Imprecision Medicine Combination Immunotherapy

Combination Immunotherapy Workshop

SITC

November 6, 2014

Activity Summary: Concurrent and Sequenced Cohorts from 004

Nivolumab (mg/kg) + IPI (mg/kg)	N	ORR[a], %	CR, %	Aggregate Clinical Activity Rate	≥80% tumor burden reduction at 36 wks[b], %
Concurrent Cohorts 1-3	53	42	17	70	42
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

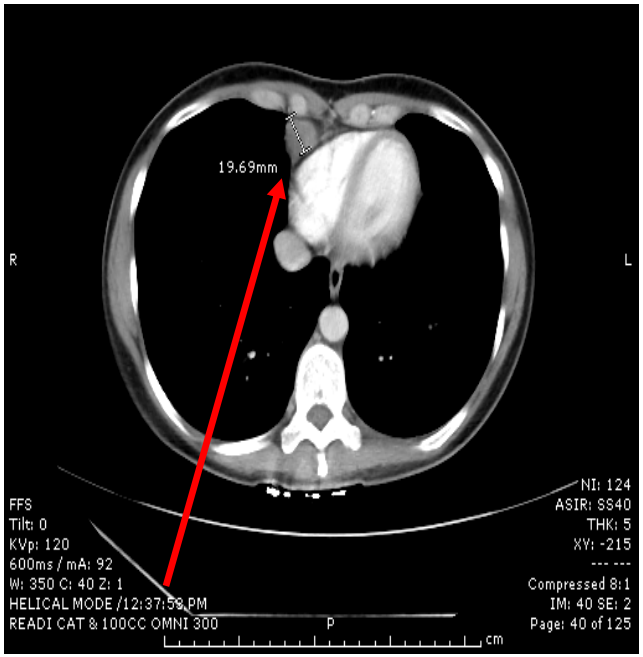
[a]per RECIST, [CR+PR]/N x 100; [b] Best overall response; [c]Cohort 8: Phase 2/3 trial; last patient, first dose Nov 2013. [d]2 confirmed and 2 unconfirmed responses

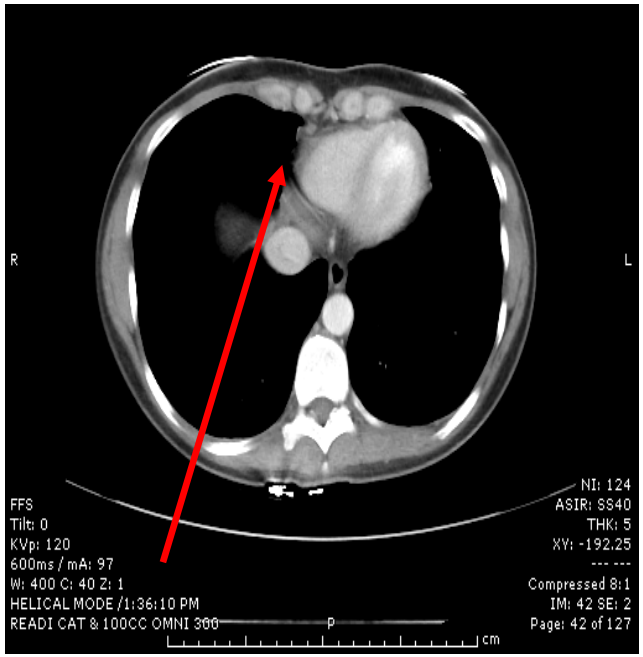
n: no. response-evaluable pts.

Yale Ipi/Nivo Cohort

- Cohorts 1-3, N=25
  - Confirmed PR/CR – 10 (40%)
    - **7 ongoing near CR**
    - **1 CR ->PD at approx. 2.5 years -> reinduced -> near CR**
    - **1 CR -> PD in node and then in brain, DOD at approx. 2 years**
    - **1 PR -> PD -> DOD at > 4 years after multiple therapies**
  - **Of 15 PD/unconfirmed OR:**
    - **Unconfirmed PR -> early brain met + later bowel mets – now NED with gamma knife RT + surgery**
    - **1 inevaluable – response in brain mets and small systemic DZ (lung/liver) -2 brain mets RX with GK-RT → now NED > 1 year**
    - **Mixed Resp at 12 weeks -> off due to tox (lipase)→ CR with further ipi alone, single local recurrence resected**
    - **uPR -> off due to LFTs→PD on steroids→ stable PR with further ipi alone**
    - **1 prolonged irPR—PD → reinduction-> alive with PD**
    - **1 irSD→ PD→ reinduced at approx 3.5 years**
    - **1 SD → PD → PR to TIL**
  - **8 deaths (6 non-responders)**
    - **4 at dose level 1**
    - **1 ocular primary**

