sum of target lesions at baseline (cm)	IL-2 cycles	Duration of response (days)	Best response by PET/CT
1	M	64	0	251	1	Melanoma	1 Mediastinum (6.1)	27.4	6	745+	CR
2	M	59	0	148	1	Melanoma	1 RLL (1.2)	3.8	6	381	CR
3	M	61	0	—	1	Renal	1 L Hilum (2.7)	7.7	2	61	PD
4	M	62	1	—	1	Renal	1 LLL (2.4)	23.2	4	543+	CR
5	M	61	0	—	2	Renal	1 R Hilum (1.0)	2	2	61	PD
6	F	64	0	165	2	Melanoma	1 RUL (0.5)	4.1	6	530+	CR
							1 LLL (0.7)				
7	M	61	0	192	2	Melanoma	1 RML (1.8)	5	6	577+	CR
8	M	65	1	144	3	Melanoma	1 RLL (2.1)	7	2	62	PD
9	M	51	0	135	3	Melanoma	1 Hepatic (1.4)	7.5	2	60	PD
							1 Hepatic (1.4)				
10	F	64	0	—	3	Renal	1 RUL (1.0)	1.0	2	422+	PR*
							1 RLL (2.1)				
11	M	61	1	1087	3	Melanoma	1 Hepatic (3.6)	24.3	6	399+	CR
							1 Hepatic (3.5)				
12	M	61	0	—	3	Renal	2 RLL (1.5)	8.6	6	362	PD
							1 LLL (2.1)				

*Patient had a new lymph node metastasis after IL-2 that regressed spontaneously without other medical treatment.

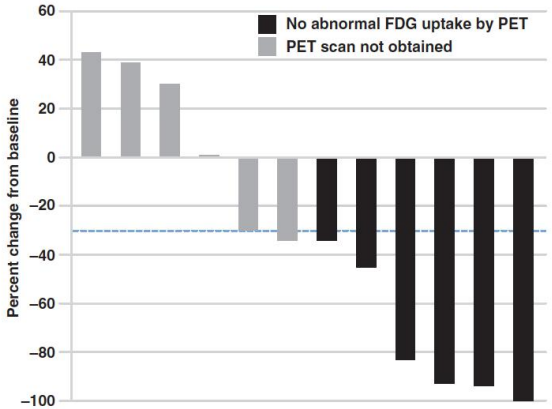
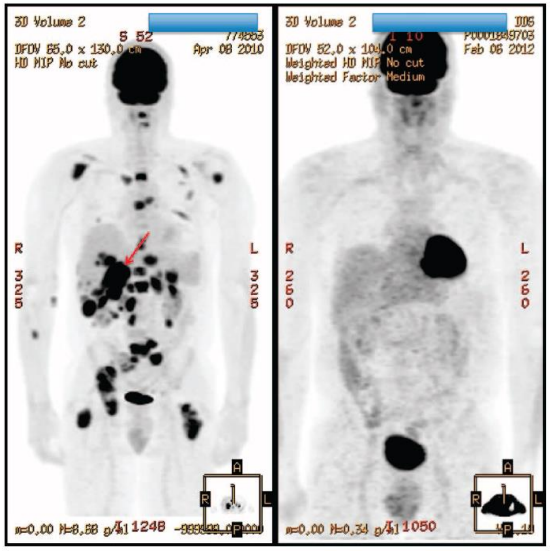


Fig. 1. Waterfall plot of best tumor response by RECIST criteria of all target lesions not treated with SBRT. Each bar represents the response of an individual patient. A dashed line is placed at 30% to indicate the minimum regression of tumor to qualify for a PR by RECIST criteria of target lesions.

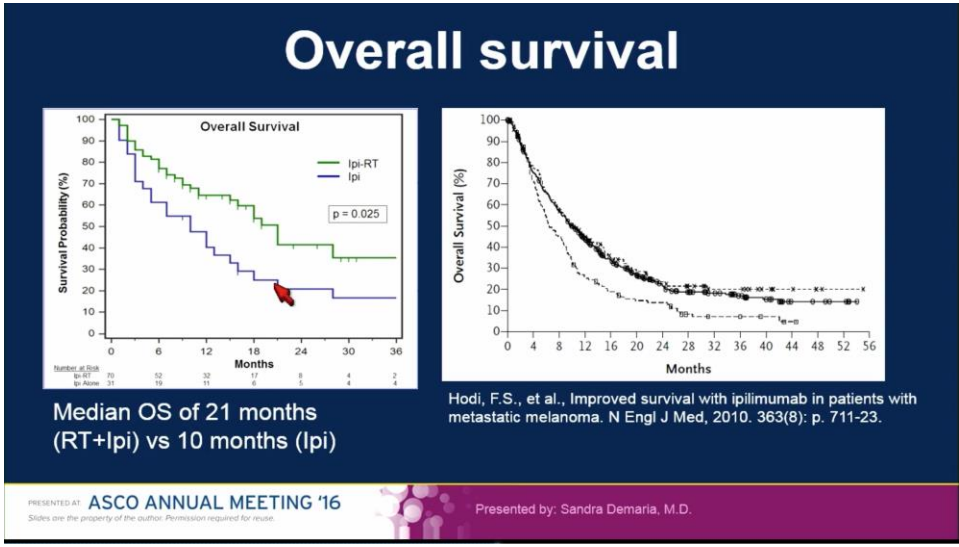


Case

- 4/15/16-Ipi #1

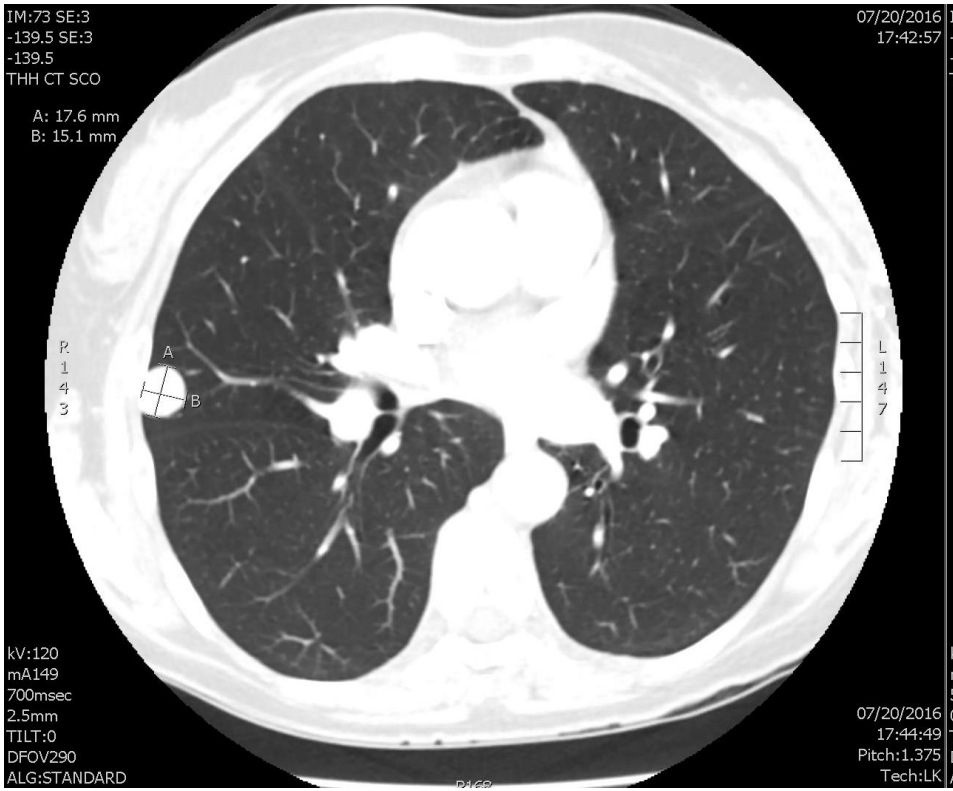
- 4/27/16-XRT to pancreas
  - Dose/Fx (cGy): 660
  - #Fx: 5 / 5
  - Total Dose (cGy): 3,300
  - End Date: 5/6/2016

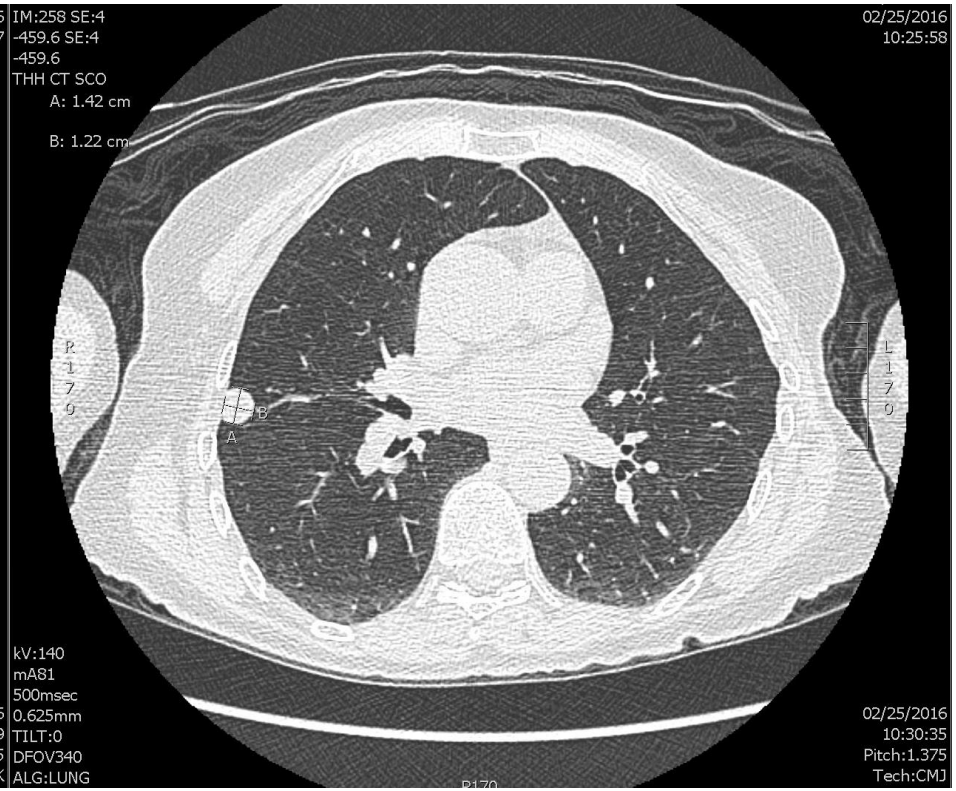
- 5/13/16-Ipi #2
- 6/3/16 - Ipi #3
- 6/24/16-Ipi #4



Cutaneous melanoma

Case





7/20/16

17x15mm

2/25/16

14x12mm

Next “best” step?

Ipilimumab (future)

- Combination with other partners (the other side of Ipi/Nivo)
  - Local injections, XRT
  - Other check points
  - Cytokines, vaccines
- Combination in other tumor types
- Toxicity modulation strategies
  - Schedule and dosing
  - Combination with other medications (GMCSF)
- Decreased use as single agent front line

Case

CHIEF COMPLAINT: Metastatic melanoma to skin, LN, liver and lung

Foundation :BRAF V600E, NRAS Q61K, PIK3CB E552K, TERT promoter -124C>T, PTEN loss, FAS loss, CDKN2A loss, CDKN2B loss

ONCOLOGY HISTORY: 58 y/o woman with metastatic melanoma. Briefly,

7/2014-RIGHT index finger lesion shave bx = T3B breslow depth 2.5mm.

8/2015 WLE and SLN 0/6 of right axilla=T4bN0. Adjuvant radiation to distal right finger over 15 treatments.

