Combinations of Anti-cancer Immune Therapies Built on Checkpoint Inhibition

Combination Approach in Cancer

SITC 28th Annual Meeting

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B7-H1/TIL correlation in melanoma

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Histology	Total	Number of cases/total cases (%)				*P**
		B7-H1+†		B7-H1−		
		TIL+‡	TIL−	TIL+	TIL−	
Benign nevi	40	14/14 (100)	0/14 (0)	4/26 (15)	22/26 (85)	<0.0001
Primary melanomas (in situ or invasive)	54	19/19 (100)	0/19 (0)	15/35 (43)	20/35 (57)	<0.0001
Metastases	56	23/24 (96)	1/24 (4)	7/32 (22)	25/32 (78)	<0.0001
All	150	56/57 (98)	1/57 (2)	26/93 (28)	67/93 (72)	<0.0001

*Fisher's exact test, two-sided, was conducted on the 2 × 2 matrix defined by B7-H1 (±) expression and TIL (±) for each lesion type. †More than 5% melanocytes with membranous expression on IHC. ‡Including mild, moderate, and severe lymphocyte infiltrates and their associated histiocytes/macrophages.

41 % 1% 13% 45%

Immune Profile- Tumor/Host

- Assessment of T cell infiltrate (yes/no)
  - Location of T cell infiltrate and quantity
  - **T cell phenotypes (CD8, CD4, Treg, CD8/Treg ratio)**
  - T cell cytokine production (TH1 versus Th2)
  - Inflammatory gene signatures (stratify?) + Chemokine profile
  - T cell health - anergy or exhaustion (multiple markers to include PD-1, BTLA, TIM3, LAG3, CD80, others)
  - T cell antigen specificity (by expression of CD137 or OX40)
- **Checkpoints/Inhibitors by tumor or infiltrating cells** (protein level)
  - PD-L1, PD-L2, B7-H3, B7-H4, CD200/CD200R, HLA-G, IDO, arginase, TGF-beta, IL-10, VEGF, **others**
- Other immune cells (MDSC) and phenotype/function
- Tumor HLA expression and preservation of Ag presentation
- Vasculature (integrins, PD-L1?)
- Systemic factors – Cytokines, YKL-40, MICA/MICB, Treg, MDSC, Evidence of Ag-specific responses
- Host genetic factors (SNPs)/PD biomarkers

Biological Goal of Combinations with a Checkpoint Inhibitor

- Induce Ag-specific T cells (not present before)
  - Vaccine, Release Ag with RT/targeted agent/chemoRx
- Provide more Ag-presenting cells
- Activation/Modulation of APC
  - Anti-CD40 +TLR, anti-VEGF?
- Drive T-cell expansion to expand pool of Ag-specific T cells
  - Cytokines, vaccines, co-stimulation (CD27, CD137, OX40, GITR, ICOS)
- Change a suppressive systemic (deviated) cytokine/other environment
  - Th1 cytokines, Anti-YKL-40, Reduce MICA/MICB,
- Remove other regulatory checkpoints/suppressive factors for T-cell activation/expansion in periphery (LN)
  - CTLA-4, ?
- **Drive T-cells into microenvironment**
  - CTLA-4, GITR, anti-VEGF, pro-inflammatory agents, targeted agents
- Expand/activate/change ratio of T-cells in microenvironment
  - Cytokines, vaccines, co-stimulation (CD27, CD137, OX40, GITR, ICOS)
- **Remove other checkpoints/ T-cell suppression in microenvironment**
  - Treg (CTLA-4), cytokines and anti-cytokines, Ido, arginase, multiple checkpoints (PD-1 pathway, other B7-H, KIR, HLA-G, CD200, TIm3, LAG3)
- Restore tumor Ag presentation

- **Problem -→ Identifying the critical deficiency(ies) in individual patients**

History of Immune Modulatory Combinations in the BC (before checkpoints) era

- Enormous number of phase 1 trials with cytokines, vaccines, and antibodies (ADCC)
- Most did not go beyond phase 1 or phase 2
- Very few randomized trials
- No successful randomized trials
  - IL-2 + gp100 peptide vaccine?

Endpoints for Combinations with CTLA-4 or PD-1 pathway blockade

• ORR	~15% - **30-40%**
• iRC RR -	+5-10% to ORR
• CR –	low rate but undefined
• CBR/DCR –	**should never be used**
• **Aggregate clinical activity -**	**?**
• 'Deep' (> 80% regression) responses -	?
• Median duration of response –	19 months to 24 months
• Median PFS -	< 4 months
• 1-year and 2 year PFS –	25/10% to 36/27%
• 3 year PFS	?
• Median Survival –	10-12 to **16.8 months**
• 1- year and 2-year survival	47/29% to 62/43%

Data apply to metastatic melanoma, may vary by prior Rx

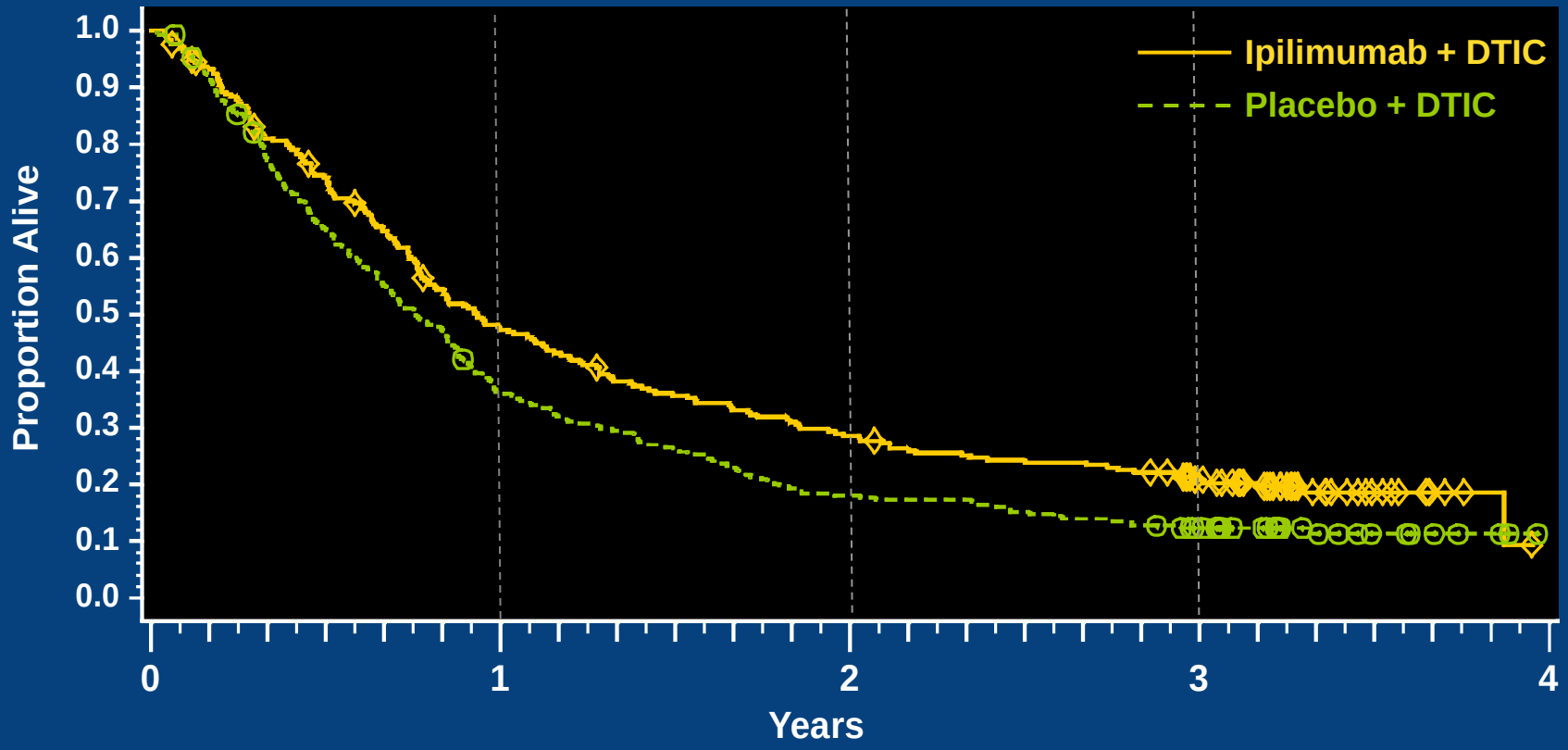
Immune Modulatory Combinations – Ground Rules

- Compared to single agent:
  - Potentially different toxicity and activity profile
  - Not necessarily amplification or addition to single agent profile
  - May not follow single agent predictive or PD biomarker profile
- Should not undertake combination unless:
  - Compelling rationale (biology, correlative study, preclinical data)
  - Clear/`meaningful' prospective criteria for go-no go decision in phase 1-2
  - Expect large increase in overall activity in unselected populations (high signal gain) or
  - Selection criteria for populations with defined expected activity (combination addresses specific biology), and/or
  - Commitment to conduct appropriate phase 2 and randomized trials to establish superiority of combination to single agents
  - **Otherwise -fugheddaboutit**

Anti-CTLA4 Combinations

- **Chemotherapy (DTIC, Temozolomide, Fotemustine, CBDCA/paclitaxel)**
- **Radiation**
- **Targeted Agents**
  - BRAF inhibitors (Vemurafenib, dabrafenib +/- trametinib)
  - Other small molecule targeted agents
  - **Antibodies against signaling receptors (EGFR?)**
- Vaccines (long peptides, whole proteins, cells)
- Cytokines or anti-Cytokines (**IL-2, Interferon-alfa, GM-CSF**, IL-15, IL-12, **IL-21**, Anti-TGF-beta, others)
- Anti-angiogenesis agents (**bevacizumab, sunitinib**)
- **Anti-CD40**
- **Anti-PD1** or PD-L1
- **IDO or arginase inhibitors**
- Anti-CD137 or anti-OX40
- Anti-GITR
- Adoptive Cell Therapy?