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





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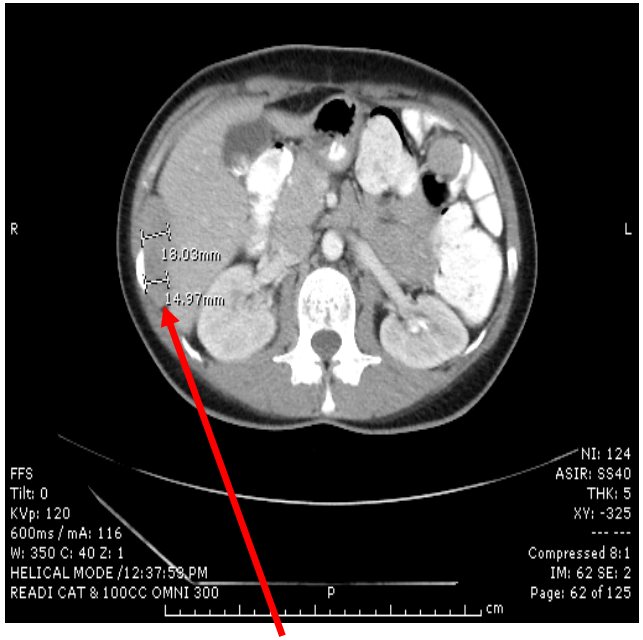