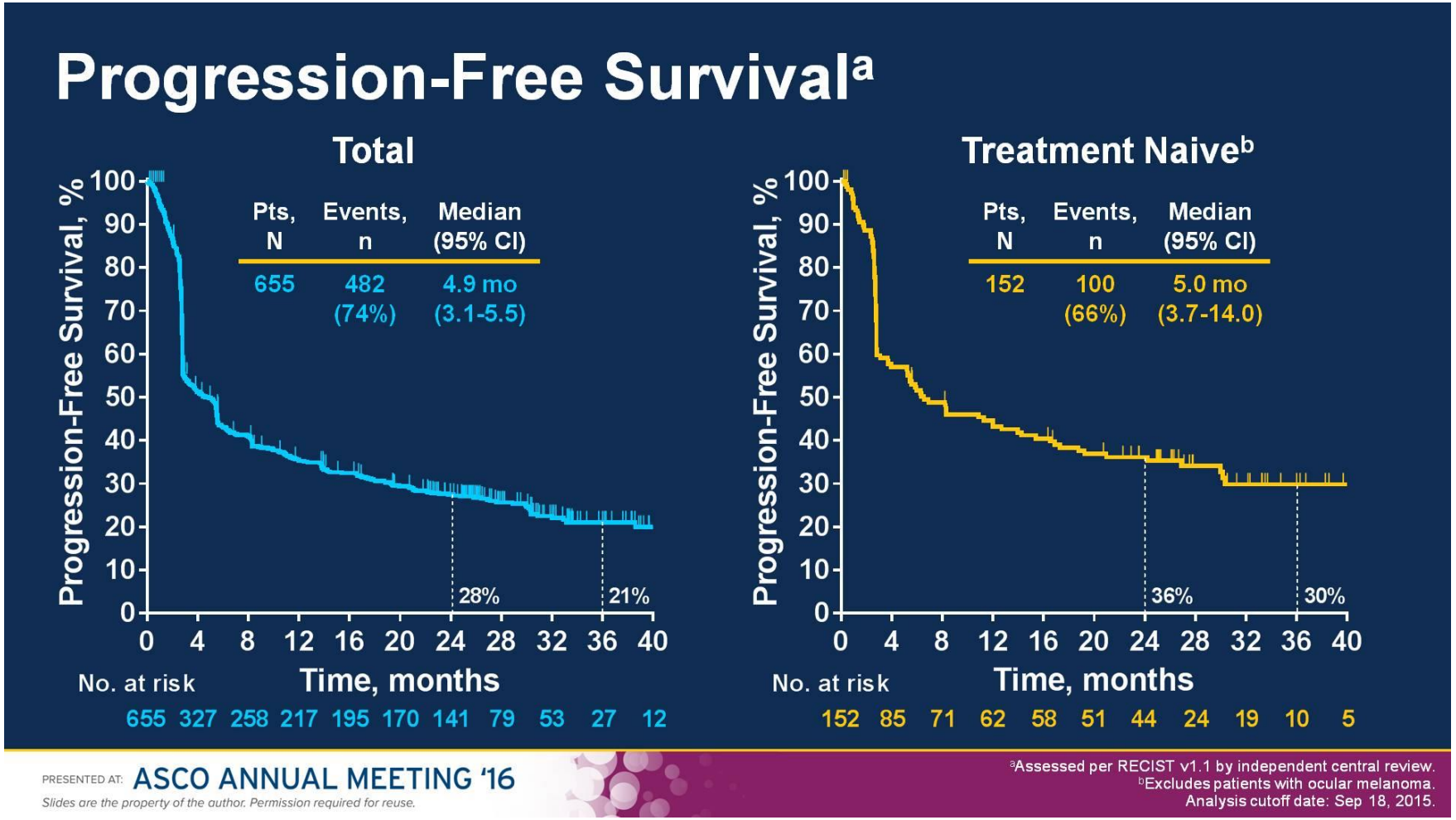
12/2014-Right forearm lesion.

2/26/15-CT CAP skin, LN, lung and liver
MR brain negative

ECOG=1

- What is the next best treatment option?
  - Targeted agents
  - PD1
  - HD IL2
  - Ipilimumab
  - Ipi/nivo
  - TVEC
  - Clinical trial

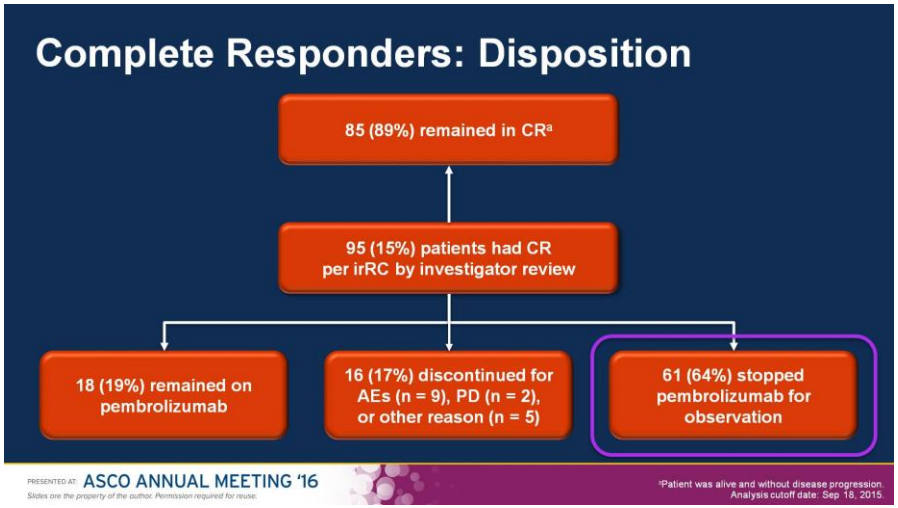
Pembrolizumab Keynote 001?

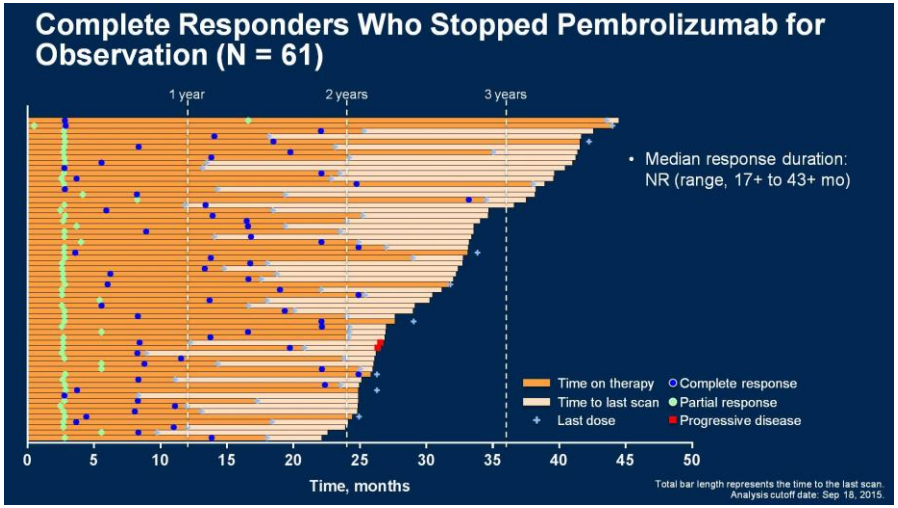


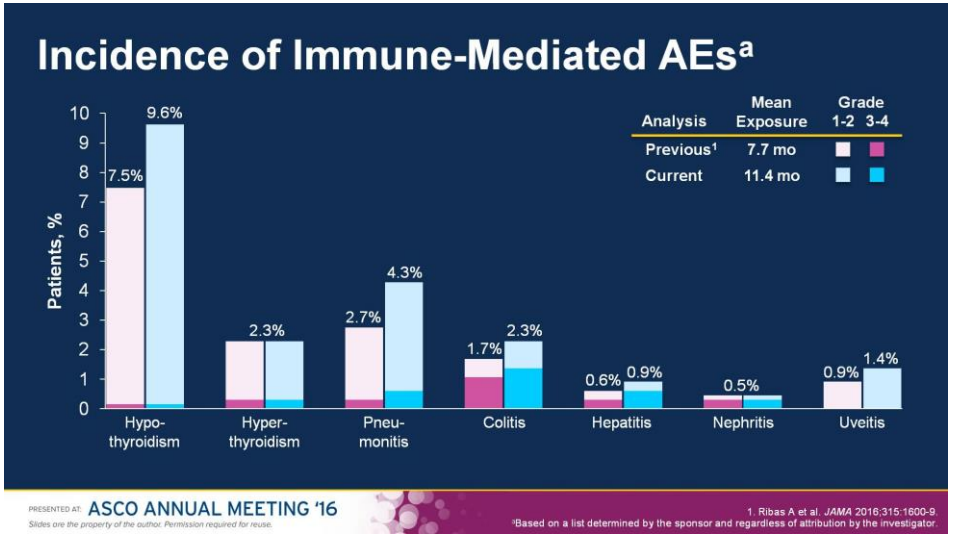
Robert ASCO 2016

655 patients with 32 months median follow up

Pembrolizumab Keynote 001





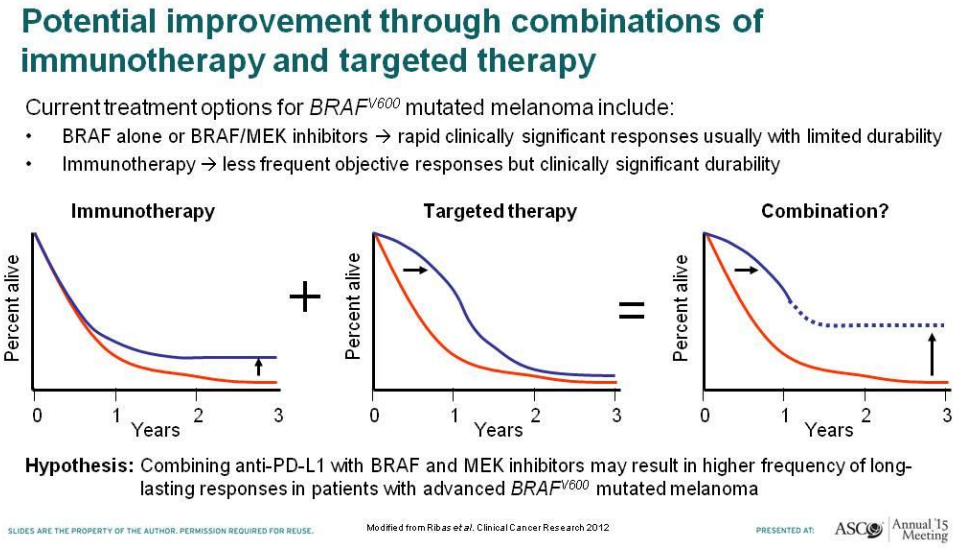


Grade 3/4 in 14% of patients

Robert ASCO 2016

Case

- 3/16/15-Started on UCLA **trial** of pembrolizumab and darafenib/trametanib.
- 6/24/15 - MRI, CTCAP - significant decrease
- 8/2015-DVT and placed on Rivaroxaban.



Ribas ASCO 2015 Keynote-022

Case

- 9/15-Progression of skin lesions
- 11/2015-LGX818/MEK162.
- 1/8/16-CT CAP with mixed response
- 3/15/16-MR brain negative
- 3/15/16-CT CAP with progression diffusely in soft tissue, LNs and lungs

Table 2. Clinical Efficacy

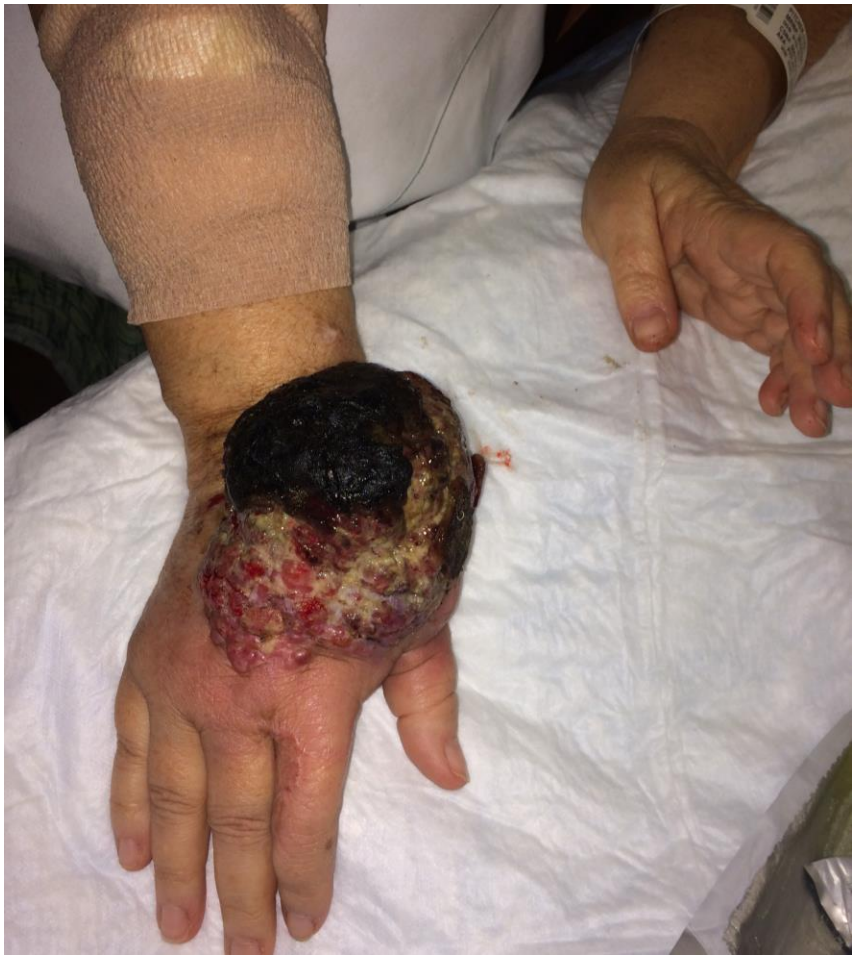
Response	Part B (n = 26) No.	Part B (n = 26) %	Part C (n = 45) No.	Part C (n = 45) %
CR	0	0	1	2
PR	4	15	5	11
SD*	13	50	20	44
PD	8	31	17	38
Not evaluable	1	4	2	4
Response rate, %	15		13	
95% CI	4 to 35		5 to 27	
Duration of response, months				
Median	7.8			
Interquartile range	4 to 12			

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
*For part C, this includes two patients with best response of non-CR/non-PD who had no baseline measurable disease at time of cross-over.