Study 024: Overall Survival



Estimated Survival Rate	1 Year	2 Year	3 Year*
Ipilimumab + DTIC n=250	47.3	28.5	20.8
Placebo + DTIC n=252	36.3	17.9	12.2

*3-year survival was a post-hoc analysis

PRESENTED AT: ASCO Annual '11 Meeting

Study 024: Tumor Response

	Ipilimumab + DTIC n=250	Placebo + DTIC n=252
Disease Control Rate, n (%)	83 (33.2)	76 (30.2)
BORR (CR + PR), n (%)	38 (15.2)	26 (10.3)
Complete response	4 (1.6)	2 (0.8)
Partial response	34 (13.6)	24 (9.5)
Stable disease	45 (18.0)	50 (19.8)
Progressive disease	111 (44.4)	131 (52.0)
Duration of response, months	19.3	8.1

BORR=Best Overall Response Rate

Patients (%) not evaluable for response (no follow-up scans): 56 (22.4) vs 45 (17.9)

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Ipilimumab 10 mg/kg + Chemotherapy Combination Results

Di Giacomo et al
Patel et al

DTIC	Temozolomide		Fotemustine	
250	N=	64	N=	86
1.6%	**CR**	**10 (15.6%)**	**irCR**	**6 (7%)**
13.6%	irPR	8 (12.5%)	irPR	19 (22%)
18%	irSD	29 (45%)	irSD	15 (17%)
15.2%	ir (PR +CR)	**28%**	ir (PR + CR)	**29%**
33.2%	DCR	73%	DCR	40%
2.8	Median PFS 6-month PFS	22 weeks / 5.1 months **45.1%**	Median irPFS, months (95% CI)	**5.3 (3.4-7.1)**
47.3 (1 year)	1-year survival rate	TE	1-year survival rate, % (95% CI)	52.6 (41.8-63.4)
11.2	Median OS	TE	Median OS, months (95% CI)	13.3 (8.9–19.9)

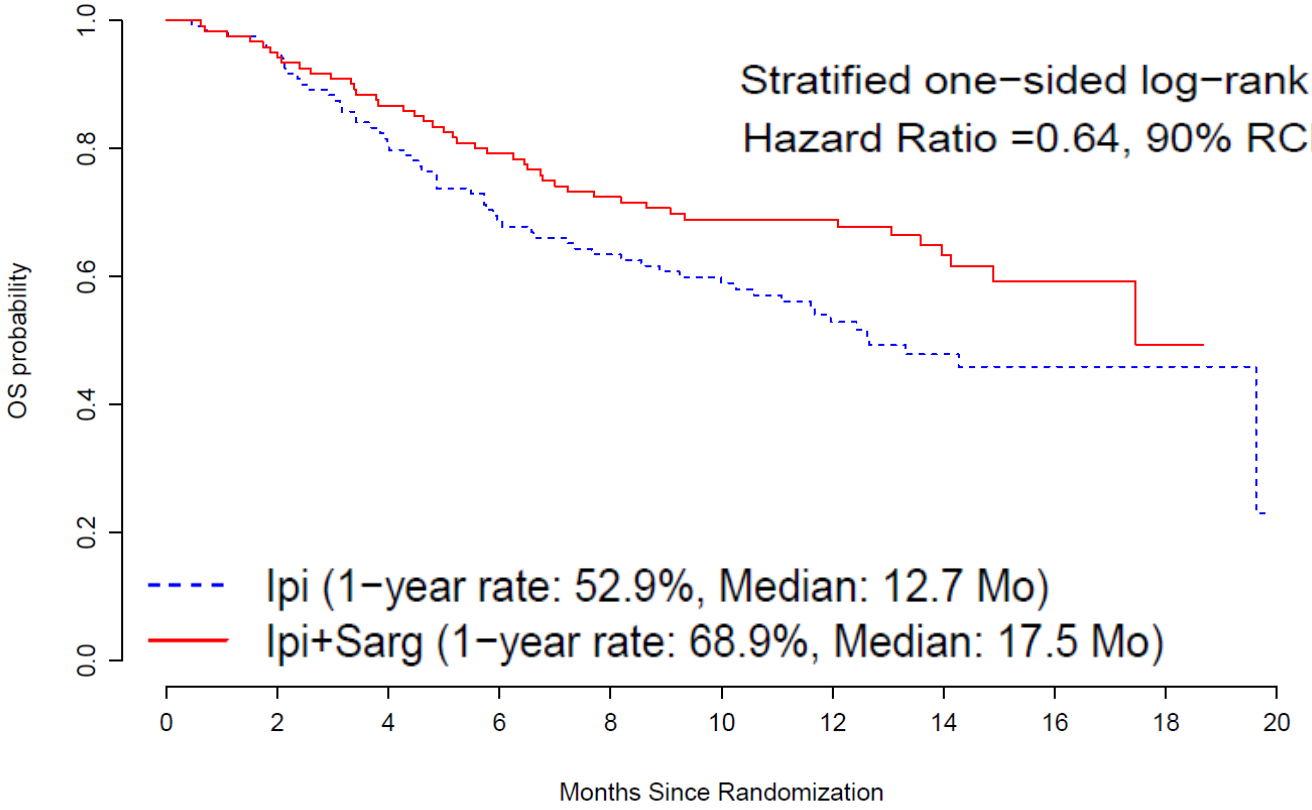
Ipilimumab Long-Term Survival Rates: Consistency Across Phase 2 Melanoma Experience

Study (10mg/kg treatment groups)	12-month survival rate % (95% CI)	24-month survival rate % (95% CI)
CA184-008 (N=155)		
Previously treated	**47.2** (39.5-55.1)	**32.8** (25.4-40.5)
CA184-022 (n=72)*		
Previously treated	**48.6** (36.8-60.4)	**29.8** (19.1-41.1)
CA184-007 (N=115)		
Previously treated – P (n=25)	**50.8** (31.5-71.1)	**24.2** (8.0–42.8)
Previously treated – B (n=37)	**49.9** (33.3-66.6)	**31.6** (16.5-47.6)
Treatment-naive – P (n=32)	**71.4** (55.2-87.2)	**56.6** (38.4-74.3)
Treatment-naive – B (n=21)	**65.9** (45.0-85.7)	**56.5** (30.6-81.0)

* For study -022, the statistics are for the 72 patients in the 10 mg/kg arm only.
CI = confidence interval. P = placebo. B = budesonide.

Source: ASCO 2009 Abstract #9033 O'Day.

Overall Survival



ORR and PFS ->
No differences

Number at risk

122	114	94	80	72	64	49	28	14	6	0	trt=Ipi
123	115	104	94	84	75	63	39	11	2	0	trt=Ipi+Sarg

	Arm A: Ipi+Sarg (n=123)	Arm B: Ipi (n=122)	Comparisons
Overall Survival (OS)			
- Median , (95% CI)	17.5 mo (14.9, NR)	12.7 mo (10.0, NR)	P1*=0.014 (Stratified Logrank test)
- 1-Year OS rate, (95% CI)	68.9% (60.6, 85.5)	52.9% (43.6, 62.2)	
- HR 90% RCI for HR	0.64 (-, 0.90)	Reference	P1* =0.014 (Stratified Cox model)

Phase 1 of Bevacizumab (10 mg/kg) + ipilimumab

- **Combination produced unexpected pattern of irAEs**
  - Less colitis, more endocrine (5/22 hypophysitis), 2 cases of uveitis
- **Clinical response higher than expected (n=22)**
  - CR/PR (32%), SD> 6 months (32%)
- **> CM and EM T-cell expansion compared to historical control**
- Demonstrated biological effects on tumor blood vessels and angiogenic T-cell recruitment

Hodi et al, ASCO 2011

Summary of Clinical Activity with IFN/Tremelimumab – Tarhini et al, ASCO 2010

		IFN/Treme
Study Size (number of patients)		37*
Response	Rate (%)	9/35 (26%)
	Durability (mo)	6, 6, 12+, 14+, 18+, 20, 28+, 30, 37+
SD	Rate (%)	14/35 (40%)
	Durability (mo)	1.5-21
DCR (%)		23/35 (66%)
PFS (median, mo)		6.4
OS (median, mo)		21

*Two patients were non-evaluable for response (no response data available)
*One unconfirmed responder→ PD → surgery → NED (16+)
*One PD→TMZ/Decitabine x2wks→ PD → NED
**One patient was non-evaluable for response

Phase 1/2 of IL-2 + ipilimumab in metastatic melanoma

- Schedule
  - Ipi days 1, 22, 43
  - IL-2 720,000 IU/kg q8h up to 15 doses, beginning days 23 and 44
- Patients
  - 12 in dose escalation phase
  - 24 at 3.0 mg/kg of ipilimumab
- Toxicity: 5 with grade 3-4 autoimmunity
- Activity
  - Objective RR: 25%
  - CR – 17% (6 patients: 77+, 74+, 72+, 71+, 71+, and 69+ months)
  - Median survival – 16 months

PD-1/PD-L1 Pathway Antagonist: Combinations

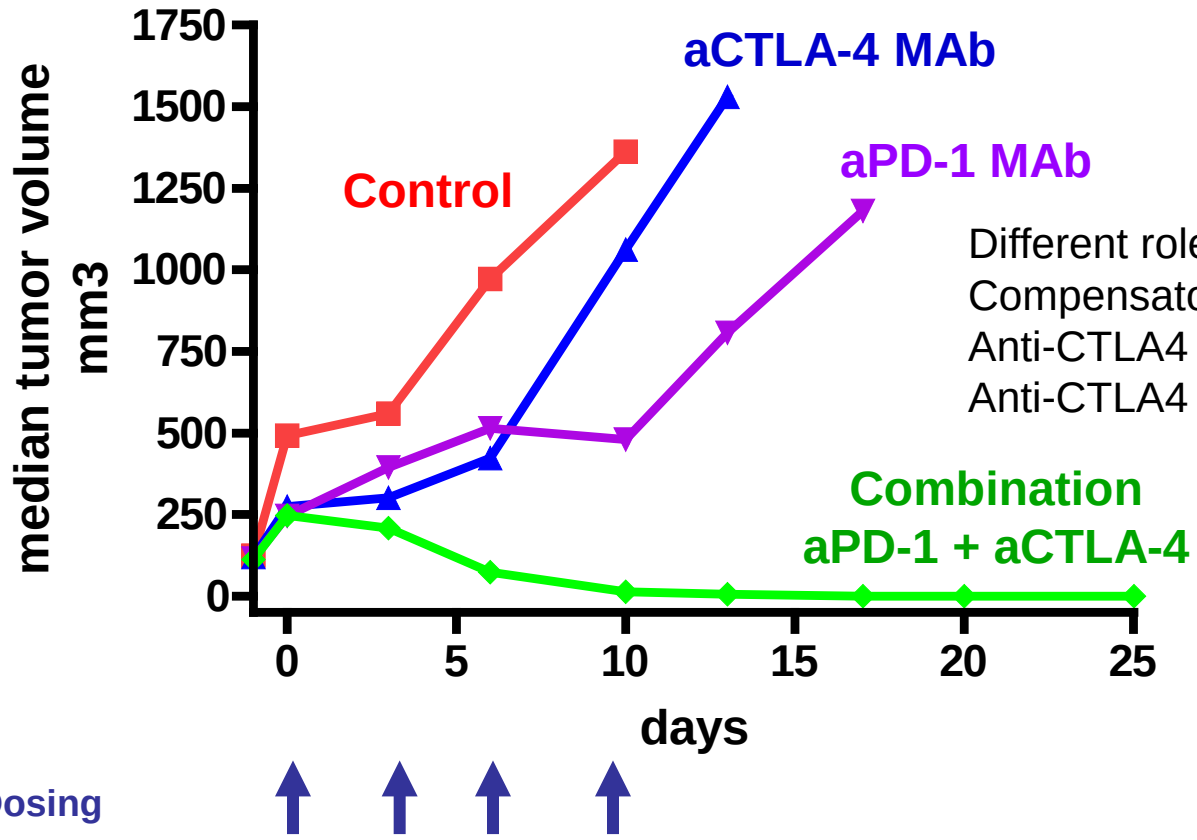
- Non-Inflamed Tumors: Expand and/or drive T-cells into microenvironment
  - Other immune therapies (**anti-CTLA-4**, co-stimulatory agents?, IFNs, gamma-chain cytokines, targeted delivery of TLR, TCR-CD3 fusion proteins)
  - Targeted agents (vemurafenib, RTKis)
  - Anti-VEGF/anti-angiogenesis
  - Epigenetic modifiers
  - Dasatinib?
  - Vaccines?
  - Adoptive T-cell therapy (TIL, CARs, or TCR-modified PBL)
- Inflamed Tumors: Other agents that block T-cell inhibitory mechanisms within tumor
  - Anti-LAG3, anti-TIM3
  - Blockade of other exhaustion molecules
  - Blockade of other B7-H family members
  - Anti-PD-L1?
  - IDO inhibitors