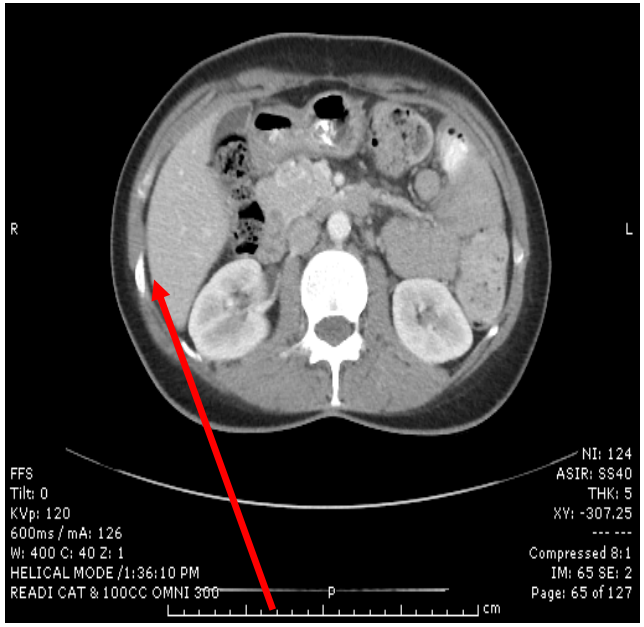

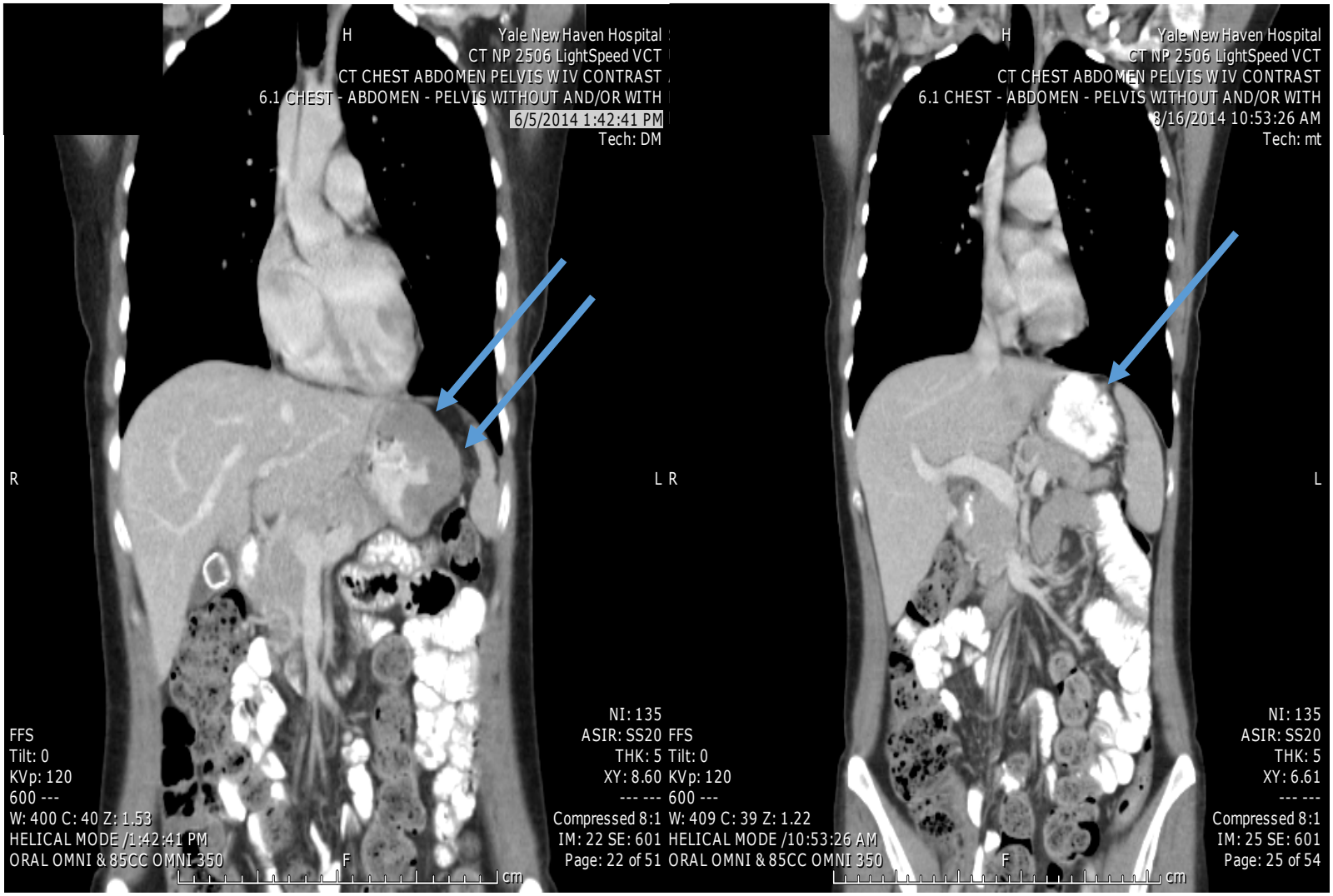
H
Yale New Haven Hospital
CT NP 2506 LightSpeed VCT
CT CHEST ABDOMEN PELVIS W IV CONTRAST
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KVp: 120