Johnson JCO 2014

Combined BRAF (Dabrafenib) and MEK Inhibition (Trametinib) in Patients With *BRAF*V600-Mutant Melanoma Experiencing Progression With Single-Agent BRAF Inhibitor

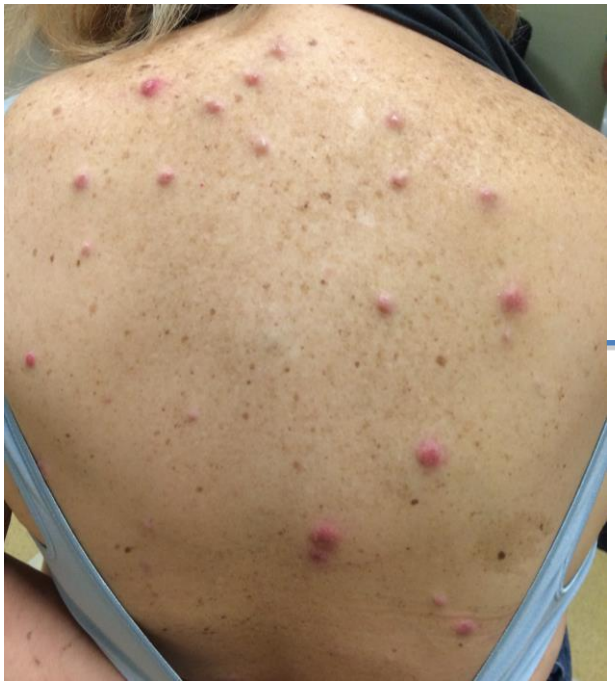
What is the next best option?



- XRT
- Ipilimumab
- Ipilimumab+Nivolumab
- HD IL2
- Amputation

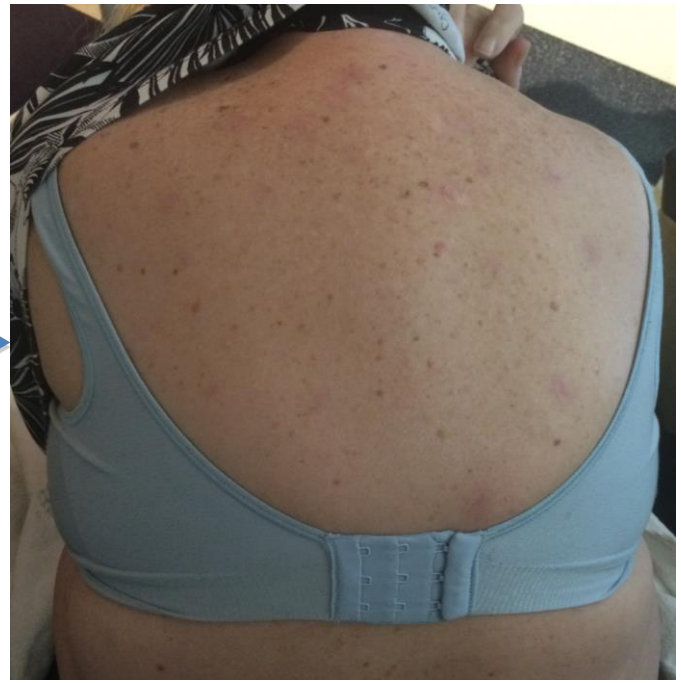
Hbg=5.6

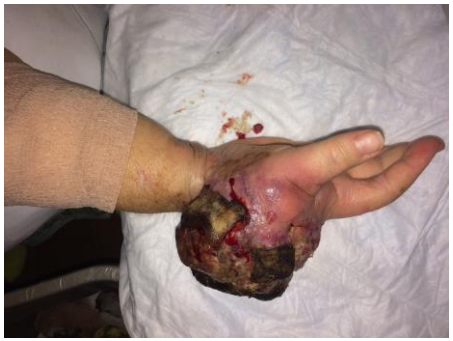
Case

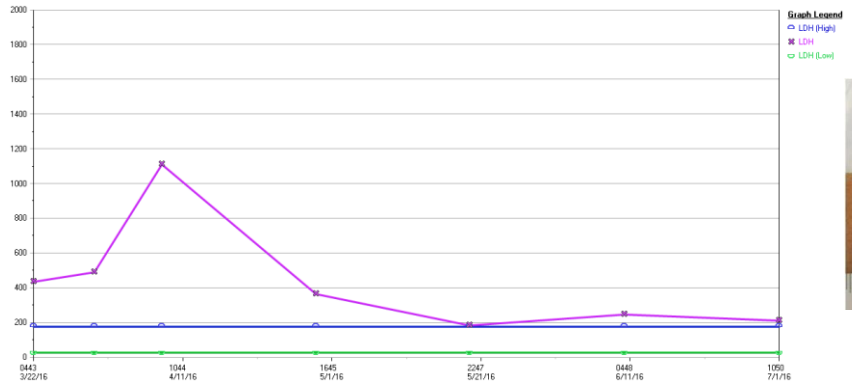


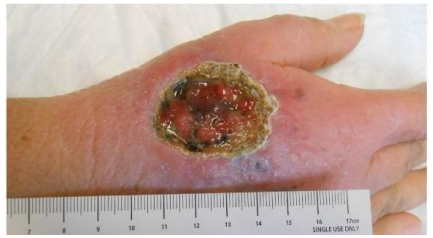
Ipi/Nivo x4

XRT to hand x 3fx

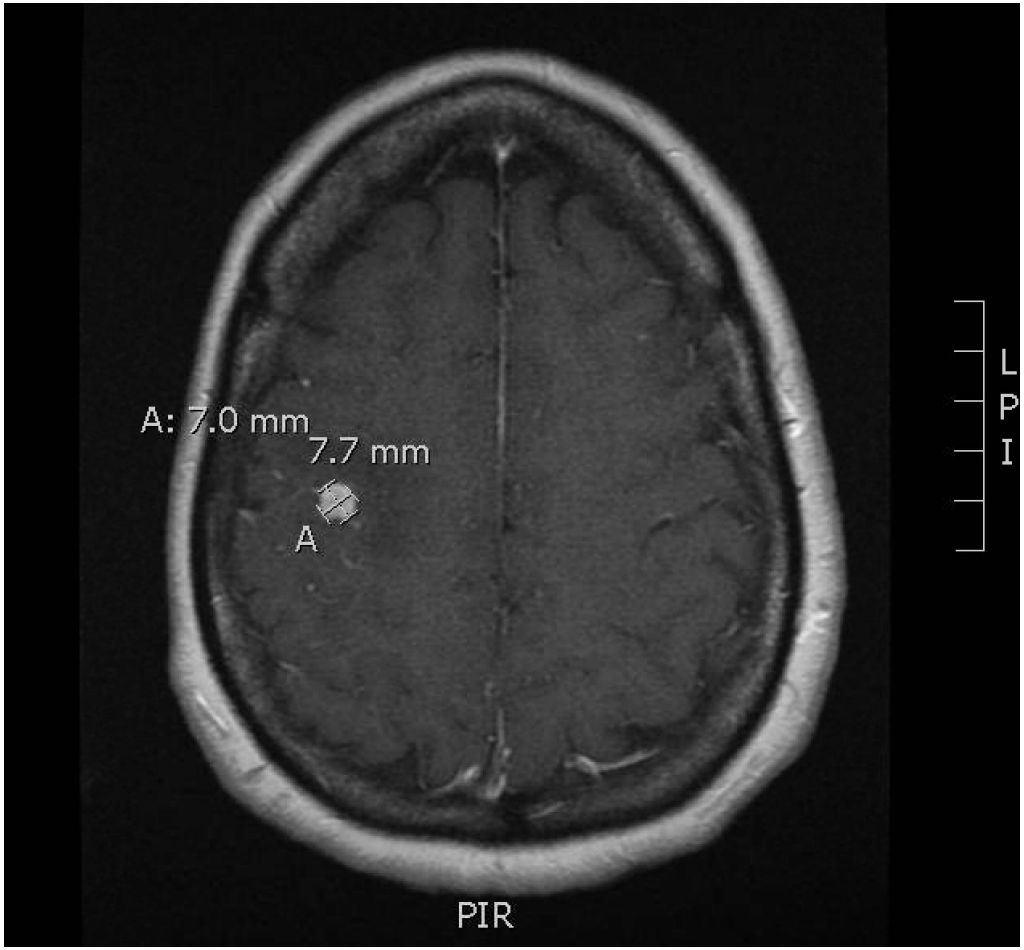








Case



- Treatment options?
  - SRS
  - WB-XRT
  - Continue on to single agent PD1
  - Resection

6-30-16 MR brain 5 lesions with largest 8mm

3-15-16 MR brain normal

Case

Chief complaint: Recurrent metastatic cutaneous melanoma.

BRAF: V600E

Oncology History: 43 y/o Caucasian man with locally recurrent cutaneous melanoma of the left LE.

4/09-Dark lesion on the medial aspect of left knee

8/09-Changed in size

9/09-WLE. Spindle cell neoplasm4/09-Dark lesion on the medial aspect of left knee

8/09-Changed in size

9/09-WLE. “Spindle cell neoplasm”

10/09-2 'spots' appeared at the edge of the resection--punch biopsy=same tumor. NO further WLE, NO lymph node evaluation.

11/11-Noted swelling in the groin. NOT tender. NO fevers.

11/17/11-FNA=melanoma.

Melanoma RF: NO melanomas, NO related cancers

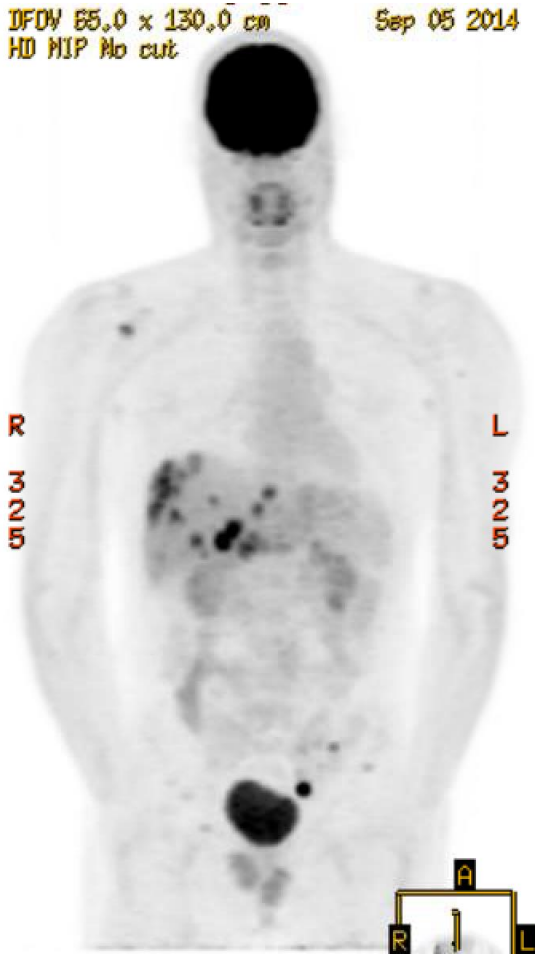
Case

- 12/23/11-LEFT groin dissection
  - Four lymph nodes out of ten with metastatic melanoma (**4/10**).
- 1/12-6/12-**Adjuvant chemotherapy** outside UCSD
- 3/22/13-LEFT groin dissection
  - *A: Groin, left, lymphadenectomy -Metastatic melanoma in two of six lymph nodes (**2/6**).*
  - *B: Groin, left iliac region, lymphadenectomy -No evidence of malignancy in one lymph node (0/1).*
  - *Addendum: Per patient request (via Dr. Bouvet), the largest metastasis measures 1.3 cm across, including an adjacent focus of extracapsular extension into perinodal fibrofatty tissue (slide A3).*
- 3/25/14-PET/CT with LN and liver lesion
- 4/10/14-MR liver with a single liver lesion c/w metastatic disease
- 5/16/14-LEFT groin dissection, liver metastasis ablation (x2 in the RIGHT lobe)
  - *A: Lymph node, external iliac, excision -Metastatic malignant melanoma in one of one lymph node (**1/1**).*
  - *B: Lymph node, external iliac, excision -Metastatic malignant melanoma in one of one lymph node (**1/1**).*
  - *C: Lymph node, external iliac, excision -Metastatic malignant melanoma in five of five lymph nodes (**5/5**).*
  - *Addendum 5/23/14 for comment on extent of the tumor: The tumor shows extensive extra-nodal extension into surrounding adipose tissue. The largest metastasis measures 1.6 cm.*

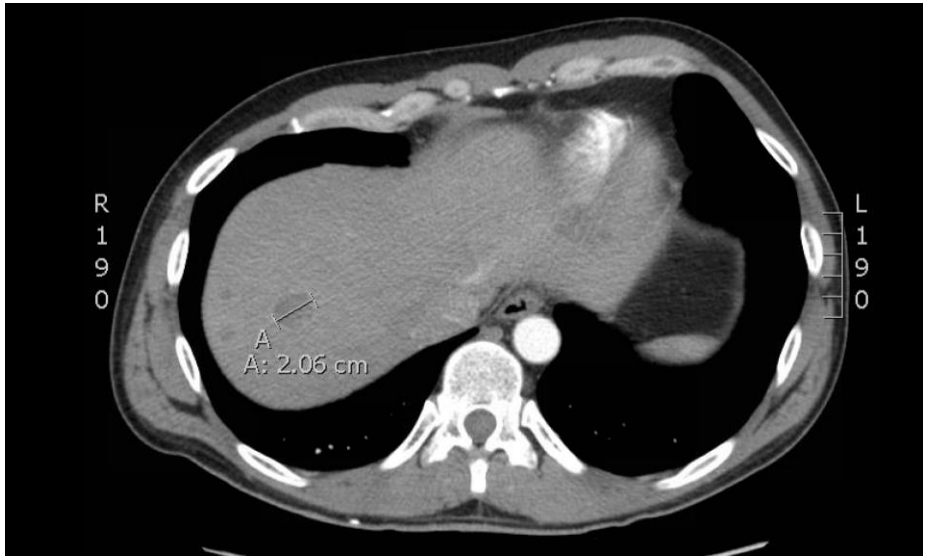
Case

- 9/5/14-PET/CT

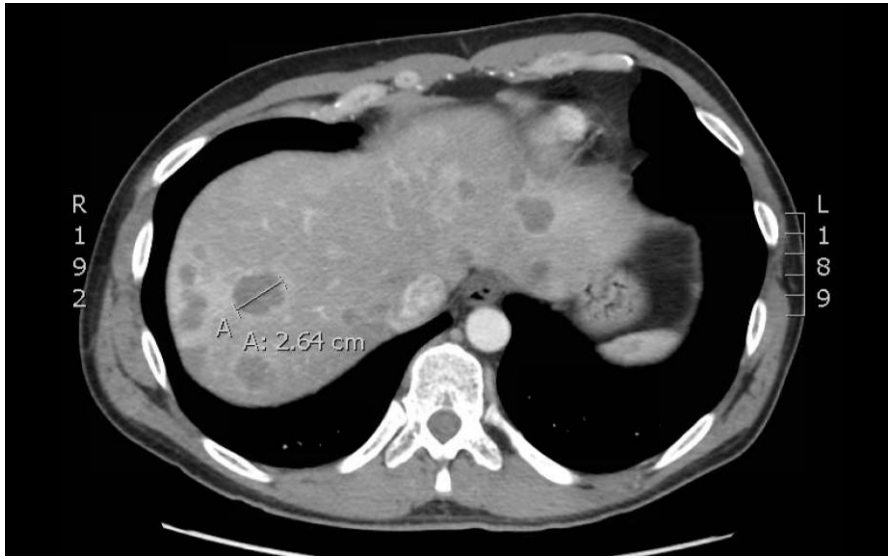
  Compared with prior PET-CT 5/5/2014, multiple new abnormal foci are present throughout the bones, including right scapula, left proximal humerus, ribs, pelvic bones and left proximal fibula. Multiple new foci are also present throughout the liver. Persistent focal activity is noted in the left pelvic sidewall lymph node. FDG PET imaging findings are compatible with progression of malignancy.