PD-1 Pathway Blockade Combinations

- Ipilimumab (anti-CTLA-4) – in multiple malignancies
- Tremelimumab (anti-CTLA-4)
- Vemurafenib (LFTs?)
- Dabrafenib - Trametinib
- Bevacizumab
- IFNs – RCC/melanoma
- Erlotinib (EGFRi) – NSCLC
- Sunitinib or Pazopanib (VEGFRi) – RCC
- IL-21 – RCC/NSCLC
- anti-LAG3
- anti-KIR
- peptide vaccines
- Chemotherapy
- Anti-OX40

Synergistic Activity with Anti-PD-1 and Anti-CTLA-4 Antibodies

Combination of Non-Efficacious Doses of anti-PD1 and anti-CTLA-4 Antibodies is Efficacious in Mouse Model



Different roles in T cell Differentiation-
Compensatory upregulation
Anti-CTLA4 elimination of tumor Treg
Anti-CTLA4 induced tumor T cell infiltration

Provided by Alan Korman, BMS

Table 1. Cynomolgus monkey toxicology signal with concurrent nivolumab and ipilimumab treatment[6]

Group	Male/ Female	Treatment	Dose mg/kg	Diarrhea[a] n/N	Mean Spleen Weight[b] Male/Female Grams	Spleen Pathology[c] n/N	Gastrointestinal Tract Pathology[d] n/N
1	5/5	Control	—	0/10	3.9/2.8	0/6	0/6
2	5/5	Nivolumab Ipilimumab	10 3	2/10	4.0/3.6	2/6	2/6
3	5/5	Nivolumab Ipilimumab	50 10	4/10	6.1/4.05	4/5	3/5

[a]Incidence of repeated diarrhea
[b]Mean spleen weight on day 30
[c]Incidence of lymphoid follicle hypertrophy or marginal zone expansion
[d]Minimal, diffuse lymphoplasmacytic inflammation in the lamina propria with concurrent enlargement of the colonic or pelvic lymph nodes
n/N defines the number of positive observations (n) among those animals evaluated (N)

Clinical activity and safety of nivolumab (anti-PD-1, BMS-936558, ONO-4538) in combination with ipilimumab in patients with advanced melanoma

Jedd D. Wolchok,[1] Harriet Kluger,[2] Margaret K. Callahan,[1] Michael A. Postow,[1] RuthAnn Gordon,[1] Neil H. Segal,[1] Naiyer A. Rizvi,[1] Alexander M. Lesokhin,[1] Kathleen Reed,[2] Matthew M. Burke,[2] Anne Caldwell,[2] Stephanie A. Kronenberg,[1] Blessing U. Agunwamba,[1] William Feely,[3] Quan Hong,[3] Christine E. Horak,[3] Alan J. Korman,[4] Jon M. Wigginton,[3] Ashok Gupta,[3] and Mario Sznol[2]

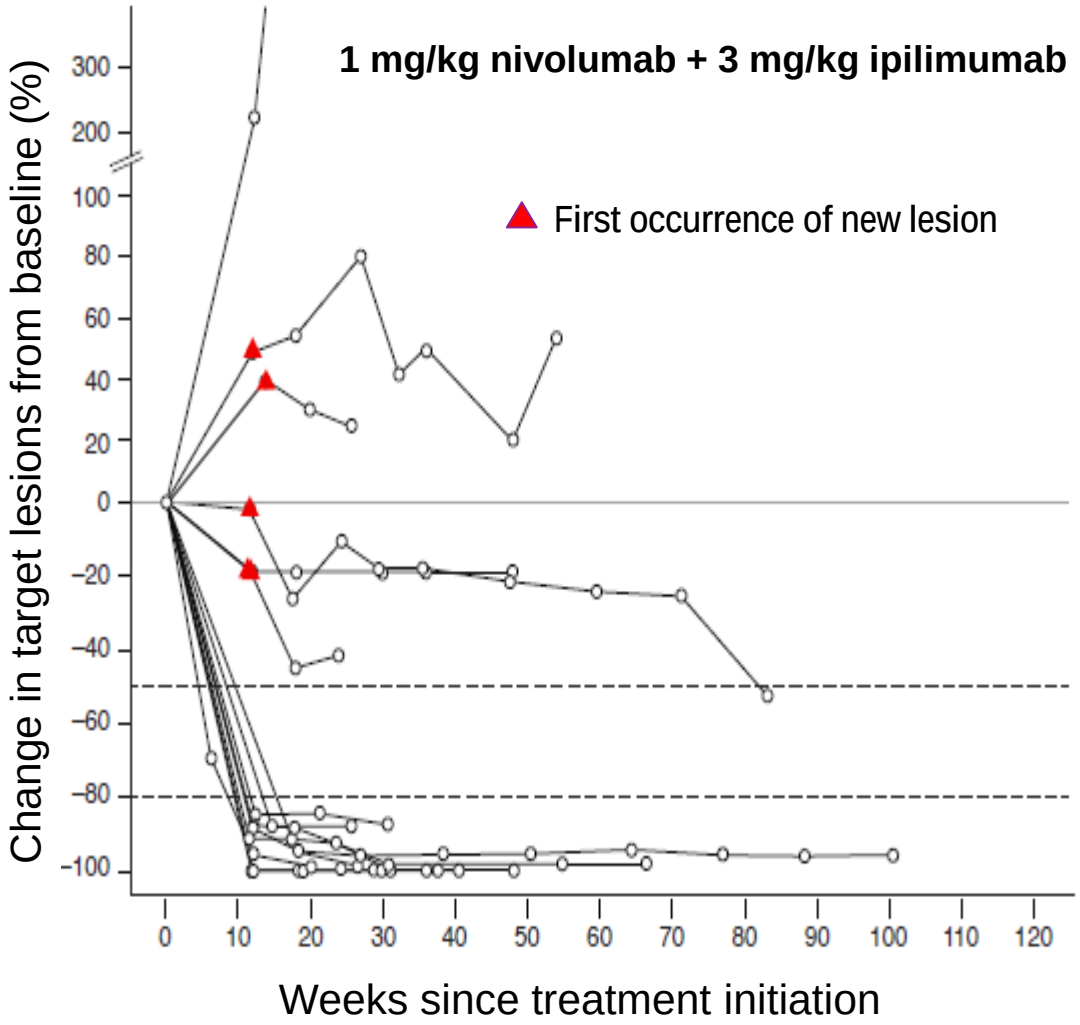
[1]Ludwig Center at Memorial Sloan-Kettering Cancer Center, New York, NY; [2]Yale University School of Medicine and Yale Cancer Center, New Haven, CT; Bristol-Myers Squibb, [3]Princeton, NJ and [4]Redwood City, CA

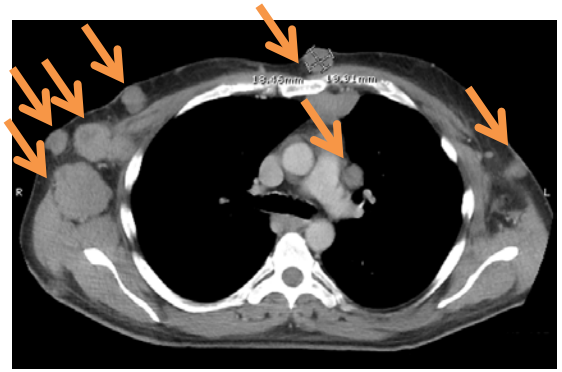
Clinical Activity: Concurrent Regimen

Dose (mg/kg)		Response Evaluable Patients n	CR n	PR n	Objective Response Rate % [95% CI]	Aggregate Clinical Activity Rate % [95% CI]	≥80% Tumor Reduction at 12 wk n (%)
Nivolumab	Ipilimumab						
0.3	3	14	1	2	21 [5-51]	50 [23-77]	4 (29)
1	3	17	3	6	53 [28-77]	65 [38-86]	7 (41)
3	1	15	1	5	40 [16-68]	73 [45-92]	5 (33)
3	3	6	0	3	50 [12-88]	83 [36-100]	0
Concurrent		52	5	16	40 [27-55]	65 [51-78]	16 (31)

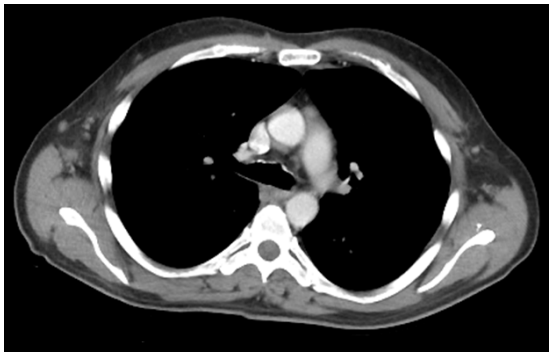
- With 1 mg/kg nivolumab + 3 mg/kb ipilimumab, 53% of patients had confirmed objective responses (3 CRs and 6 PRs)
- All 9 of these had ≥80% tumor reduction, 7 at 12 weeks and 2 at their first assessment, which was after week 12
- ≥80% tumor reductions appear infrequently (<10%) in the nivolumab and ipilimumab monotherapy experiences