600 ---
W: 409 C: 39 Z: 1.22
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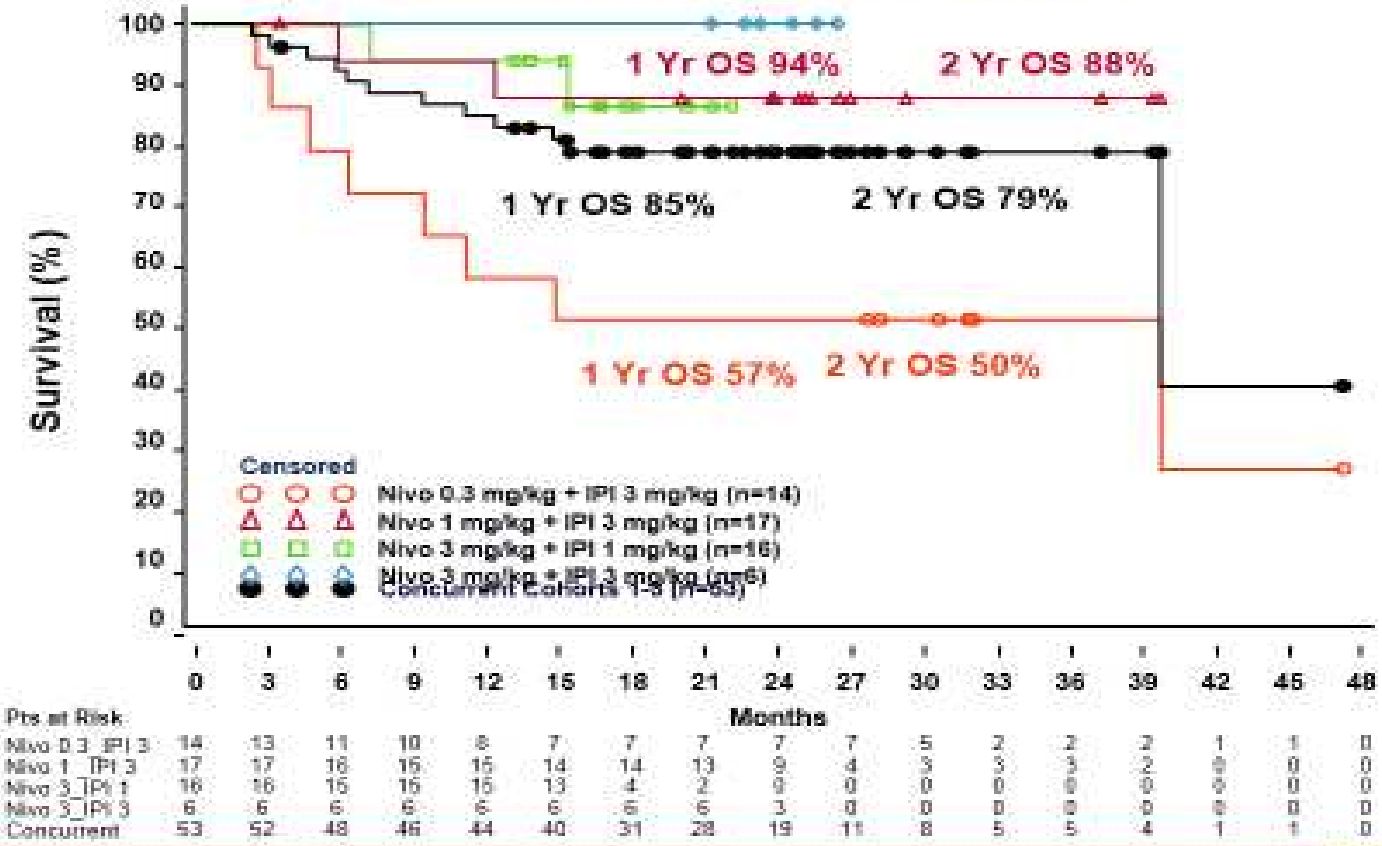
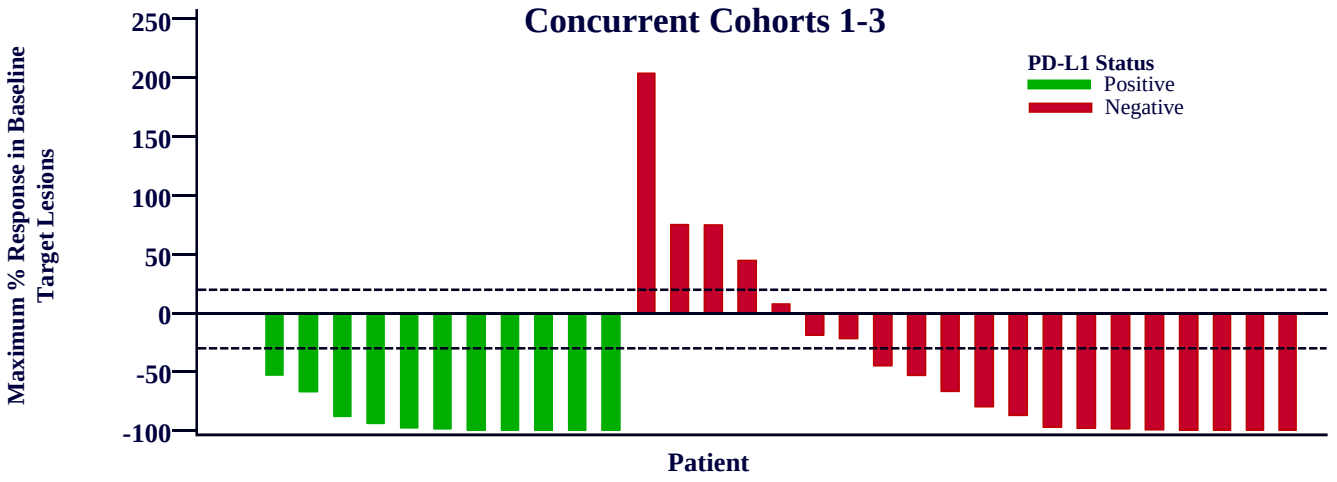
Overall Survival for Concurrent Therapy by Dose Cohort