Case



9-5-14

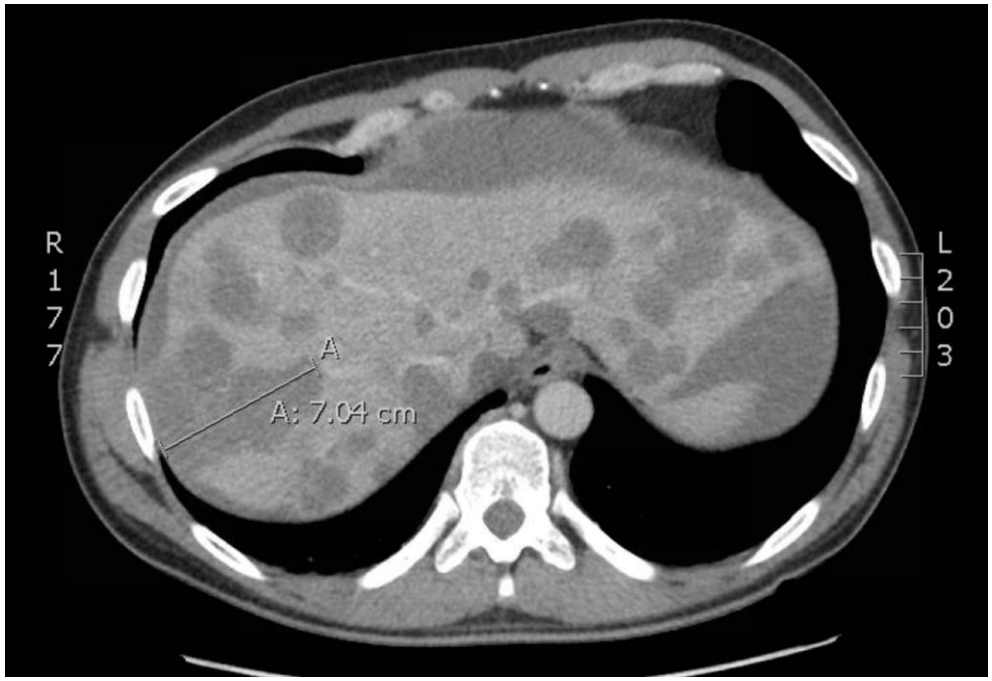


10-27-14

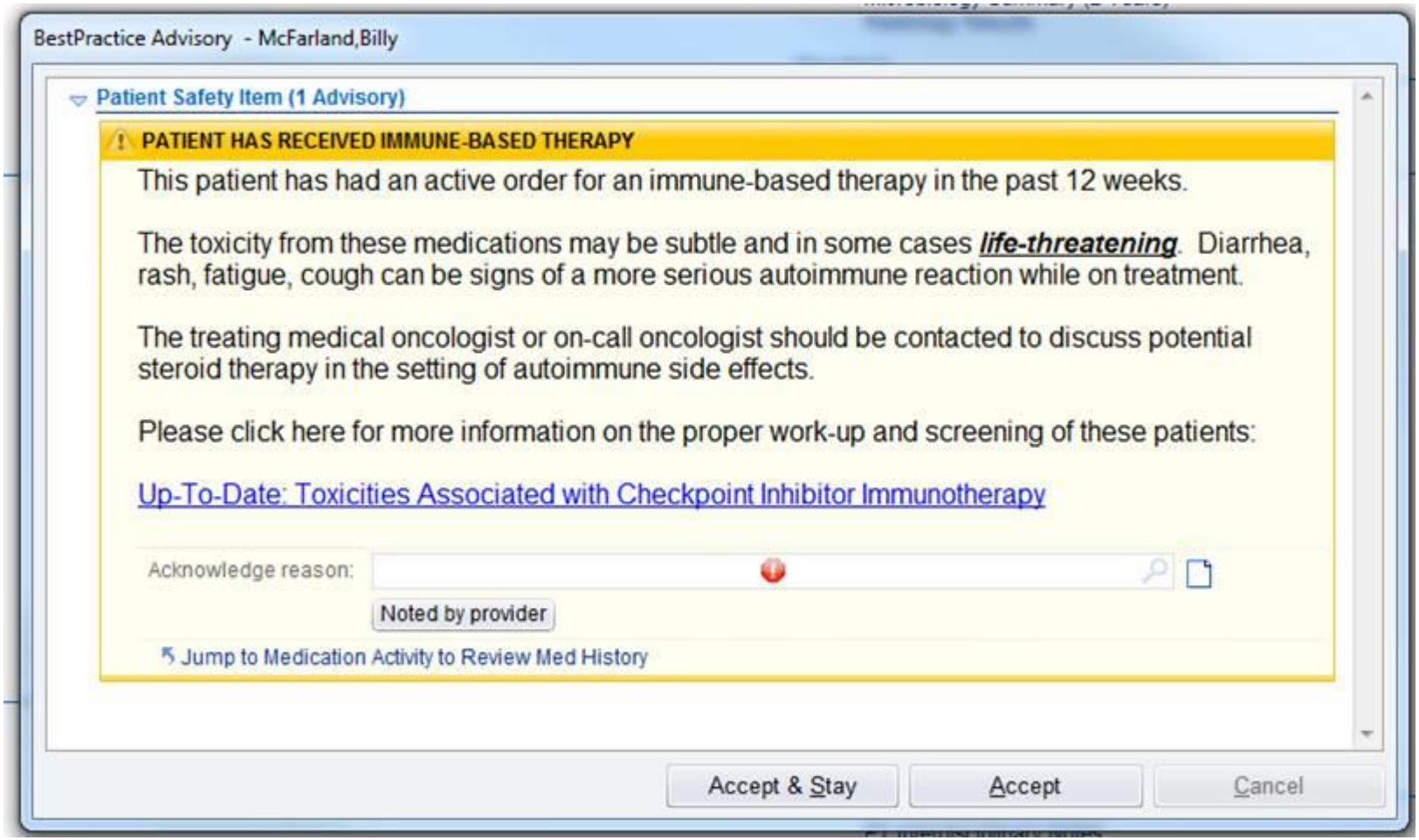
New baseline with rapid progression

Case

- 11/10/14-**C1D1 of Ipi+Nivo.** IRB 14-1407, CA209218
- 12/3/14-Intermittent abdominal discomfort. Weight stable. NO fevers. Bowels normal. Mild itching. Working. ECOG=1. **Deferred C2D1 due to transaminitis AST=380**
- 12/14/14-**Prednisone 100mg daily,** AST=245. **Autoimmune Hepatitis**
- 12/15/14-ED evaluation for acute abdominal pain. Subcapsular liver bleed.

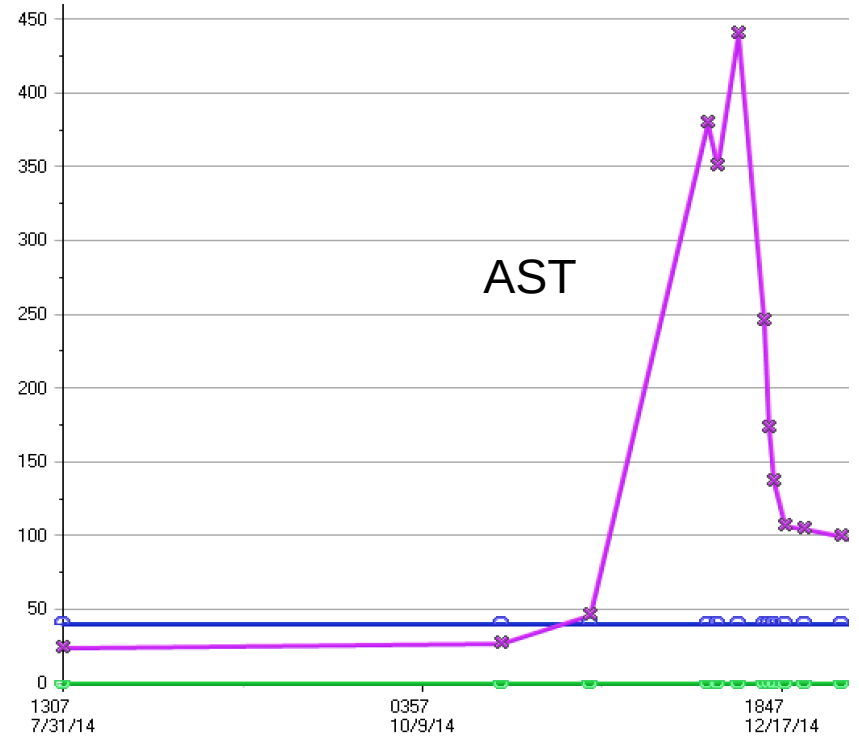


12-15-14

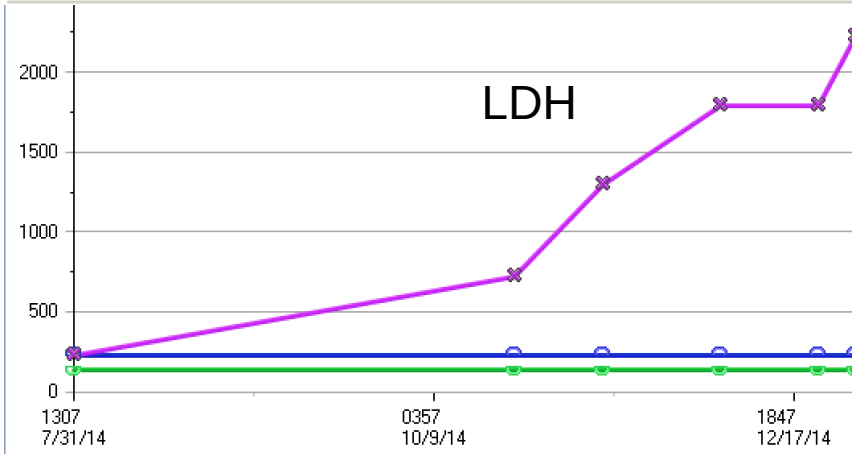

BestPractice Advisory - McFarland,Billy
Patient Safety Item (1 Advisory)
PATIENT HAS RECEIVED IMMUNE-BASED THERAPY
This patient has had an active order for an immune-based therapy in the past 12 weeks.
The toxicity from these medications may be subtle and in some cases life-threatening. Diarrhea, rash, fatigue, cough can be signs of a more serious autoimmune reaction while on treatment.
The treating medical oncologist or on-call oncologist should be contacted to discuss potential steroid therapy in the setting of autoimmune side effects.
Please click here for more information on the proper work-up and screening of these patients:
Up-To-Date: Toxicities Associated with Checkpoint Inhibitor Immunotherapy
Acknowledge reason:
Noted by provider
Jump to Medication Activity to Review Med History
Accept & Stay
Accept
Cancel