Rapid and Durable Changes in Target Lesions



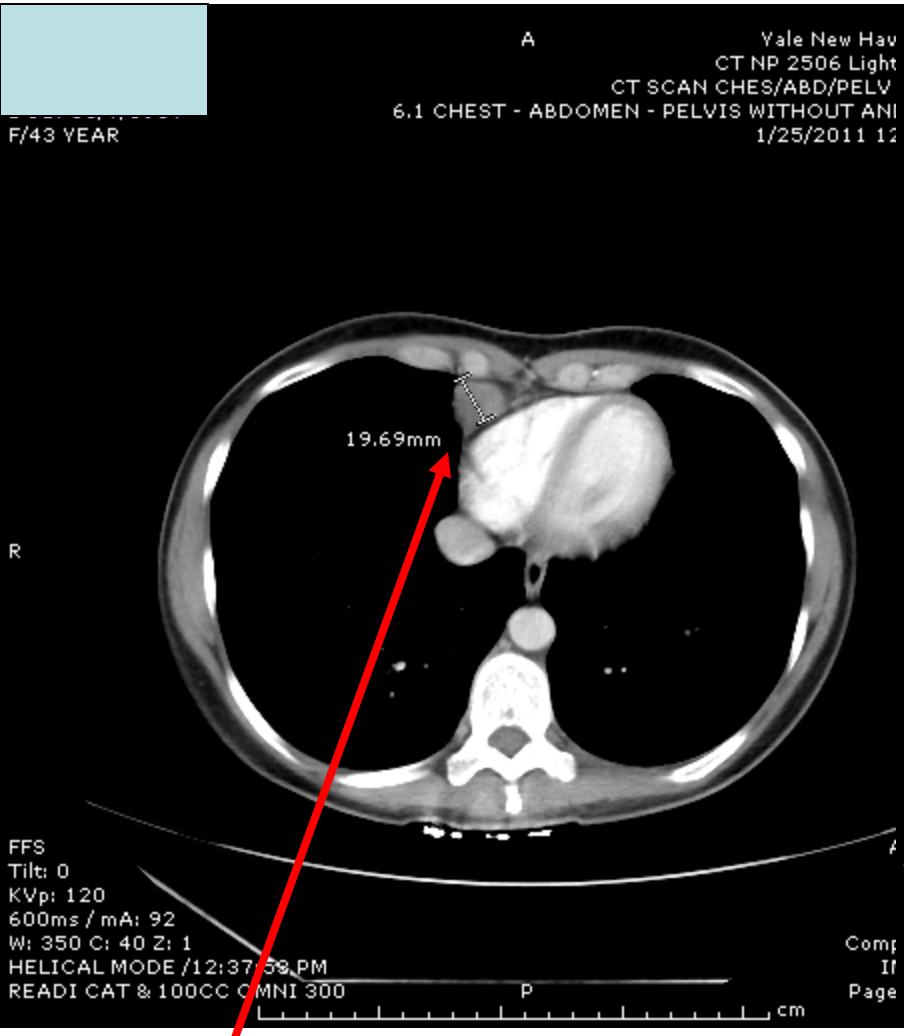


Pre-treatment



12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown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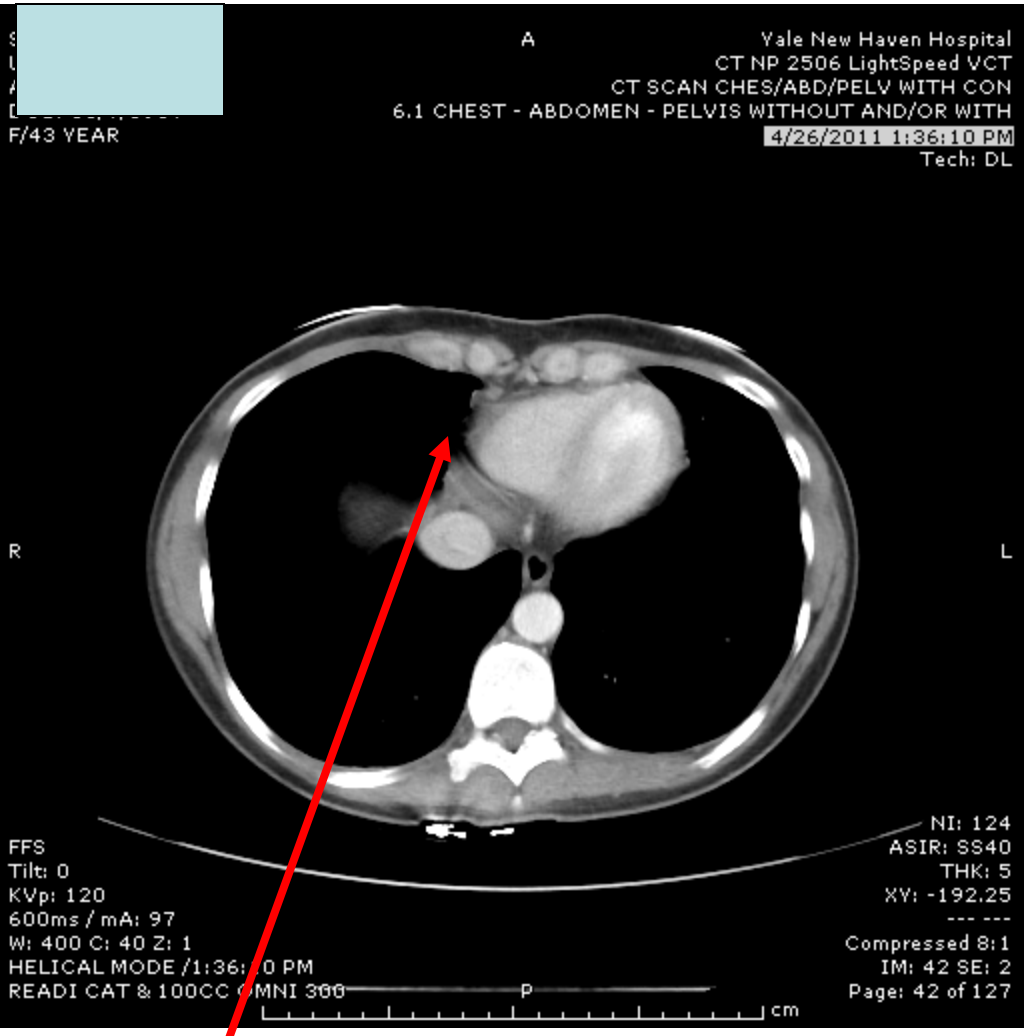
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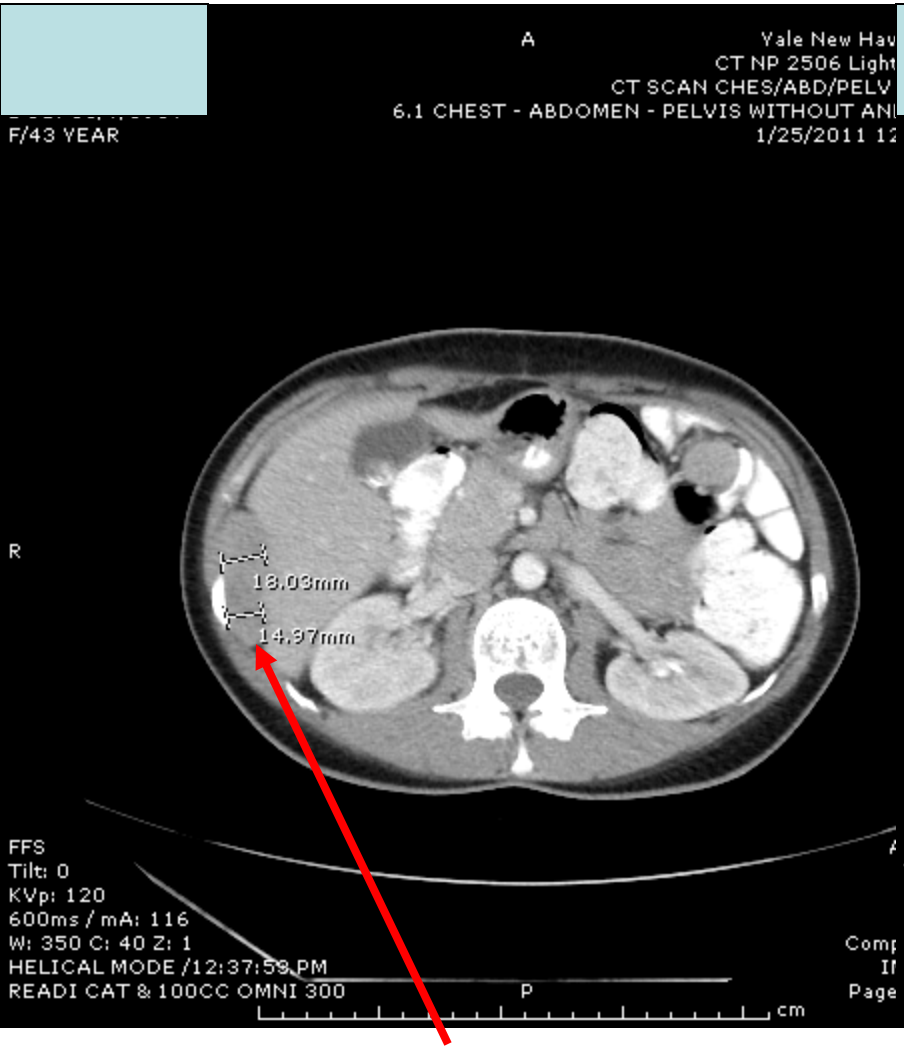