Pts at Risk																	
Nivo 0.3 IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1 IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3 IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3 IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

ORR by PD-L1 Status (5% cutoff)

Cohort [n]	Evaluable Samples	ORR, n (%)	
PD-L1 Status		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)



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 Partial response Stable disease Progressive disease Unable to determine	 0 9 (43) 5 (24) 5 (24) 1 (5)	 1 (4) 10 (43) 8 (35) 3 (13) 1 (4)
24-week PFS, % (95% CI)	65 (40-82)	64 (41-80)

[a]Due to the high percentage of ongoing responses, median duration of response may be misleading; [b]Median follow-up 36.1 weeks; [c]Median 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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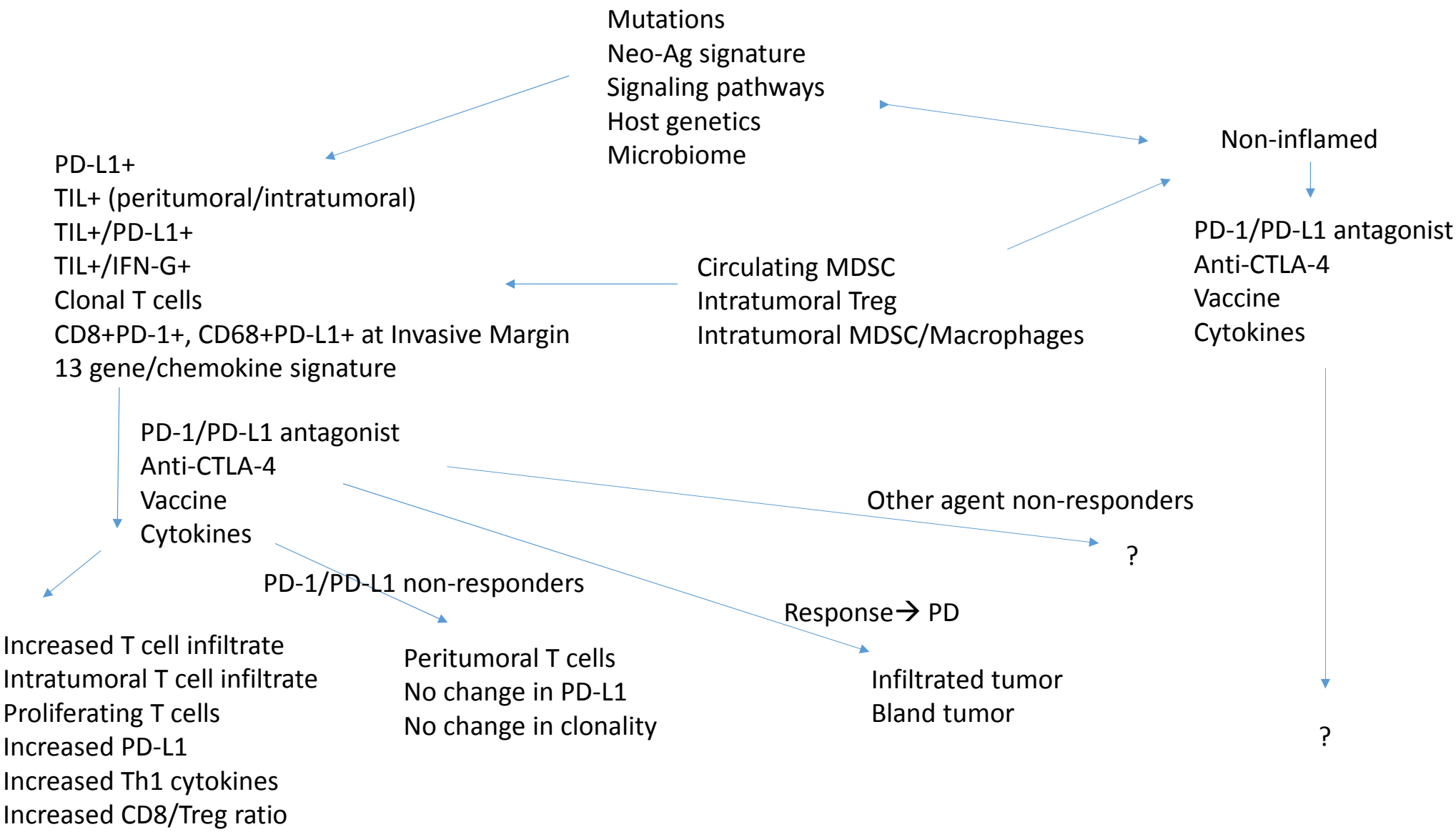
Presented By Hans Hammers at 2014 ASCO Annual Meeting