Case

- 12/23/14-Prednisone75mg daily, AST=104



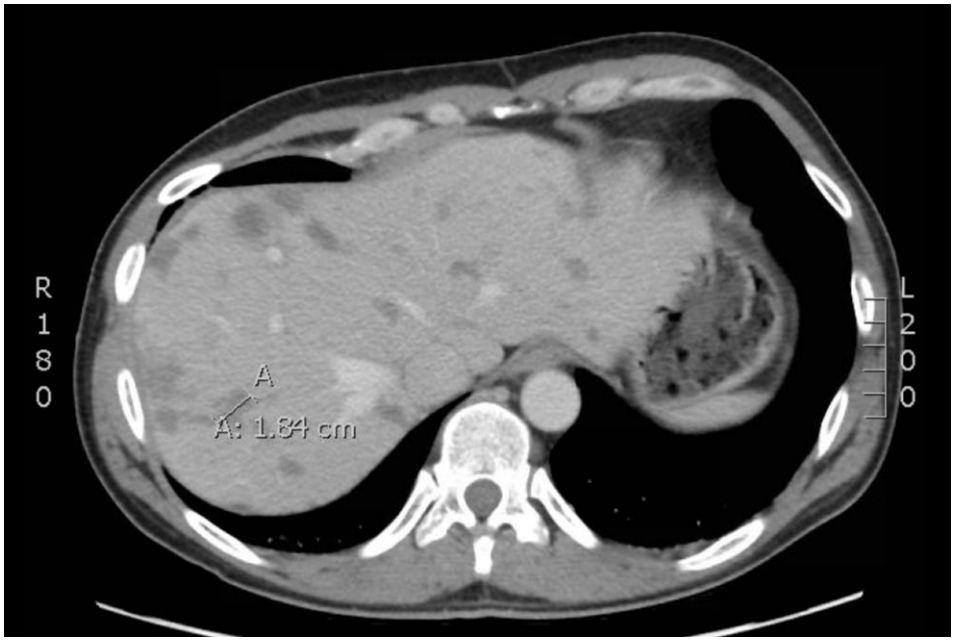
- 1/14/15-**Stopped steroids, AST=54**



LDH however was continuing to rise

Case

- 1/15/15-**Dabrafenib/trametinib**
- 2/13/15-Felt better “2 days after the medications”. NO pain. Eating OK. Weight good. Biking. Rash in the beginning of therapy that resolved. NO rash, NO itching. ECOG=0
- 3/16/15-Stopped Dabrafenib/Trametanib



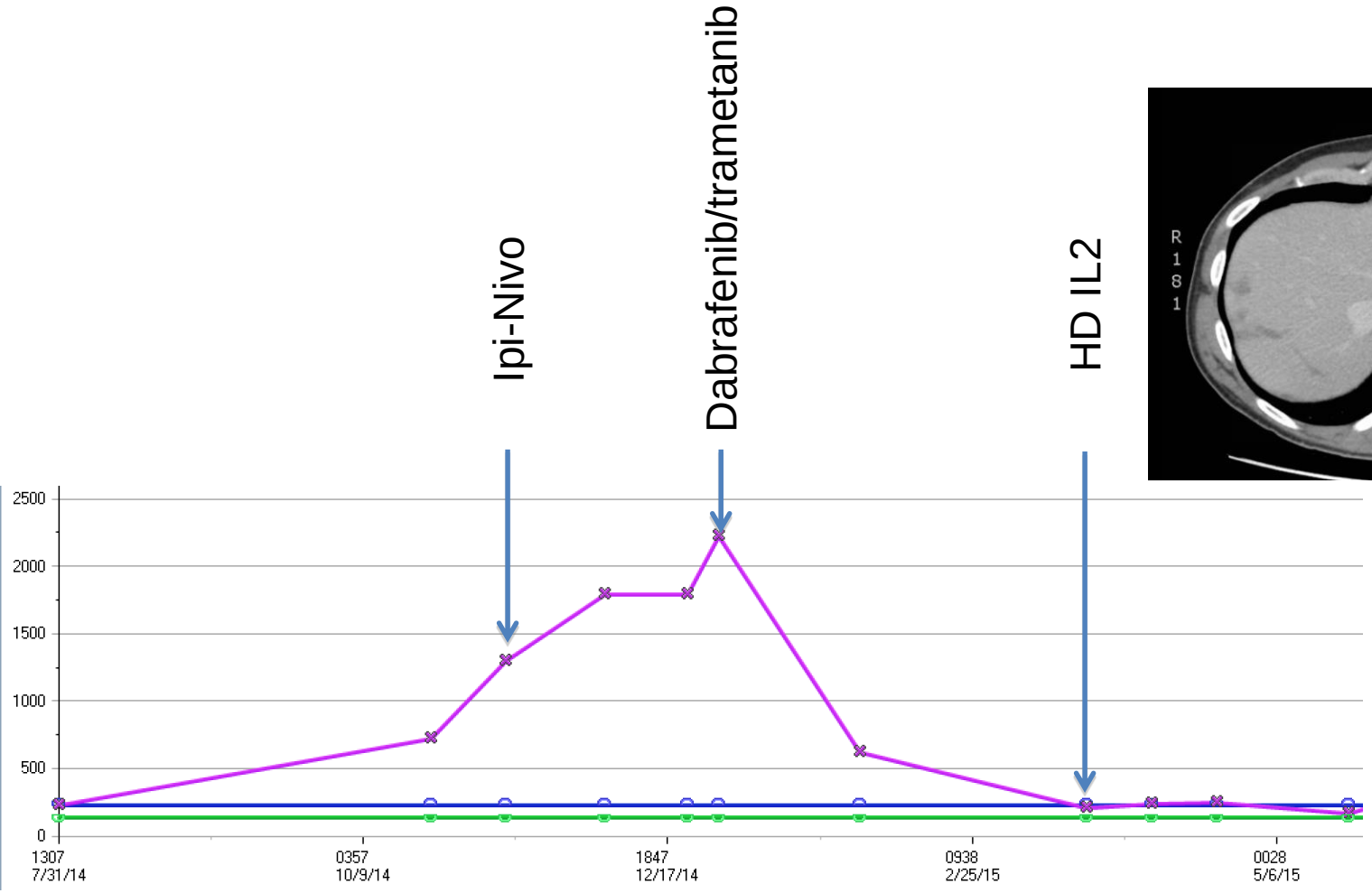
3-17-15

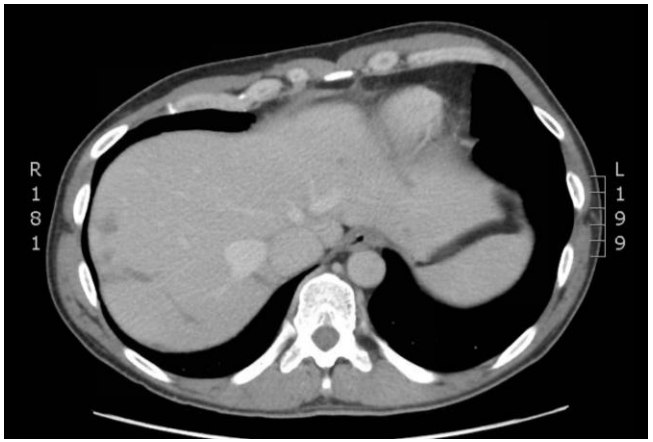
Case

- 3/23/15-**High-dose IL2 course 1, cycle 1.** A double lumen PICC line inserted into the RIGHT upper extremity. **FOURTEEN** doses of 66mIU

- 4/7/15-**High-dose IL2 course 1, cycle 2.** A double lumen PICC line inserted into the RIGHT upper extremity. **THIRTEEN** doses of 77mIU

Case


Ipi-Nivo
Dabrafenib/trametanib
HD IL2
2500
2000
1500
1000
500
0
1307
7/31/14
0357
10/9/14
1847
12/17/14
0938
2/25/15
0028
5/6/15


R
1
8
1
L
1
9
9

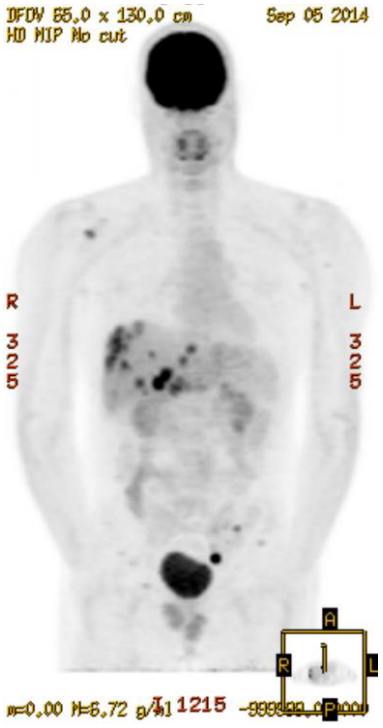
5/12/15

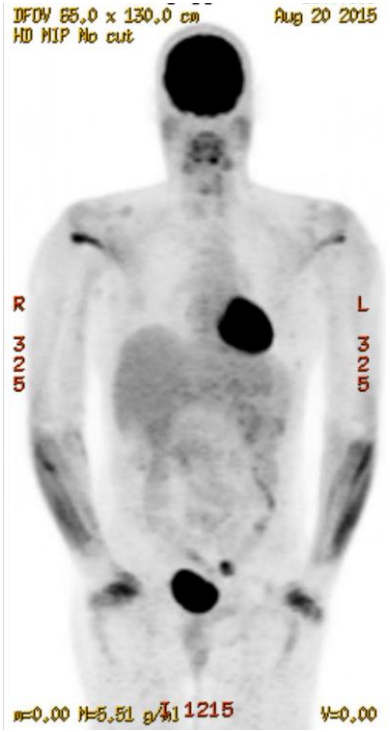
Case

5/22/15-**High-dose IL2 course 2, cycle 1.** A double lumen PICC line inserted into the RIGHT upper extremity. **FOURTEEN** doses of 66mIU

6/5/15-**High-dose IL2 course 2, cycle 2.** A double lumen PICC line inserted into the RIGHT upper extremity. **THIRTEEN** doses of 66mIU

Case



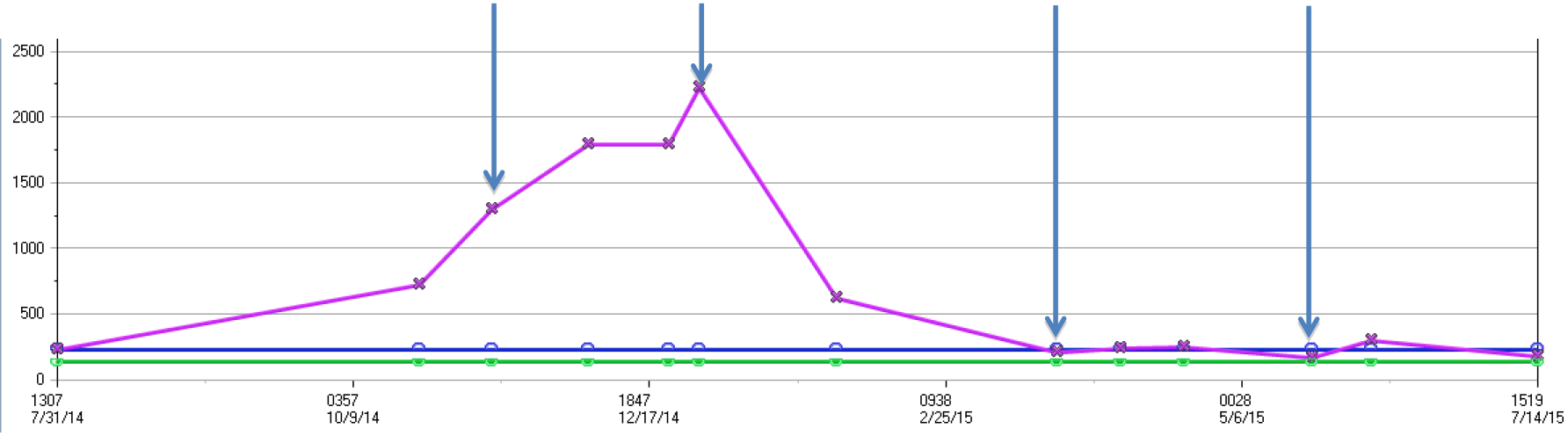


Ipi-Nivo

Dabrafenib/trametanib

HD IL2

HD IL2



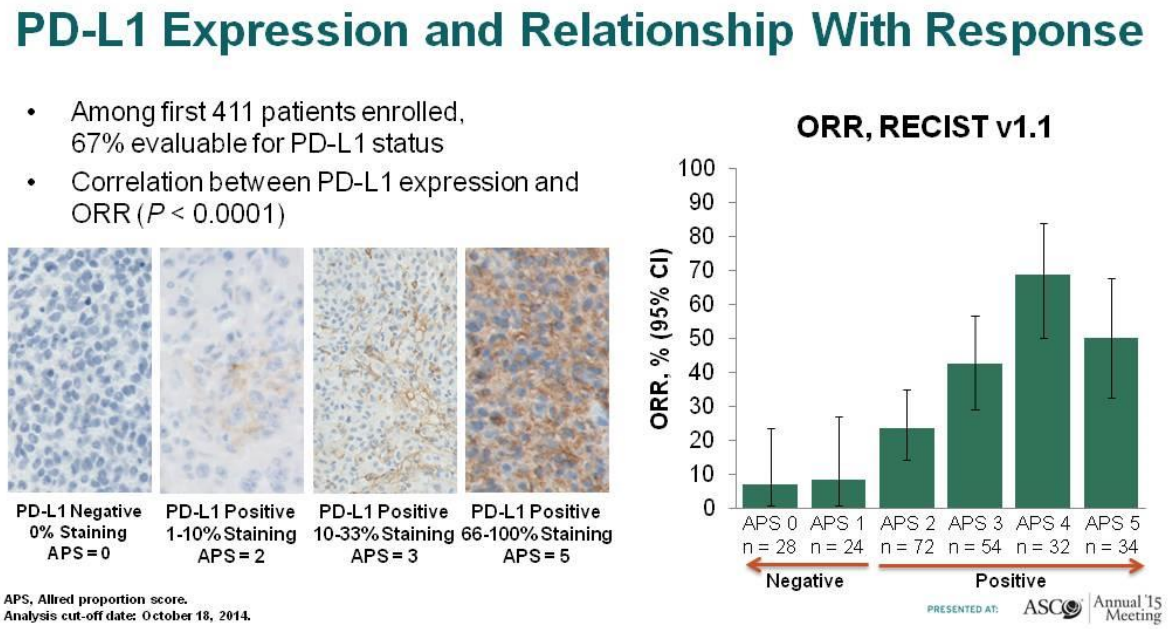
Case

- 11/6/15-Biposy of LEFT chest wall lesion =melanoma. PDL1 staining low
- 12/28/15-PET/CT-Left chest wall lesions
- 2/25/16-CT CAP- Increase skin lesions, liver and abdominal LNs

- Options?
  - BRAF/MEK
  - Ipi/Nivo
  - Clinical trial
  - Ipilimumab
  - Pembrolizumab or Nivolumab

How to pick beyond clinical indications?