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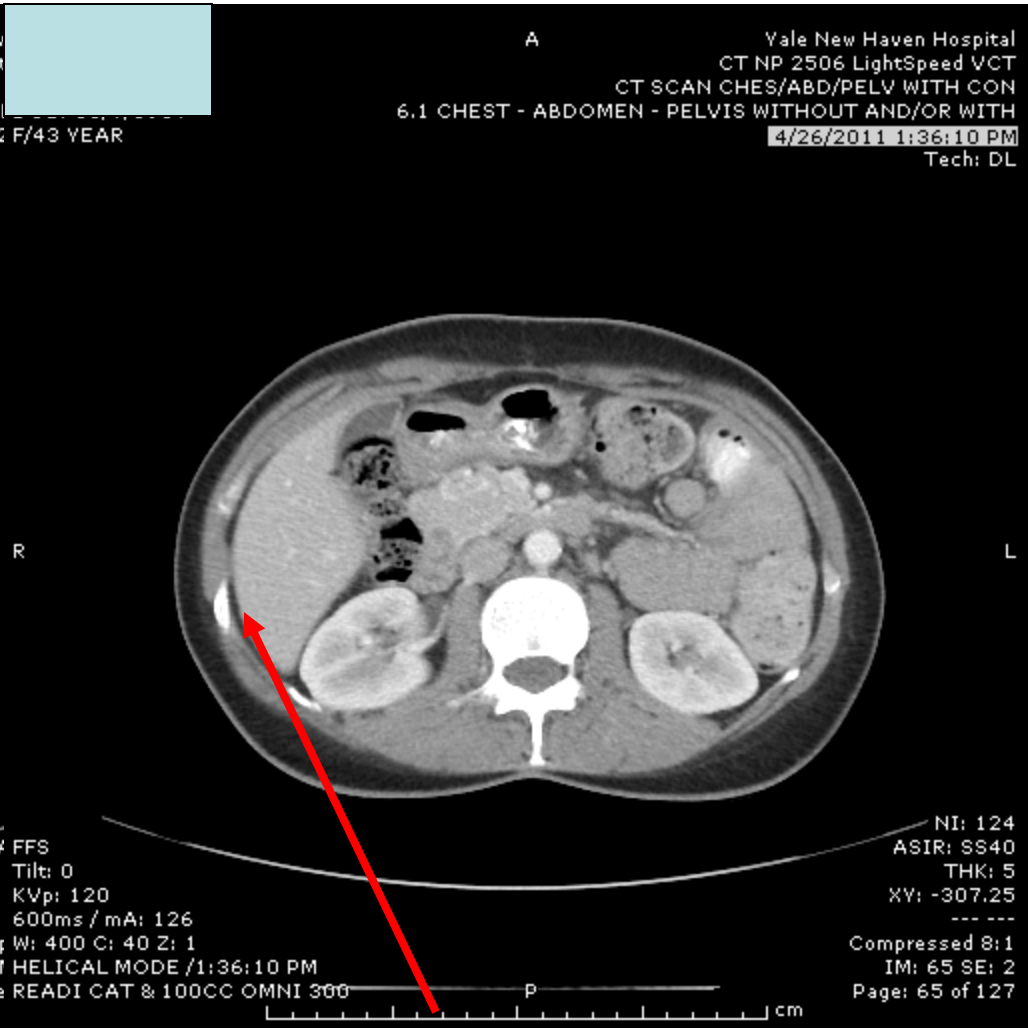
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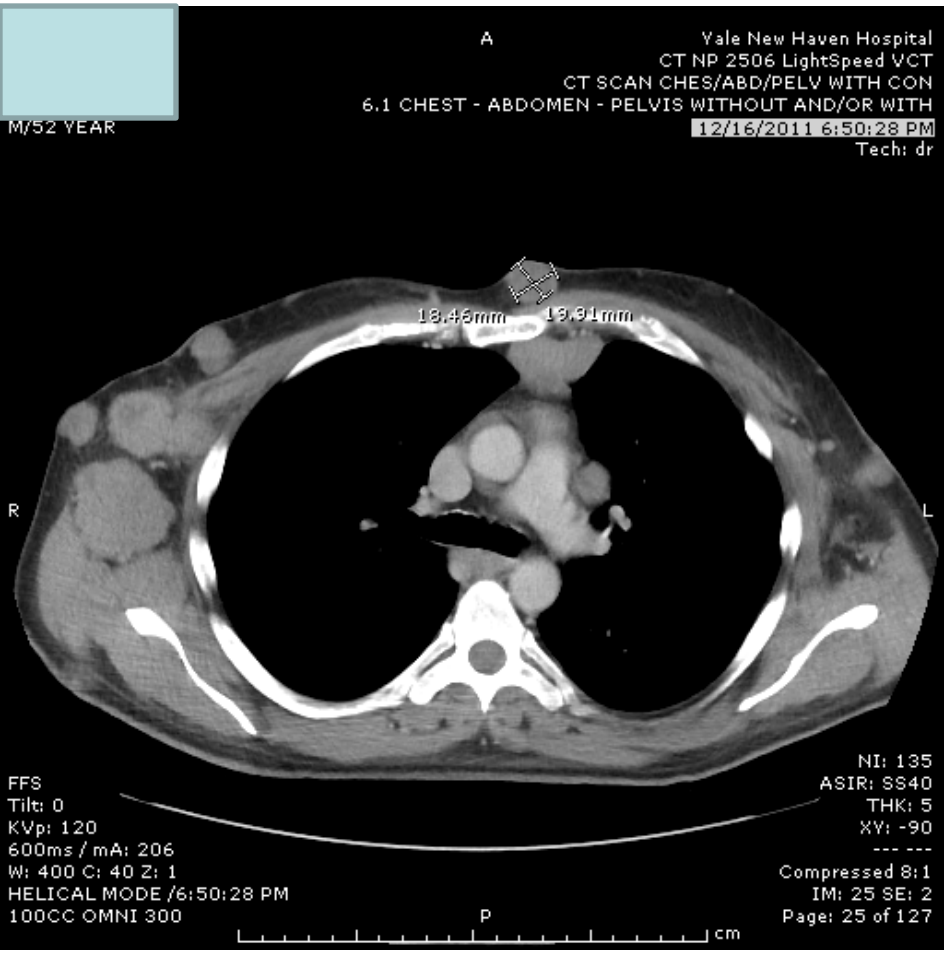
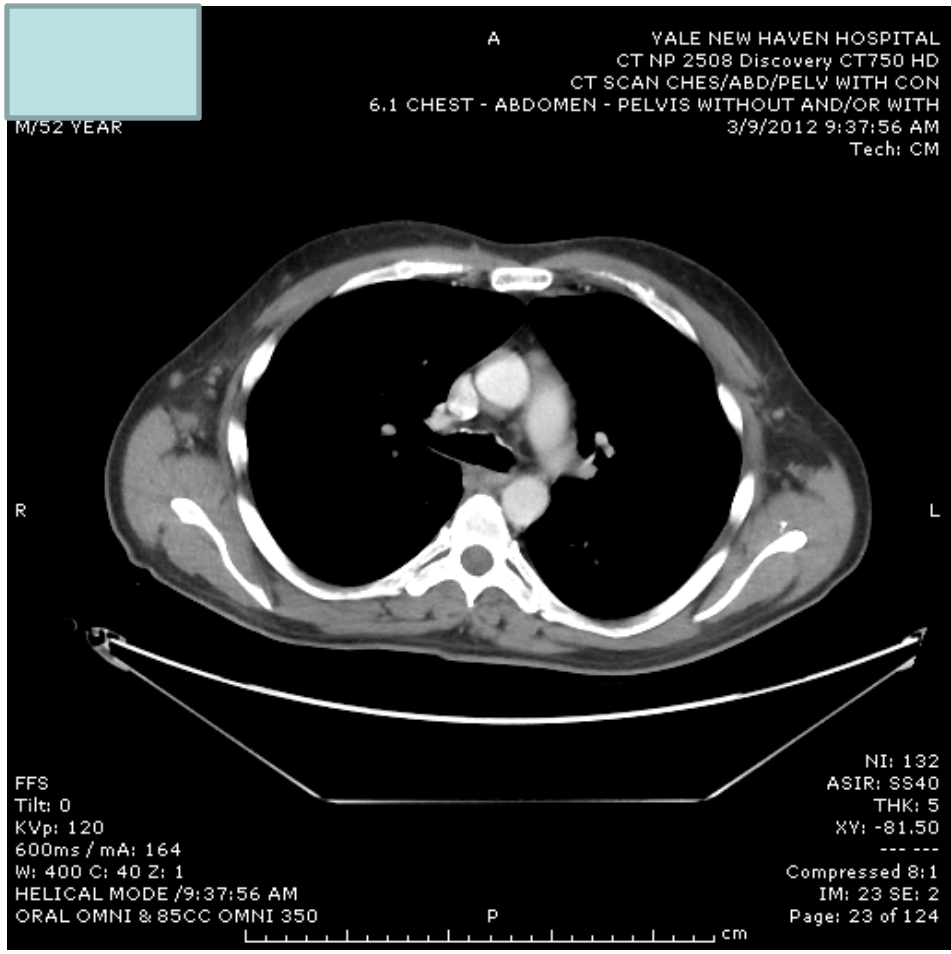
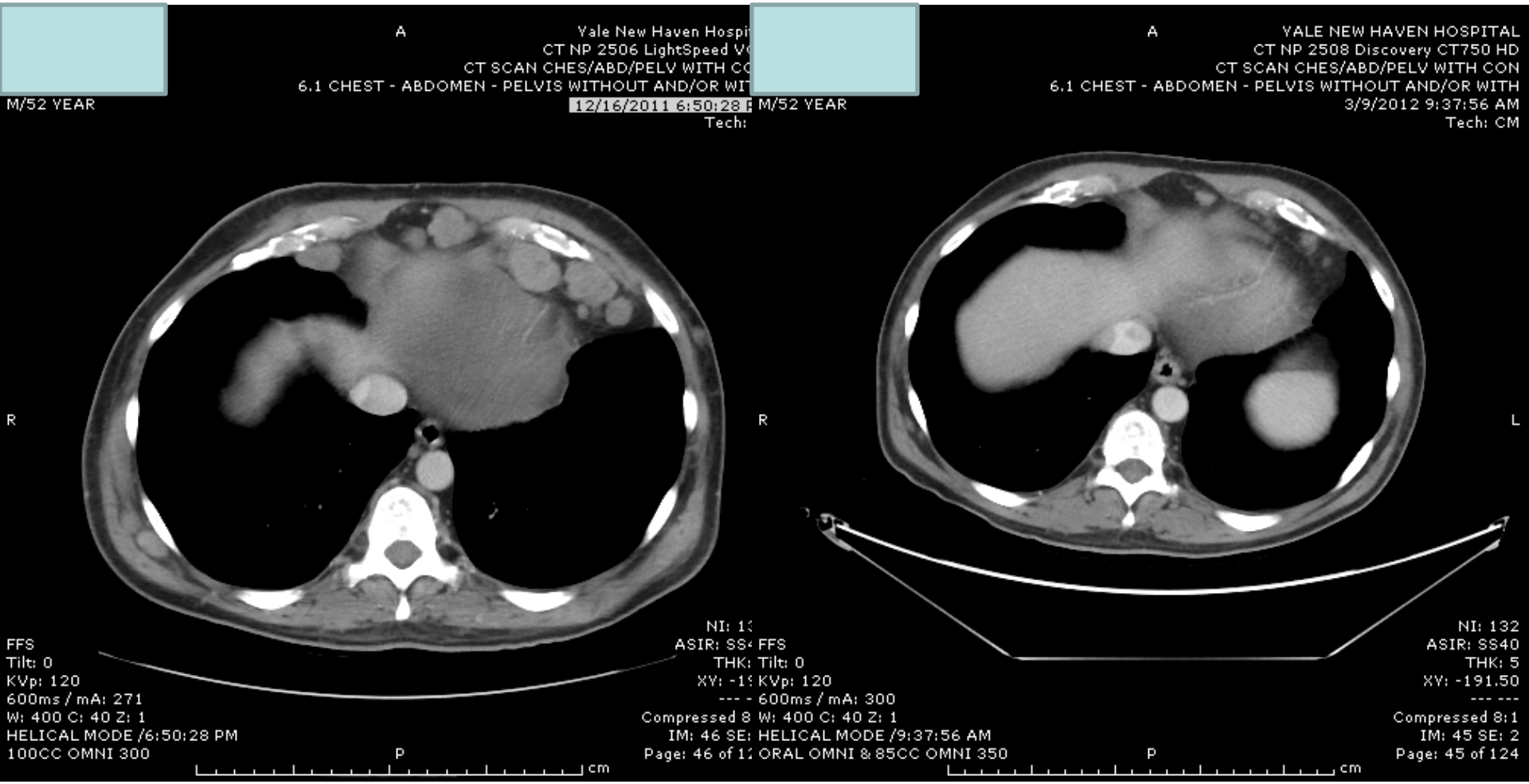
Response to ipi/anti-PD1, 3/1 dose level