Positive and Negative Clinical Signals for Combinations

- IL-2, cytokines and vaccines – almost all negative or equivocal
- Anti-CTLA-4
  - IL-2 (higher CR rate?)
  - Interferon-alfa (increased OS, PFS, ORR)
  - GM-CSF (increased survival)
  - Bevacizumab (increased OS, PFS)
  - IDO (early data)
  - T-Vec (early data)
  - Anti-CD40?
- Anti-PD-1/anti-PD-L1
  - Anti-CTLA-4 (melanoma, RCC, but not lung?)
  - Bevacizumab (renal, but not colon?)
  - IL-21 (termination of trial)


Mutations
Neo-Ag signature
Signaling pathways
Host genetics
Microbiome
PD-L1+
TIL+ (peritumoral/intratumoral)
TIL+/PD-L1+
TIL+/IFN-G+
Clonal T cells
CD8+PD-1+, CD68+PD-L1+ at Invasive Margin
13 gene/chemokine signature
Non-inflamed
PD-1/PD-L1 antagonist
Anti-CTLA-4
Vaccine
Cytokines
Circulating MDSC
Intratumoral Treg
Intratumoral MDSC/Macrophages
PD-1/PD-L1 antagonist
Anti-CTLA-4
Vaccine
Cytokines
Other agent non-responders
?
PD-1/PD-L1 non-responders
Response→ PD
Increased T cell infiltrate
Intratumoral T cell infiltrate
Proliferating T cells
Increased PD-L1
Increased Th1 cytokines
Increased CD8/Treg ratio
Peritumoral T cells
No change in PD-L1
No change in clonality
Infiltrated tumor
Bland tumor
?

Non-Immunotherapy
VEGF/VEGFRi
RT
Molecular targets
ChemoRx

Antigen Presenting Cell or Tumor	T-lymphocyte	Function (excluding Treg)
Peptide-MHC	T cell receptor	Signal 1
CD80/CD86 (B7.1, B7.2)	CD28/CTLA-4	Stimulatory/inhibitory
CEACAM-1	CEACAM-1	inhibitory
CD70	CD27	stimulatory
LIGHT	HVEM	stimulatory
HVEM	BTLA, CD160	inhibitory
PD-L1 (B7-H1)	**PD-1** and CD80	Inhibitory (Th1)
PD-L2 (B7-DC)	PD1 and ?	Inhibitory (Th2) or stimulatory
OX40L	OX40	stimulatory
4-1BBL	CD137	stimulatory
CD40	CD40L	Stimulatory to DC/APC
B7-H3	?	Inhibitory or stimulatory
B7-H4	?	inhibitory
PD-1H (Vista)	?	inhibitory
GAL9	TIM-3	inhibitory
MHC class II	LAG-3	inhibitory
B7RP1	ICOS	stimulatory
MHC class I	KIR	Inhibitory or stimulatory
GITRL	GITR	stimulatory
CD48	2B4 (CD244)	inhibitory
HLA-G, HLA-E	ILT2, ILT4; NKG2a	inhibitory
MICA/B, ULBP-1, -2, -3, and -4+-	NKG2D	Inhibitory or stimulatory
CD200	CD200R	inhibitory
CD155	TIGIT/CD226	Inhibitory/stimulatory

IDO
Treg
MDSC
Macrophages
TGF-beta

Vaccines
Cytokines

Immune Inhibitory Molecules LAG-3 and PD-1 Synergistically Regulate T-cell Function to Promote Tumoral Immune Escape

Seng-Ryong Woo, Meghan E. Turnis, Monica V. Goldberg, et al.

Cancer Res 2012;72:917-927. Published OnlineFirst December 20, 2011.