- Tumor infiltration with activated T-cells is a prerequisite for response to PD-1 checkpoint blockade.



Daud ASCO 2015 Keynote 001

How to pick beyond clinical indications?

Development and analytical performance of a molecular diagnostic for anti-PD1 response on the nCounter® Dx Analysis System

Brett Wallden[1], Irena Pekker[1], Simina Popa[1], Naeem Dowidar[1], Amy Sullivan[1], Tressa Hood[1], Patrick Danaher[1], Afshin Mashadi-Hossein[1], Jared Lunceford[2], Matthew Marton[2], Ken Chang[2], Sean Ferree[1], James Storhoff[1]

[1]NanoString Technologies, Seattle, WA USA; [2]Merck & Co., Inc., Kenilworth, NJ USA

***Corresponding author** bwallden@nanostring.com

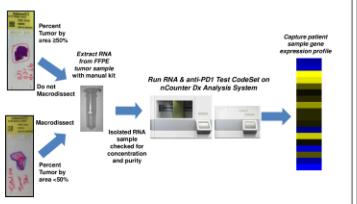
Abstract # 3034

Background: Pembrolizumab is a humanized anti-PD1 antibody that is FDA approved for use in patients with advanced melanoma and in selected patients with metastatic non-small-cell lung cancer. It has also shown clinical activity in a number of other tumor types in clinical trials, but there is need for a precise and accurate test that can identify patients most likely to benefit from therapy. Several immune-related gene expression (Gx) signatures in formalin fixed, paraffin embedded (FFPE) tissue were previously reported to enrich for responders to pembrolizumab across different tumor types[1,2]. We have developed a clinical trial assay, referred to here as the anti-PD1 Gx test, based on genes repeatedly found to be associated with improved response to pembrolizumab in a number of cancers. Here we describe the development and analytical performance of the anti-PD1 Gx test in multiple tumor types.

Overview of anti-PD1 Algorithm and Test Procedures

- The anti-PD1 Test algorithm was previously trained with 375 FFPE patient tissue samples from KEYNOTE-012 and KEYNOTE-028 and verified in 216 independent FFPE patient tissue samples from KEYNOTE-028 (anal, biliary tract, colorectal, esophageal, and ovarian) using a Discovery Research Assay (NanoString custom CodeSet).
- H&E slide is reviewed by a board-certified Pathologist to identify and confirm the presence of tumor.
- Unstained slides are deparaffinized and macrodissected to remove surrounding normal/non-tumor tissue >50%.
- Total RNA is extracted from macrodissected tumor tissue using a manual RNA isolation kit.
- Analysis is conducted on 250ng extracted RNA using the NanoString nCounter Dx Analysis System.
- Both anti-PD1 Predictor Score (aPPS) and biomarker class are output for every sample.
- ≤3 day turnaround time from a sample arriving at the lab to the results being reported.

Anti-PD1 by NanoString nCounter® Dx Analysis System

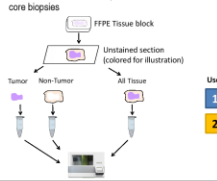


Determine anti-PD1 Predictor Score (aPPS) for each sample X by $aPPS(X) = \sum_j a_j X_j$

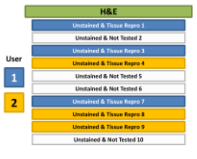
where X_j is the gene expression for gene j and a_j is the coefficient for gene j. The aPPS is then compared against predefined thresholds to determine the biomarker category.

Experimental Designs

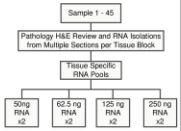
Pre-Analytical Robustness:
- Bias due to the inclusion of adjacent non-tumor tissue was tested by running RNA from 138 samples isolated with and without macrodissection on the anti-PD1 test.
- 18 samples run using NanoString's nCounter® PanCancer Immune Profiling Panel
- 26 samples analyzed by processing partial areas of slides to simulate a comparison of excisional- to-core biopsies



Analytical Reproducibility From Tissue:
- Panel of 58 FFPE blocks tested with H&E review and independent RNA isolation by 2 lab users. Testing included six replicates for most samples.
- FFPE tissues represented 10 different tumor types.



Analytical Precision From RNA:
- Panel of 45 pooled tumor RNA samples generated representing a broad range of aPPS values. Not all samples were tested at all mass inputs.
- Variance and bias due to RNA mass was tested.



Disclosures: B Wallden, J Storhoff, S Ferree, I Pekker, S Popa, A Sullivan, N Dowidar, T Hood, P Danaher, and A Mashadi-Hossein disclosed that they are employees of and shareholders in NanoString Technologies Inc. J Lunceford, M Marton, K Chang disclosed that they are employees of and shareholders in Merck & Co. Inc.

Footnote: *The NanoString anti-PD1 Test has not been FDA cleared or approved to identify patients for pembrolizumab treatment. In the United States, the anti-PD1 Test is For Investigational Use Only. The performance characteristics of this product have not been established. nCounter® PanCancer Immune Profiling Panel is for Research Use Only. Not for use in diagnostic procedures.

Citations: **(1)** Shankaran V. *et al.* "Correlation of gene expression signatures and clinical outcomes in patients with advanced gastric cancer treated with pembrolizumab (MK-3475)." *ASCO Annual Meeting Proceedings*. Vol. 33. No. 15_suppl. 2015. **(2)** Seiwert T. *et al.* "Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ head and neck cancer patients." *ASCO Annual Meeting Proceedings*. Vol. 33. No. 15_suppl. 2015.

Results

Pre-Analytical Robustness :
- 38 commercial samples were run with both the Discovery Assay and the NanoString anti-PD1 Test. The normalized gene expression assay measured by both assays were highly correlated across a wide range of gene expression (Fig. 1A).
- 104 KEYNOTE-028 FFPE patient tissues were processed using procedures and reagents from the NanoString anti-PD1 Test to translate the signature score thresholds from the Discovery Assay to the anti-PD1 Test. The assay signature score results were highly correlated even when separate tissue sections were analyzed (Fig. 1B).
- The gene expression profiles from 102 samples representing 11 different tumor types were compared to determine whether the signature score is influenced by tumor type. The scores for different tumor types were randomly distributed through the dynamic range of aPPS values, indicating the underlying extent of tumors' immune infiltrate is largely independent of the tumor type (Fig. 2).
- The NanoString test result was robust against the inclusion of up to 50% adjacent non-tumor tissue into the assay regardless of tumor type (Fig.3A). The signature scores were highly correlated (r=0.98) between macrodissected and non-macrodissected tissue. Samples from the KEYNOTE-028 trial were tested with and without macrodissection. There was no significant difference in the clinical accuracy of the test in selecting patients who responded to pembrolizumab between macrodissected and non-macrodissected tissue (data not shown).
- To further explore the relevance of surrounding non-tumor tissue on gene expression, 18 samples were analyzed using the NanoString nCounter® PanCancer Immune Profiling Panel with and without macrodissection. The expression was not significantly different with and without macrodissection in the 770 genes (FDR=1) indicating that the measurement of immune response is largely not impacted by macrodissection (Fig. 3B).
- The impact of tissue biopsy procedures on assay performance was assessed by comparing results from whole sections with matched partitioned sections of varying sizes (Fig 4). The results were highly correlated across a wide range of partition sizes

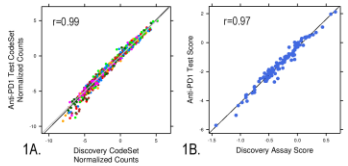


Figure 1. Discovery Assay and the NanoString Clinical Trial Assay: Comparison of **(1A)** normalized gene expression between Discovery Assay and anti-PD1 Test CodeSet designs from 38 commercially sourced samples and **(1B)** signature scores from 104 KEYNOTE-028 samples processed and analyzed using the Discovery Assay and anti-PD1 Test procedures.

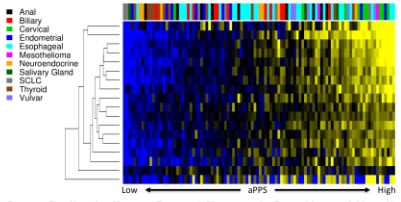


Figure 2. The Algorithm Measures Extent and Phenotype of a Tumors' Immune Infiltrate Not Tumor Biology: The heatmap shows the normalized and Log_2 transformed gene expression data for 102 commercially sourced FFPE samples run with the NanoString anti-PD1 Test. The samples were sorted by algorithm score (left to right) and the tumor type is marked above each sample.

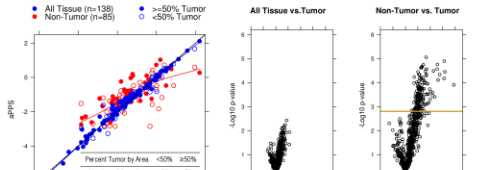


Figure 3. Impact of including adjacent non-tumor tissue on aPPS: Comparison of the **(3A)** anti-PD1 test results from slide-mounted sections that were macrodissected (Tumor) vs. those without macrodissection (All Tissue) or from adjacent non-tumor tissue (Non-tumor). Colors indicate if the All Tissue or Non-Tumor was compared to Tumor and the shapes indicate if the tissue had less than 50% tumor by area or not. **(3B)** Differential gene expression (Fold Change) between Tumor and All Tissue (all genes have FDR = 1) and **(3C)** differential gene expression (Fold Change) between Tumor and Non-Tumor (with a FDR cutoff of 5%) in NanoString's nCounter® PanCancer Immune Profiling Panel.

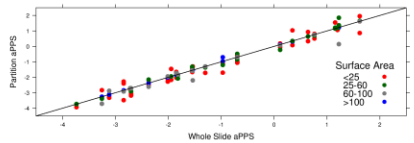


Figure 4. Comparison of signature scores from whole slides to partitioned slides: The signature scores for partitioned slides of varying area simulating the tissue sampling of small biopsies or core needle biopsies are compared to the scores from a whole slide

Analytical Reproducibility From Tissue:
- The 58 tissues are representative of the full range of aPPS values (Fig. 5). The variance components analysis estimated a total SD of 0.24 aPPS units (<5% of total aPPS range).
- Biomarker group classification concordance between tissue sections was estimated as 94.5%.

Analytical Precision From RNA :
- The variance components analysis estimated a total standard deviation from RNA of 0.13 aPPS units at 50ng RNA mass input, or ~2% of the total aPPS range. Biomarker group classification concordance at 50ng of RNA was estimated as 94.8%.
- Consistent aPPS results (mean aPPS difference < 0.26 units) and concordant biomarker calls (>98 %) across 45 samples tested at 50, 62.5, and 125ng compared to 250 ng RNA input (Fig. 6).
- The SD associated with assay lane-to-lane repeatability was estimated as 0.057 aPPS units (<1% of total aPPS range) at the nominal input mass of 250 ng.

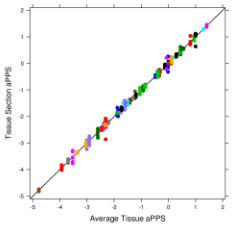


Figure 5. Reproducibility of anti-PD1 Test across 58 different tissue samples: The average tissue block aPPS compared to the individual aPPS results for all samples in the tissue reproducibility study. Samples are colored by the individual tissue sample. The 58 tumor samples represent 10 different tumor types.

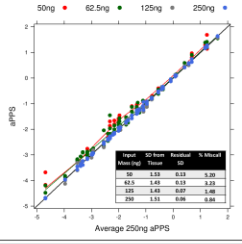


Figure 6: Impact of RNA input mass on aPPS: Data represent the average of replicates at 250ng plotted against the average of the replicates at 50, 62.5, or 125 ng of RNA mass input. Points are colored by the RNA mass. The table shows the estimated biomarker misclassification rate at each RNA mass input.

Conclusions

The NanoString anti-PD1 Gx test is a robust assay starting from FFPE tissue, which profiles immune-related Gx across multiple cancer types. With turnaround time of 3 days or less (from sample receipt to test result), the assay is well suited to clinical applications and its ability to identify patients more likely to respond to anti-PD1 therapy is being investigated in multiple indications in several studies.