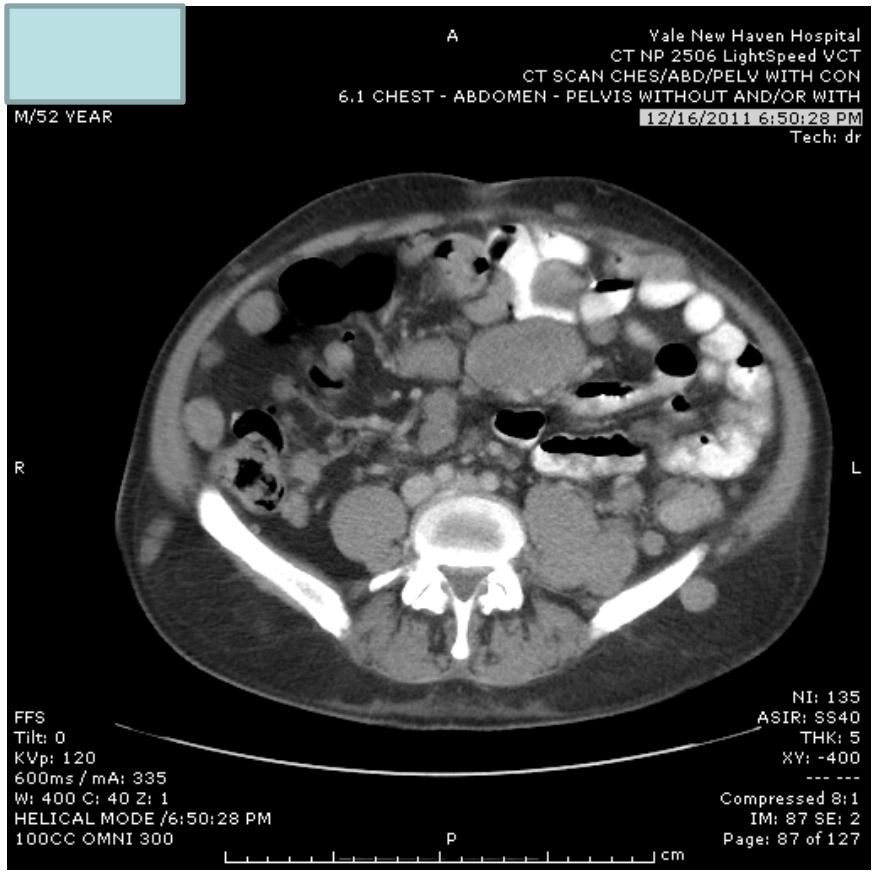


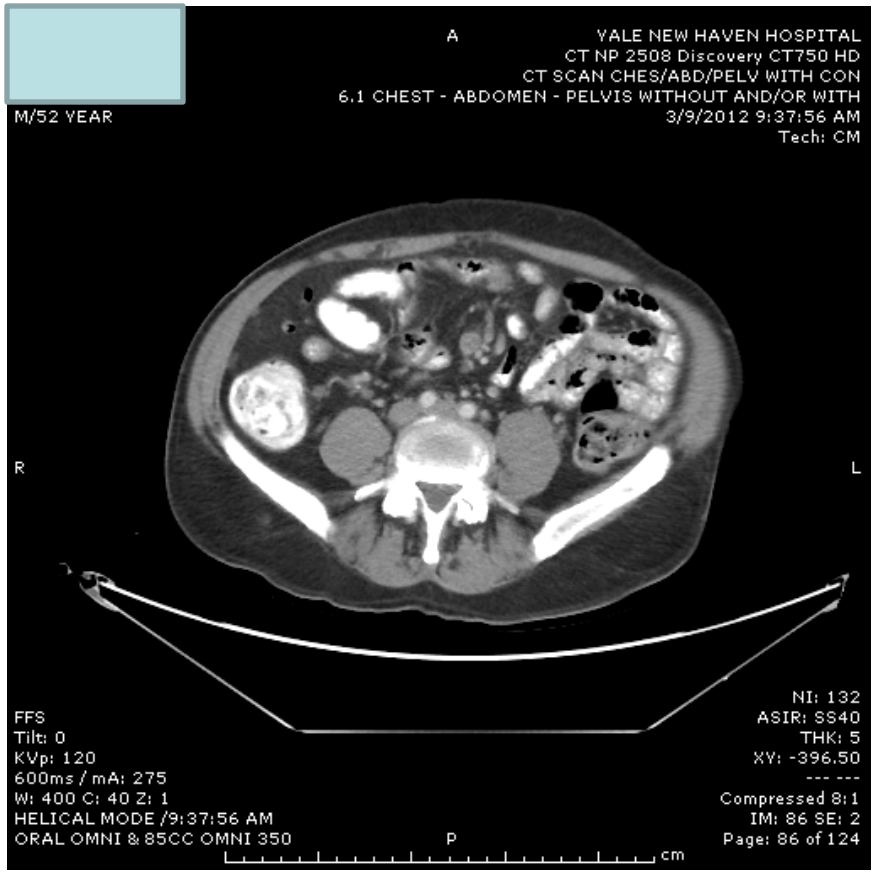


Response to ipi/anti-PD1, 3/1 dose level

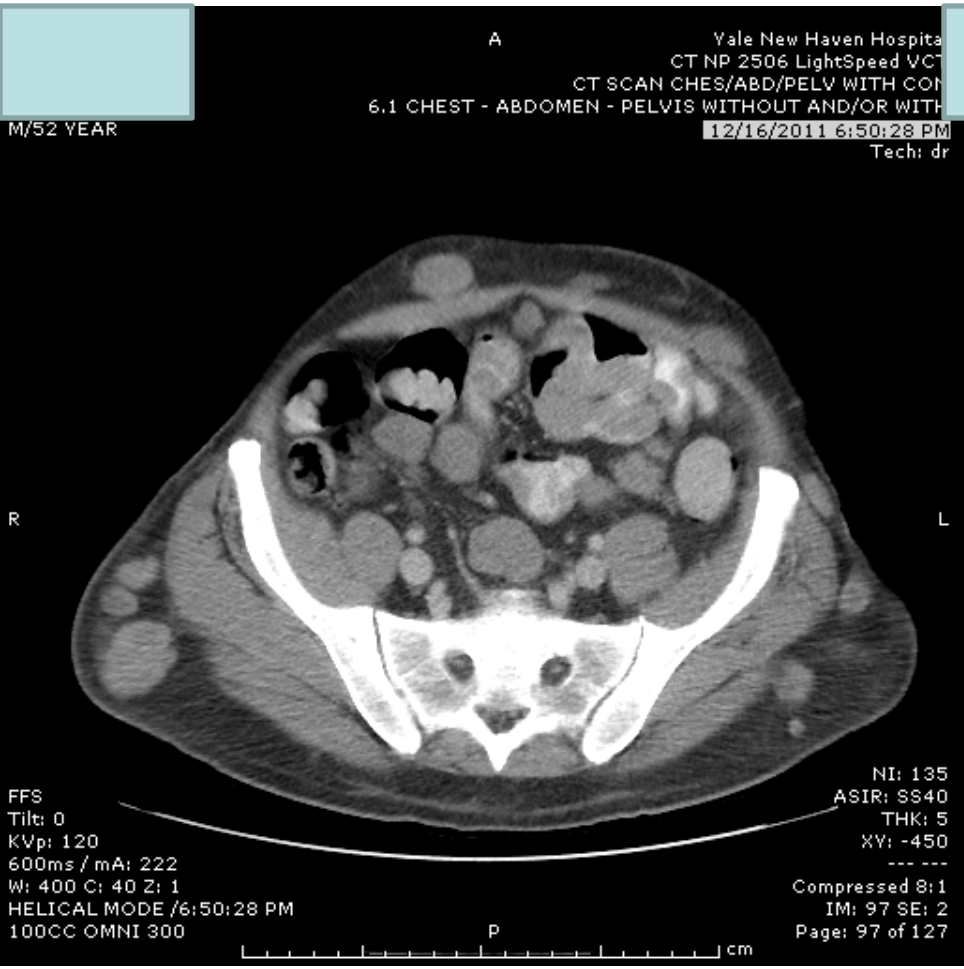


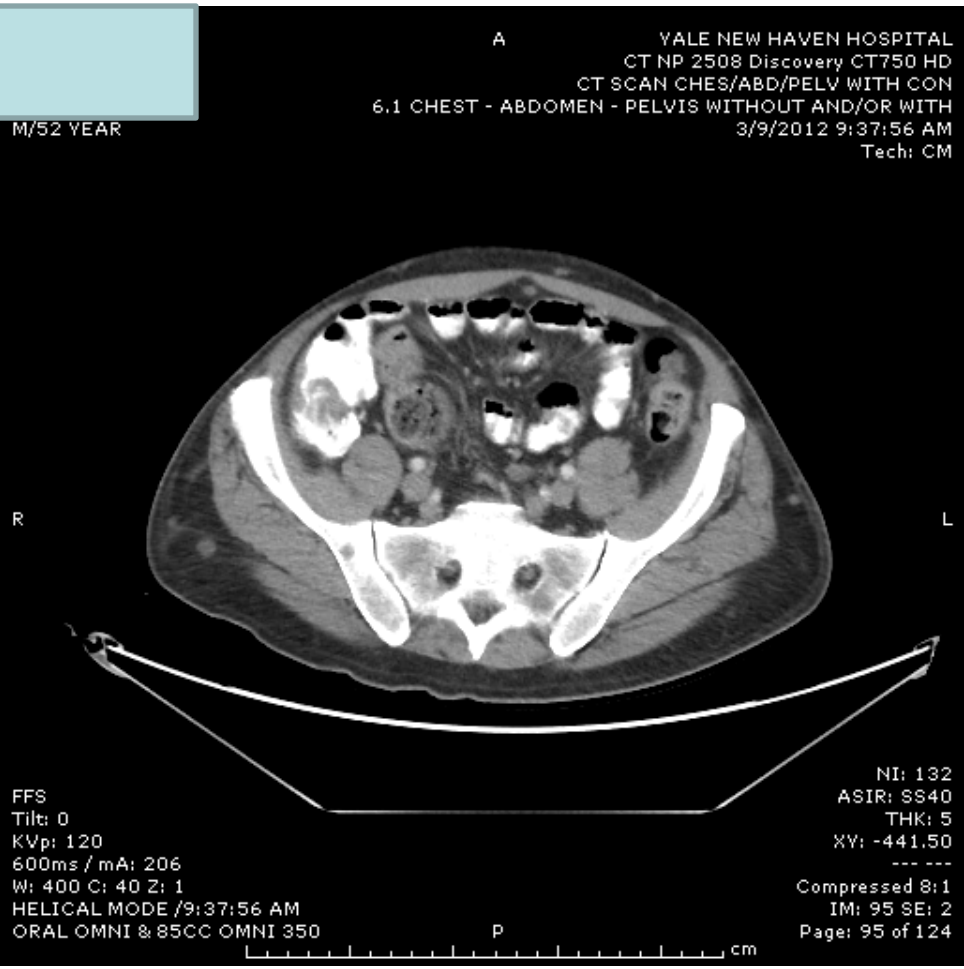
Response to ipi/anti-PD1, 3/1 dose level



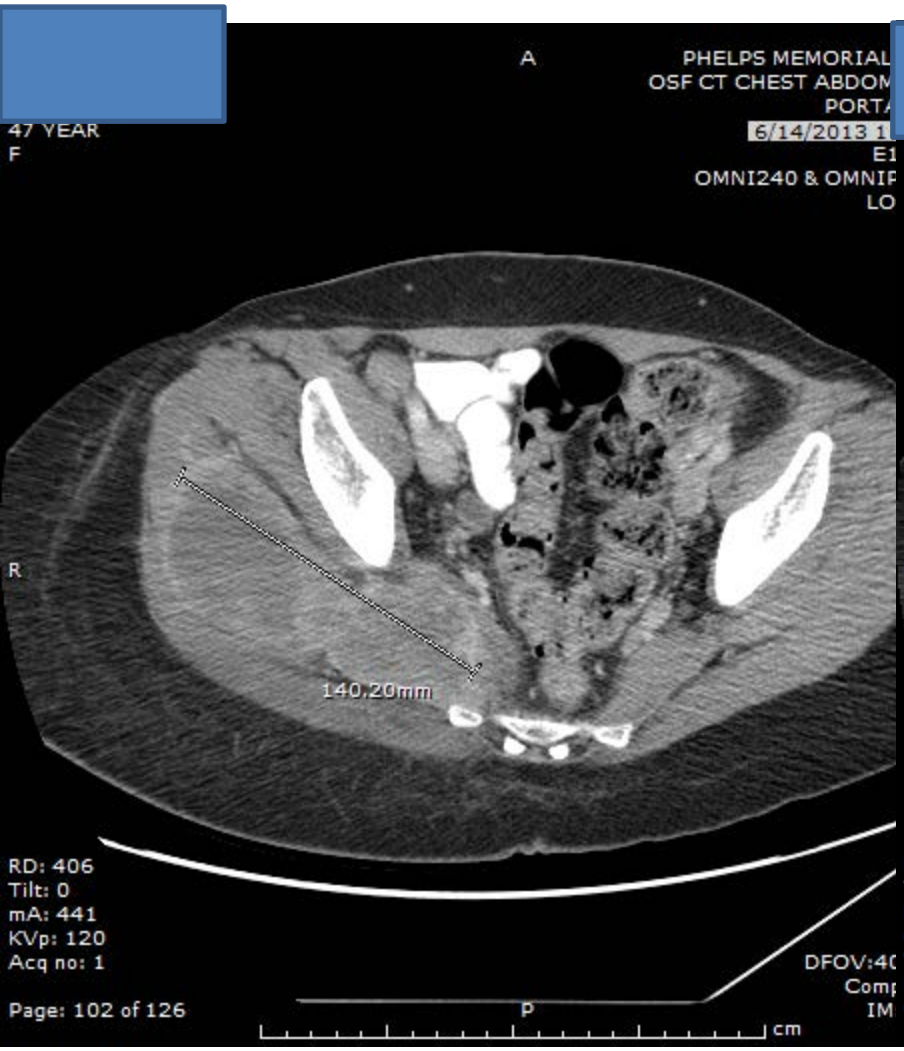


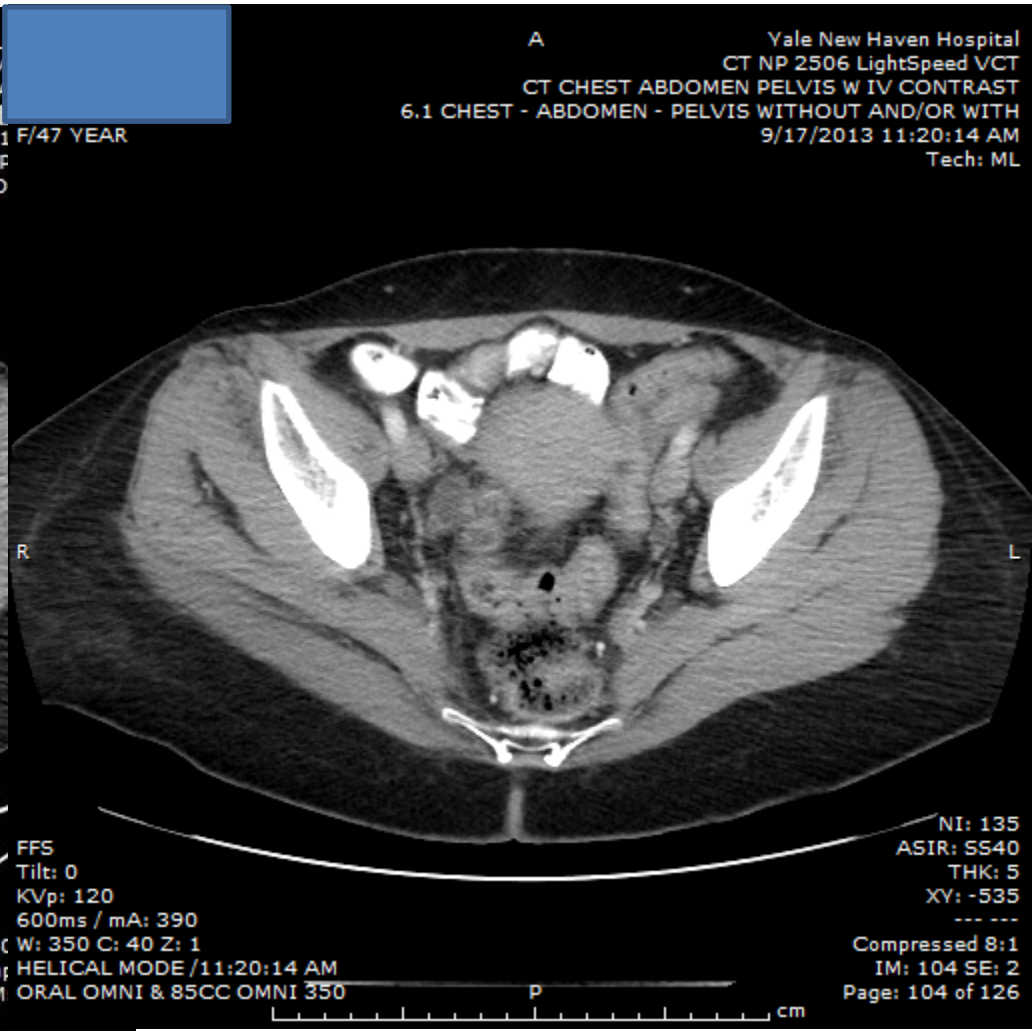
Response to ipi/anti-PD1, 3/1 dose level