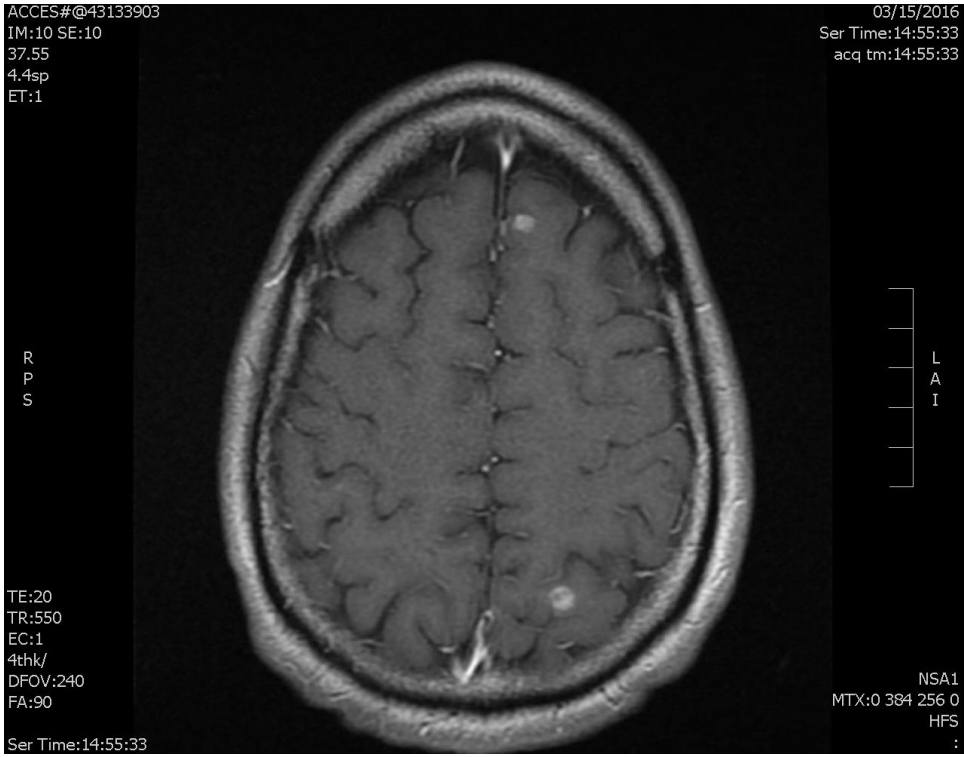
- The NanoString anti-PD1 Test is highly consistent with the Discovery Assay used to train and verify the algorithm. The accuracy of the predictor was subsequently verified in three separate all-comers (melanoma, head & neck, and bladder cancer) cohorts.
- The major source of variability in Gx across multiple tumor types was associated with the tumors' immune Gx signature rather than intra-tumor variability or even tumor type.
- The NanoString anti PD1 Test is robust against the inclusion of non-tumor tissue from multiple tumor types and provides consistent results whether a large biopsy or small biopsy sample is used.
- The analytical performance of the NanoString anti-PD1 Test offers highly reproducible test results (total SD of 0.24 aPPS units) across operators. The reproducibility of this test was verified in a separate study with multiple pathologists.
- The NanoString anti-PD1 Test is currently being used as an investigational device in patients treated with pembrolizumab in several clinical studies (NCT02628067, NCT02559687, & NCT02564263).*

An example of many developing technologies to predict response

ASCO 2016

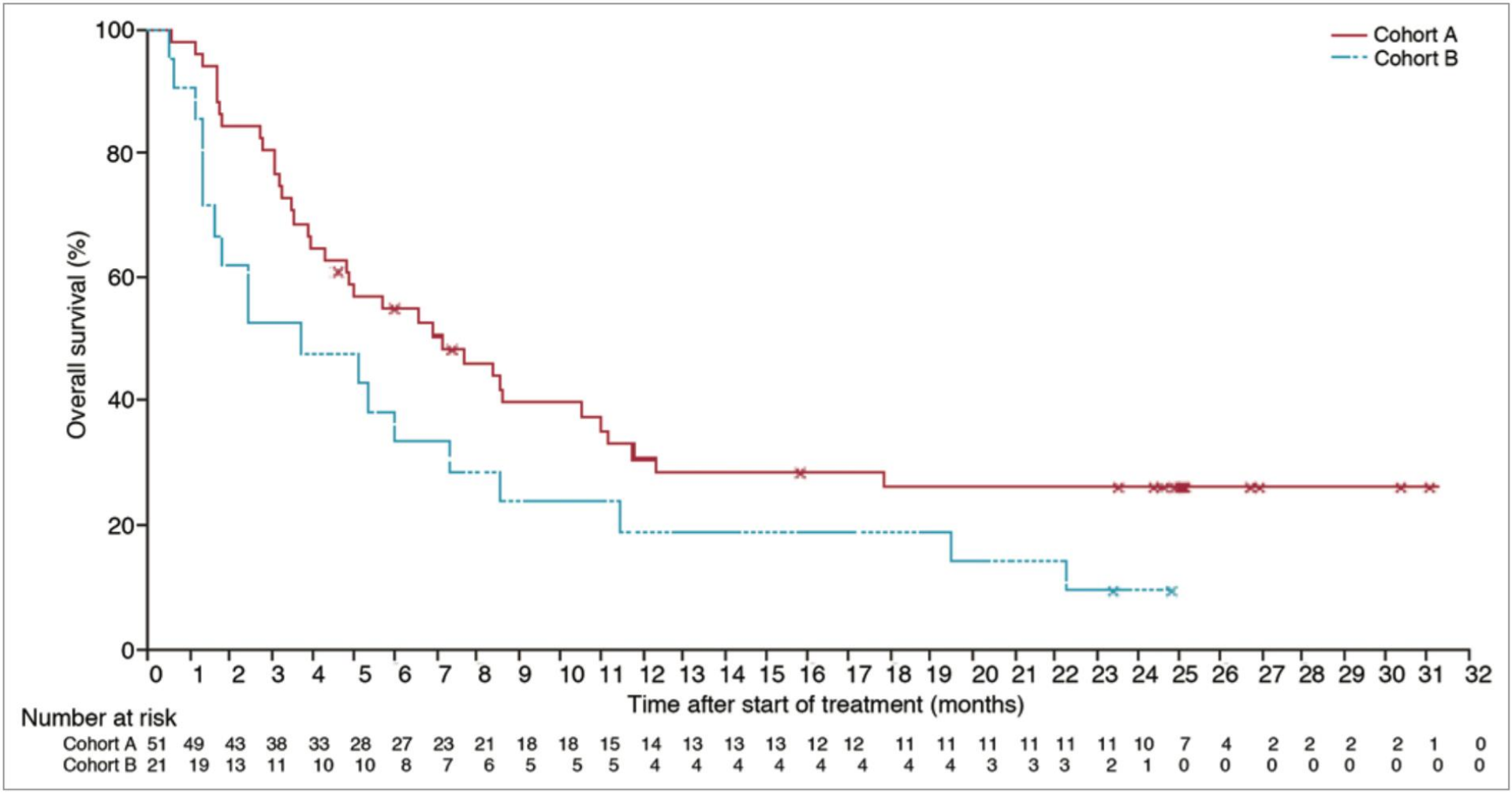
Case

- 3/7/16-**Ipi/Nivo #1**
- 3/15/16-MR brain with 4 enhancing lesions and a few possible other lesions.
- 3/16/16-NO headaches, NO nausea, NO neurologic issues. NO new lesions. NO rash. Energy good. Eating OK. ECOG=0



Options? Next best step?

Ipilimumab Therapy for Brain Metastasis



Margolin Lancet 2012 Phase 2 trial

Cohort A=NO steroids, Cohort B=steroids

PD1 therapy in brain metastasis

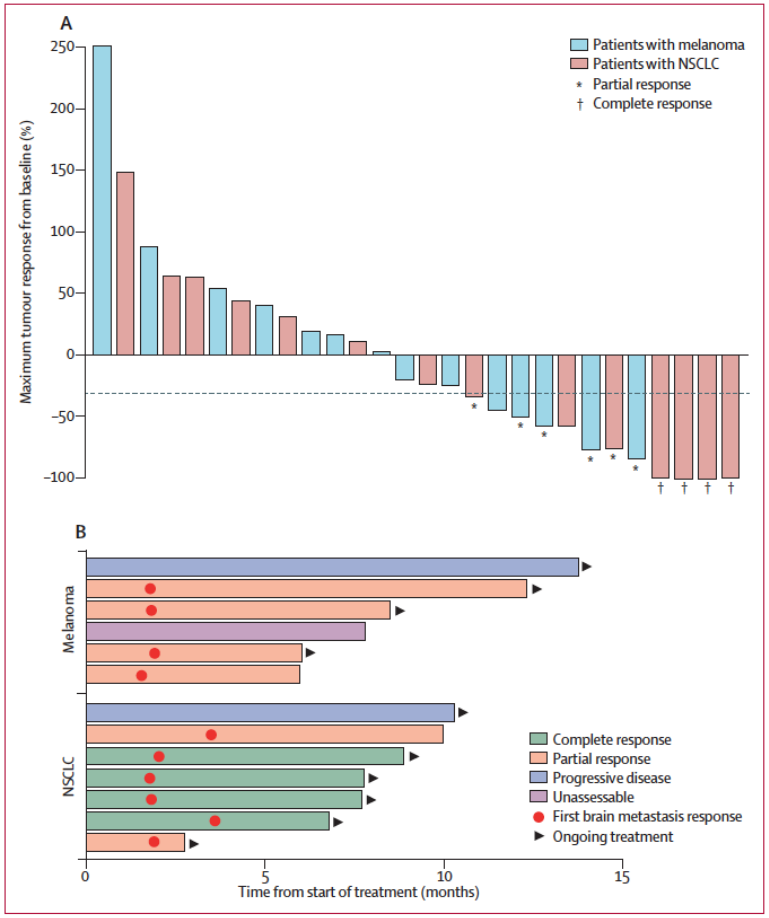
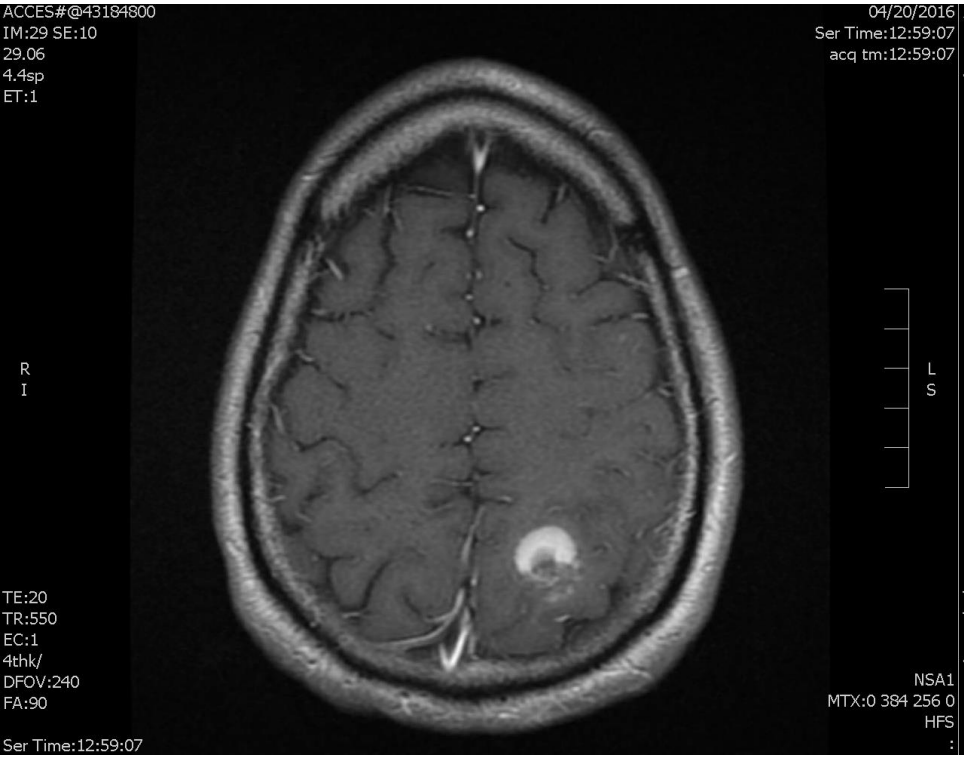


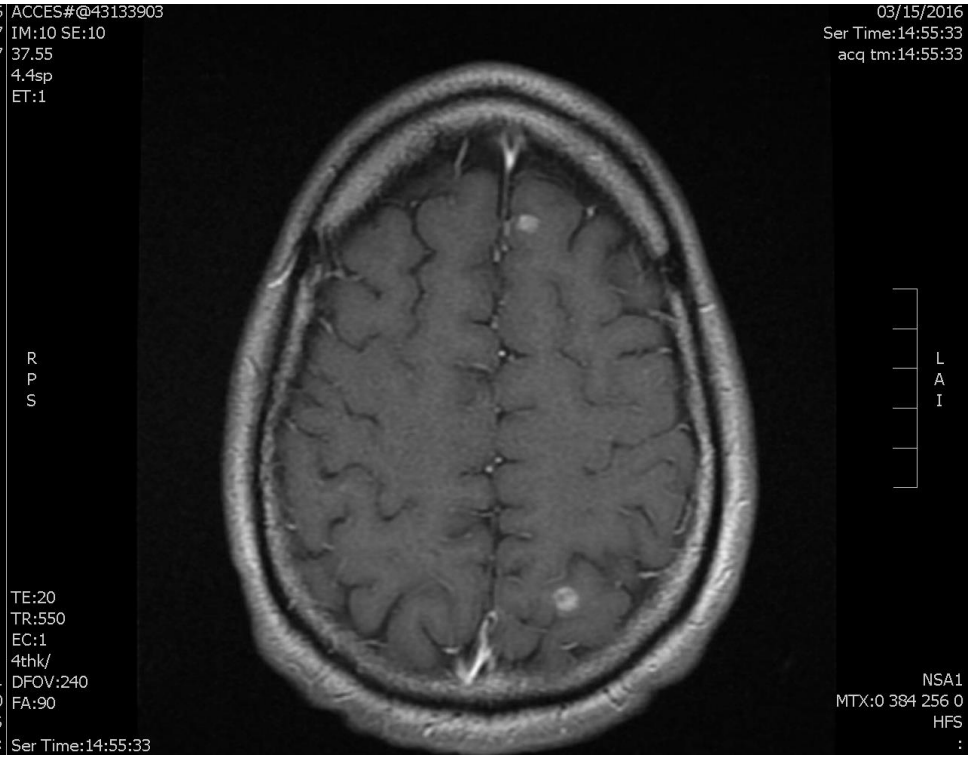
Figure: **Brain metastasis response in assessable patients with melanoma or NSCLC**