Cohort 8 response at 12 weeks

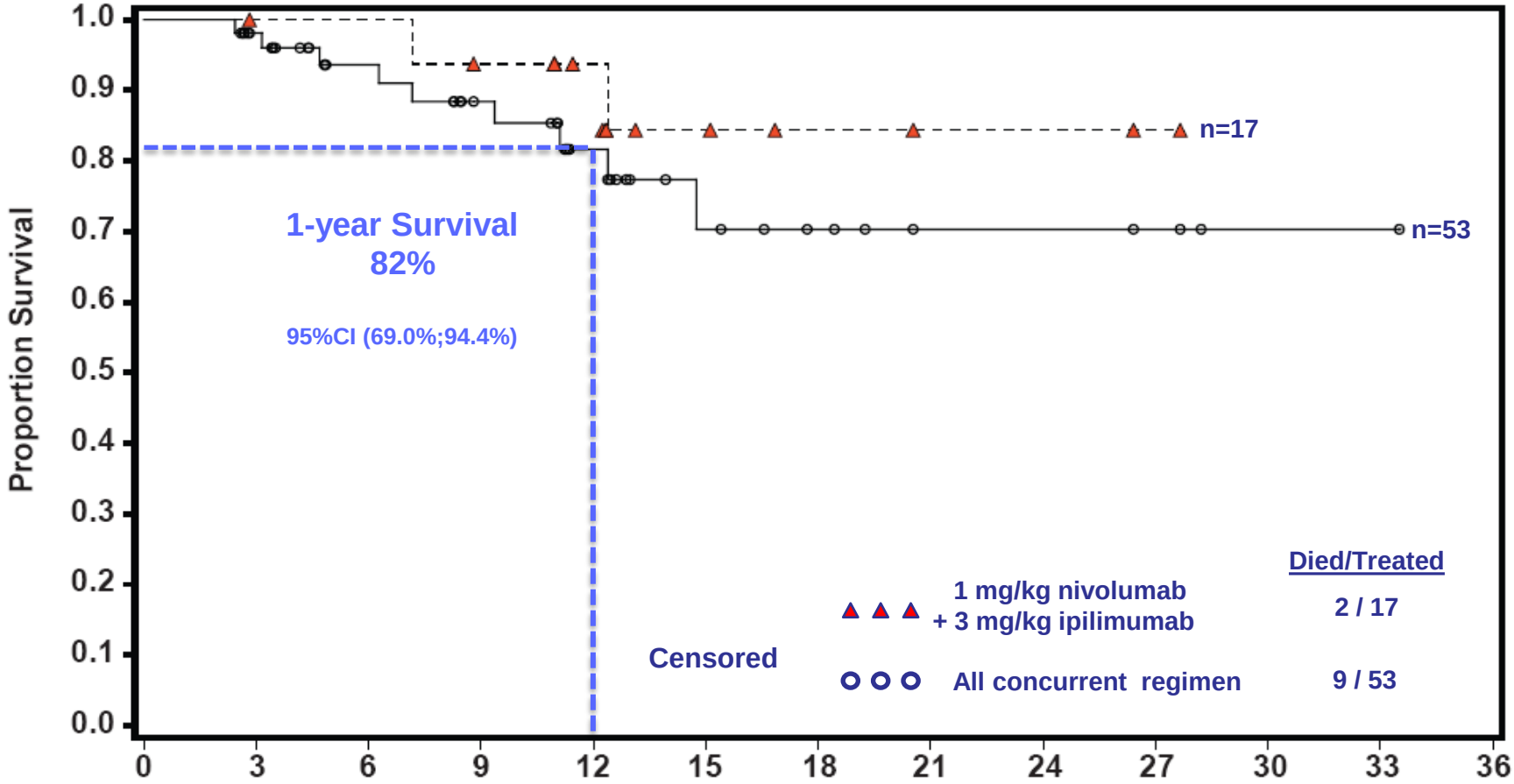




Treatment-Related Select Adverse Events Occurring in ≥1 Patient

Select Adverse Event Number of Patients (%)	Concurrent Regimen All Cohorts (n=53)		Sequenced Regimen All Cohorts (n=33)	
	All Gr	Gr 3-4	All Gr	Gr 3-4
Pulmonary	3 (6)	1 (2)	1 (3)	0
Renal	3 (6)	3 (6)	0	0
Endocrinopathies	7 (13)	1 (2)	3 (9)	2 (6)
Uveitis	3 (6)	2 (4)	0	0
Skin	37 (70)	2 (4)	8 (24)	0
Gastrointestinal	20 (38)	5 (9)	3 (9)	0
Hepatic	12 (23)	8 (15)	1 (3)	0
Infusion reaction	1 (2)	0	0	0
↑ Lipase	10 (19)	7 (13)	4 (12)	2 (6)
↑ Amylase	8 (15)	3 (6)	1 (3)	1 (3)

Preliminary Survival of Patients Treated with the Concurrent Regimen



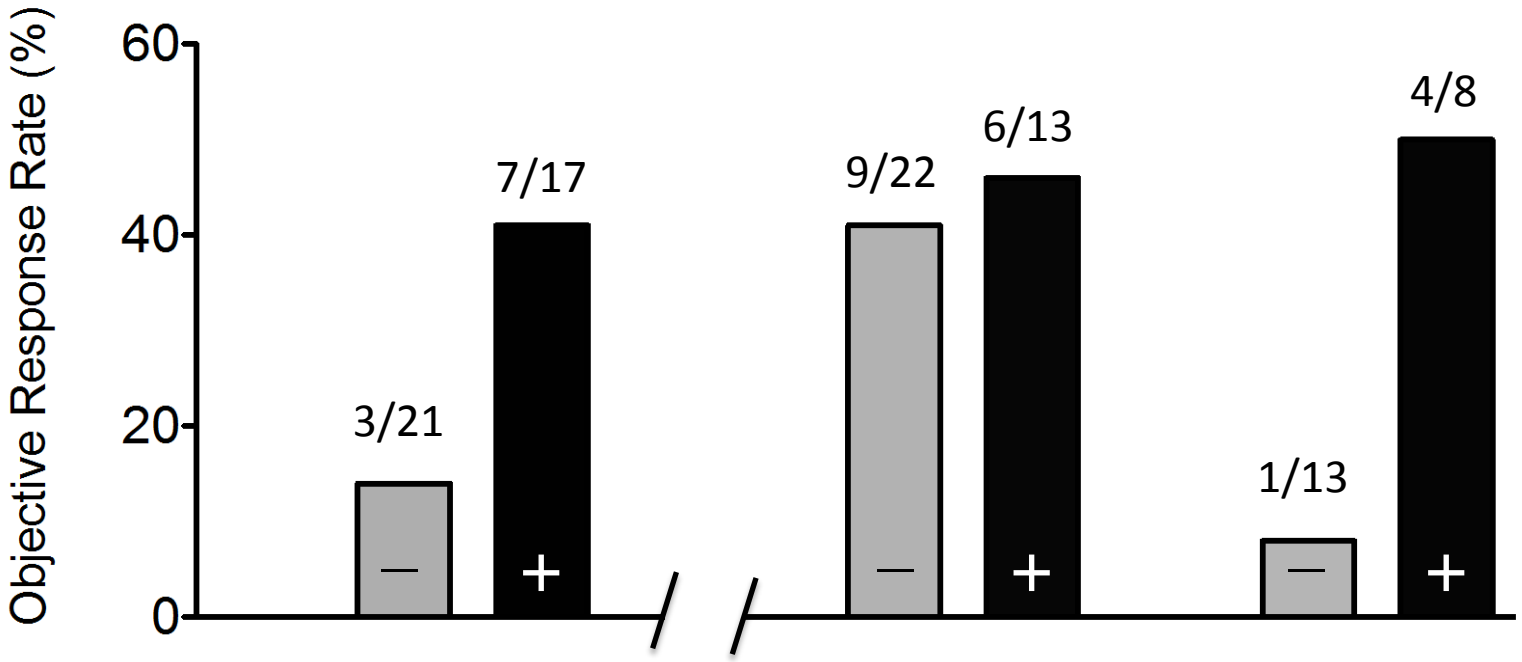
Patients at Risk

1 mg + 3 mg	17	16	16	14	10	5	3	2	2	1	0	0	0
All concurrent	53	47	36	29	19	10	7	4	4	3	1	1	0

PDL-1 Expression and Response Rate

	N	PDL1 + Positive	PDL1 - Negative
Nivolumab (Topalian, NEJM, 2012)	42	9/25 (36%)	0/17 (0%)
Nivolumab (Weber #9011)	44	8/12 (67%)	6/32 (19%)
MPDL3280A (Hamid #9010)	30	4/15 (27%)	3/15 (20%)
Nivolumab (Grosso #3016)	34	7/16 (44%)	3/18 (17%)

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)

Sequencing/Dose Considerations

- Variation in dose ratio may lead to improved toxicity profile?
- 3 studies confirm substantial anti-PD1 activity after PD on anti-CTLA4
- Various unpublished reports of OR to anti-CTLA-4 after PD on anti-PD1
  - → For sequence, final ORR/survival = concurrent therapy?
  - Or give combination if no response to single agents?
- Early data suggest single agents produce additional activity after combination (if stopped for toxicity)
- Non-cross resistance of therapies (TIL after PD on checkpoints)
- Sequence may alter subsequent activity/toxicity profile
  - Biological modulation
  - May avoid combined toxicity (LFTs with vemurafenib/checkpoint inhibitors)

Immune Profile- Tumor/Host

- Assessment of T cell infiltrate (yes/no)
  - Location of T cell infiltrate and quantity
  - **T cell phenotypes (CD8, CD4, Treg, CD8/Treg ratio)**
  - T cell cytokine production (TH1 versus Th2)
  - Inflammatory gene signatures (stratify?) + Chemokine profile
  - T cell health - anergy or exhaustion (multiple markers to include PD-1, BTLA, TIM3, LAG3, CD80, others)
  - T cell antigen specificity (by expression of CD137 or OX40)
- **Checkpoints/Inhibitors by tumor or infiltrating cells** (protein level)
  - PD-L1, PD-L2, B7-H3, B7-H4, CD200/CD200R, HLA-G, IDO, arginase, TGF-beta, IL-10, VEGF, **others**
- Other immune cells (MDSC) and phenotype/function
- Tumor HLA expression and preservation of Ag presentation
- Vasculature (integrins, PD-L1?)
- Systemic factors – Cytokines, YKL-40, MICA/MICB, Treg, MDSC, Evidence of Ag-specific responses
- Host genetic factors (SNPs)/PD biomarkers

Biological Goal of Combinations with a Checkpoint Inhibitor

- Induce Ag-specific T cells (not present before)
  - Vaccine, Release Ag with RT/targeted agent/chemoRx
- Provide more Ag-presenting cells
- Activation/Modulation of APC
  - Anti-CD40 +TLR, anti-VEGF?
- Drive T-cell expansion to expand pool of Ag-specific T cells
  - Cytokines, vaccines, co-stimulation (CD27, CD137, OX40, GITR, ICOS)
- Change a suppressive systemic (deviated) cytokine/other environment
  - Th1 cytokines, Anti-YKL-40, Reduce MICA/MICB,
- Remove other regulatory checkpoints/suppressive factors for T-cell activation/expansion in periphery (LN)
  - CTLA-4, ?
- **Drive T-cells into microenvironment**
  - CTLA-4, GITR, anti-VEGF, pro-inflammatory agents, targeted agents, ACT/TIL
- Expand/activate/change ratio of T-cells in microenvironment
  - Cytokines, vaccines, co-stimulation (CD27, CD137, OX40, GITR, ICOS)
- **Remove other checkpoints/ T-cell suppression in microenvironment**
  - Treg (CTLA-4), cytokines and anti-cytokines, Ido, arginase, multiple checkpoints (PD-1 pathway, other B7-H, BTLA, KIR, HLA-G, CD200, TIm3, LAG3)
- Restore tumor Ag presentation

- **Problem -→ Identifying the critical deficiency(ies) in individual patients**

Conclusions

- Many compelling combinations –
  - But some more than others, directed by human biology
  - Strong case for developing technology to fully characterize immune – tumor relationship in microenvironment
  - Animal model data useful but should be interpreted and used to support combination in context of human biology
- Current data suggest two main types of combinations
  - Multiple inhibitors of microenvironment and peripheral checkpoints
  - +/- approaches to drive Ag-specific T cells into tumor
- Many unresolved issues of sequence and dose issues
- Optimal management of patients will not follow clean protocol related rules
- Must be prepared to accept and manage more (and more severe) AEs for greater activity
- Must be committed to early randomized trials (in many cases) to verify findings/hypothesis
- Endpoints of trials may shift from median survival to ‘cure rates’