- Pembrolizumab given to melanoma and NSCLC with progressive brain metastasis
- 4/22 melanoma and 6/18 lung patients responded
- Intralesional bleeding and progression prior to regression noted

Case



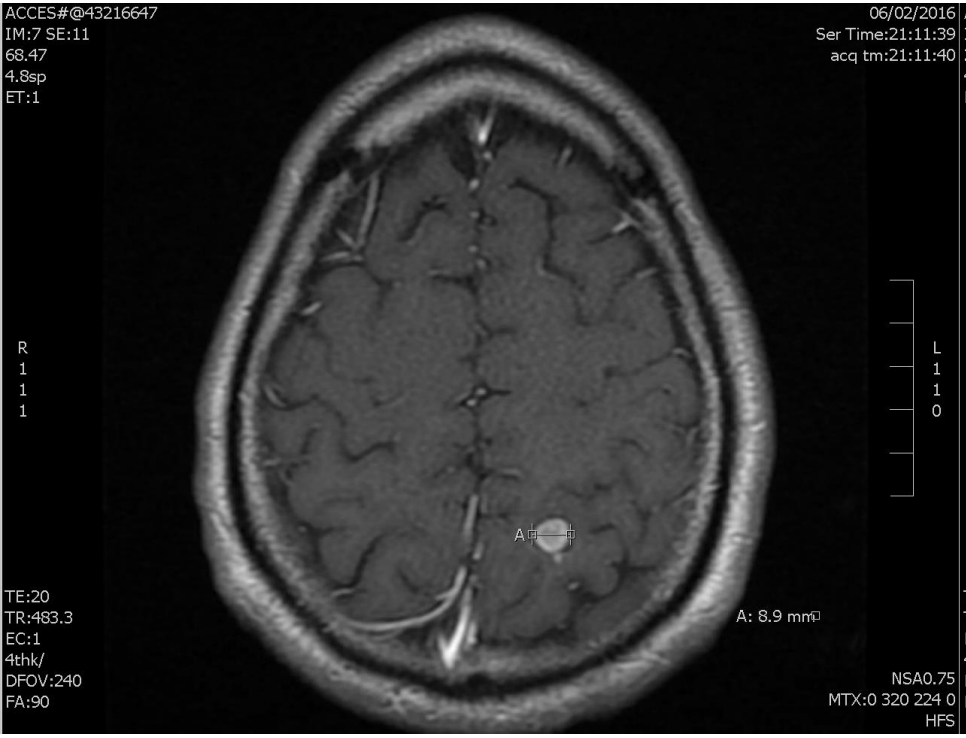
4/20/16

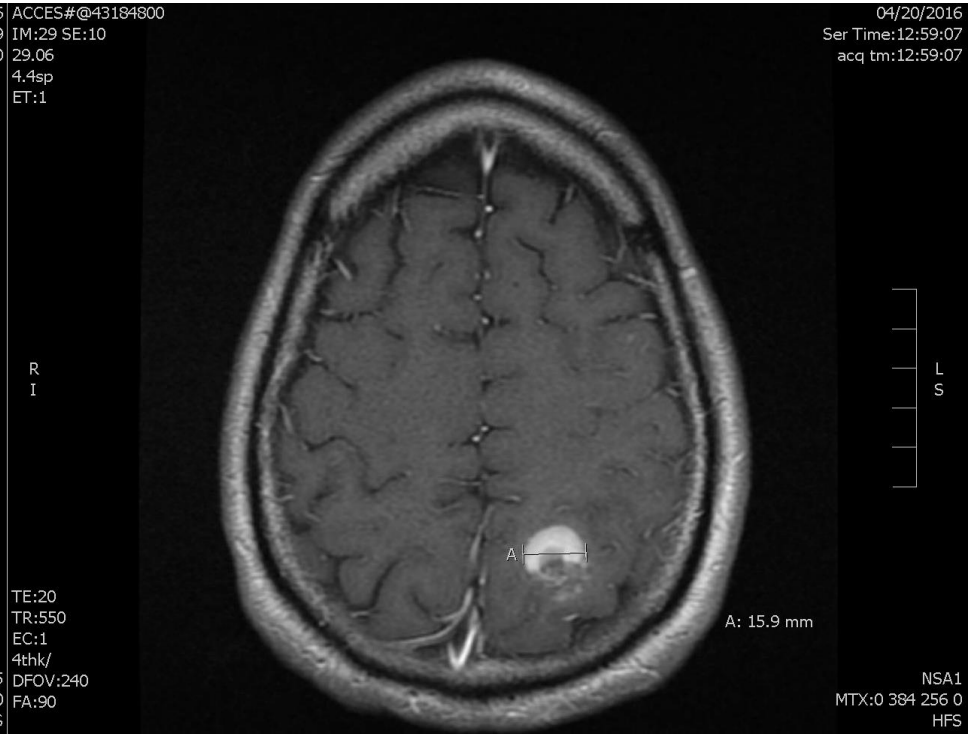


3/15/16

Continued Ipi/nivo. NO steroids
NO liver toxicity
Simulated for SRS but held

Case





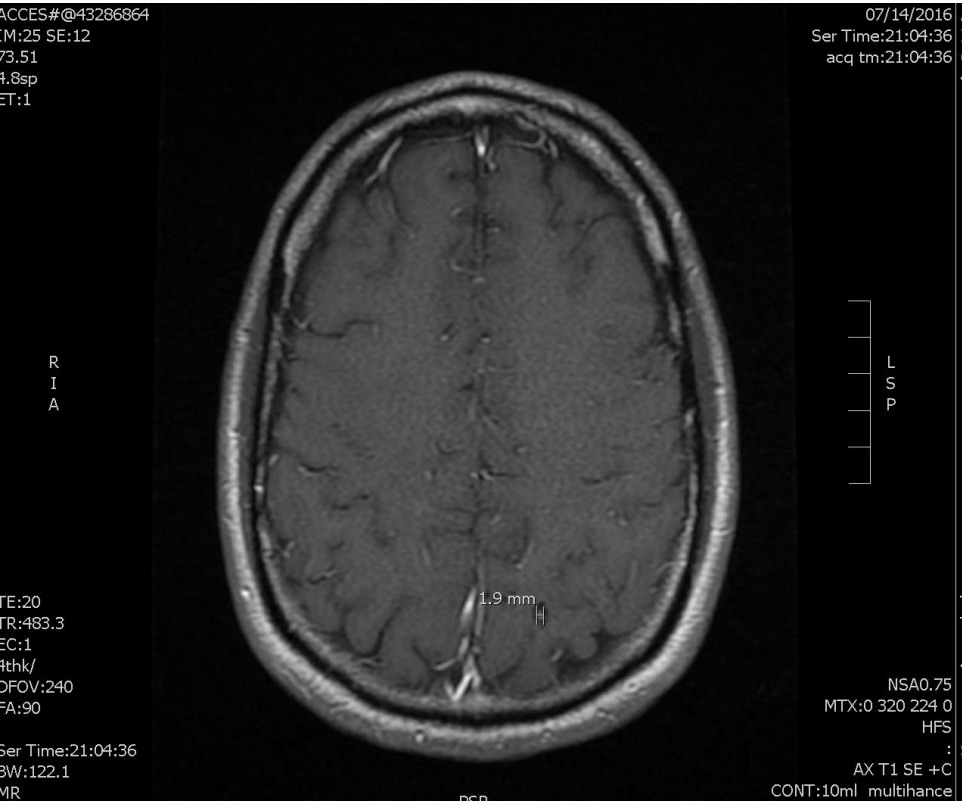
6/2/16

4/20/16

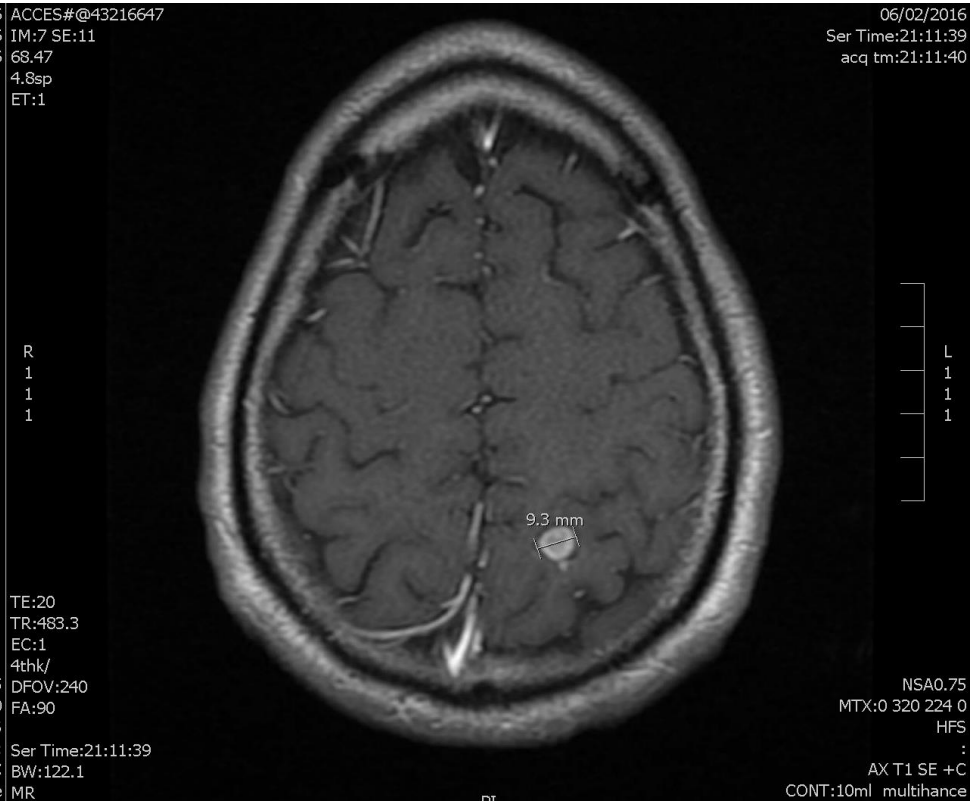
Resolution of skin disease
Improvement in mesenteric tumors

NO new brain lesions, smaller or resolved

Case



7/14/16

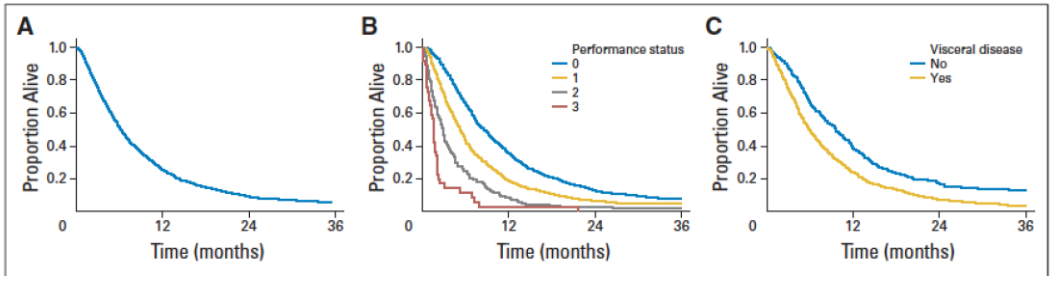


6/2/16

Immune Therapy in Melanoma

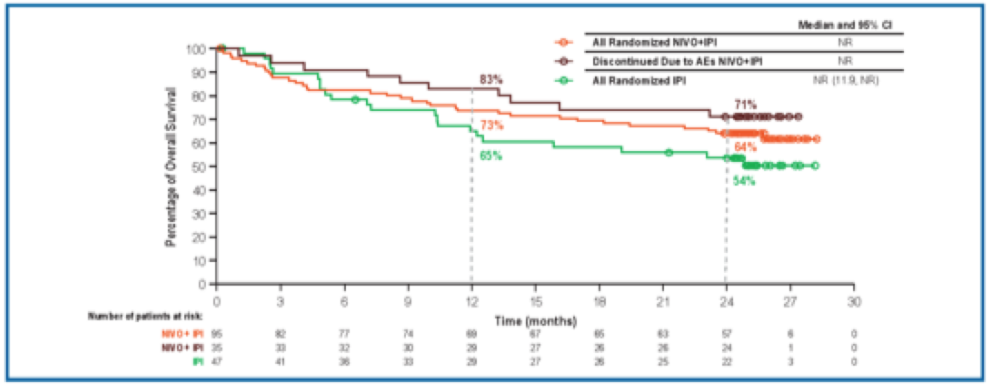
- Challenges
  - Determining which therapy for which patient
  - Toxicity management
  - Response assessment

- Sea Change



Korn JCO 2008

Figure 4A. Overall survival at 2 years of follow-up



Hodi ASCO 2016

Thank you

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