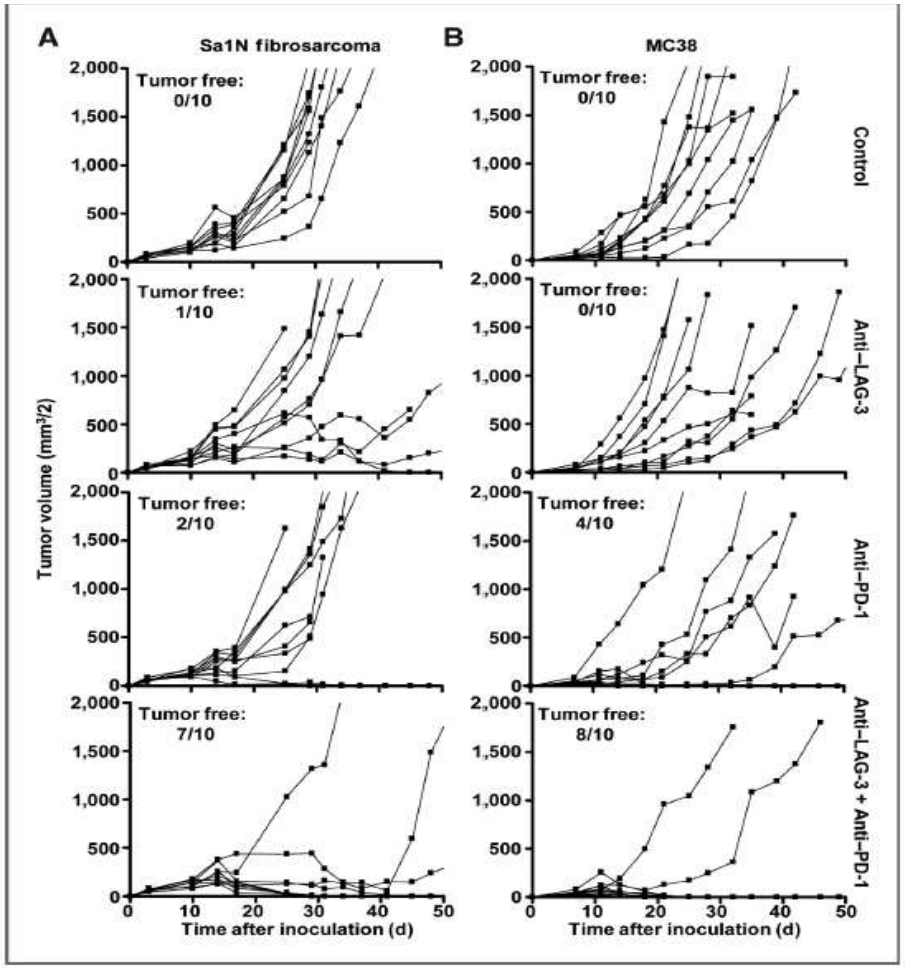


Figure 2. Combinatorial anti–LAG-3/anti–PD-1 treatment inhibits tumor growth. Mice [A/J (A); C57BL/6 (B)] were randomized on (A) on day 6 when Sa1N fibrosarcoma tumor volumes were approximately 60 $mm^3/2$, or (B) on day 7 when MC38 colon adenocarcinoma tumor volumes were approximately 40 $mm^3/2$, and treated with isotype control, anti-PD-1, anti-LAG-3, or anti-PD-1/LAG-3 combination on days 8, 11, and 14 and tumor volume determined. TGI on day 18: (A) anti–LAG-3: 18.9%; anti–PD-1: 26.2%; anti–PD-1/LAG-3: 77.3%. B, anti–LAG-3: 1%; anti–PD-1: 55%; anti–PD-1/LAG-3: 79%. Data represent 3 (Sa1N) or 4 (MC38) repeated experiments with 10 mice per group. Data were analyzed by the Maximum Likelihood method to determine synergy *P* values: (A) 0.0622 (for experiment shown; 0.0002 with all 3 experiments combined) and (B) 0.0455 (for experiment shown; 0.0366 with all 4 experiments combined) for the anti–PD-1/LAG-3 combinatorial treatment compared with anti–PD-1 and anti–LAG-3 treatments alone.

TIM3

Anti-TIM3 Antibody Promotes T Cell IFN-γ–Mediated Antitumor Immunity and Suppresses Established Tumors

Shin Foong Ngiow[1,2], Bianca von Scheidt[1], Hisaya Akiba[3], Hideo Yagita[3], Michele W. L. Teng[1,2], and Mark J. Smyth[1,2]

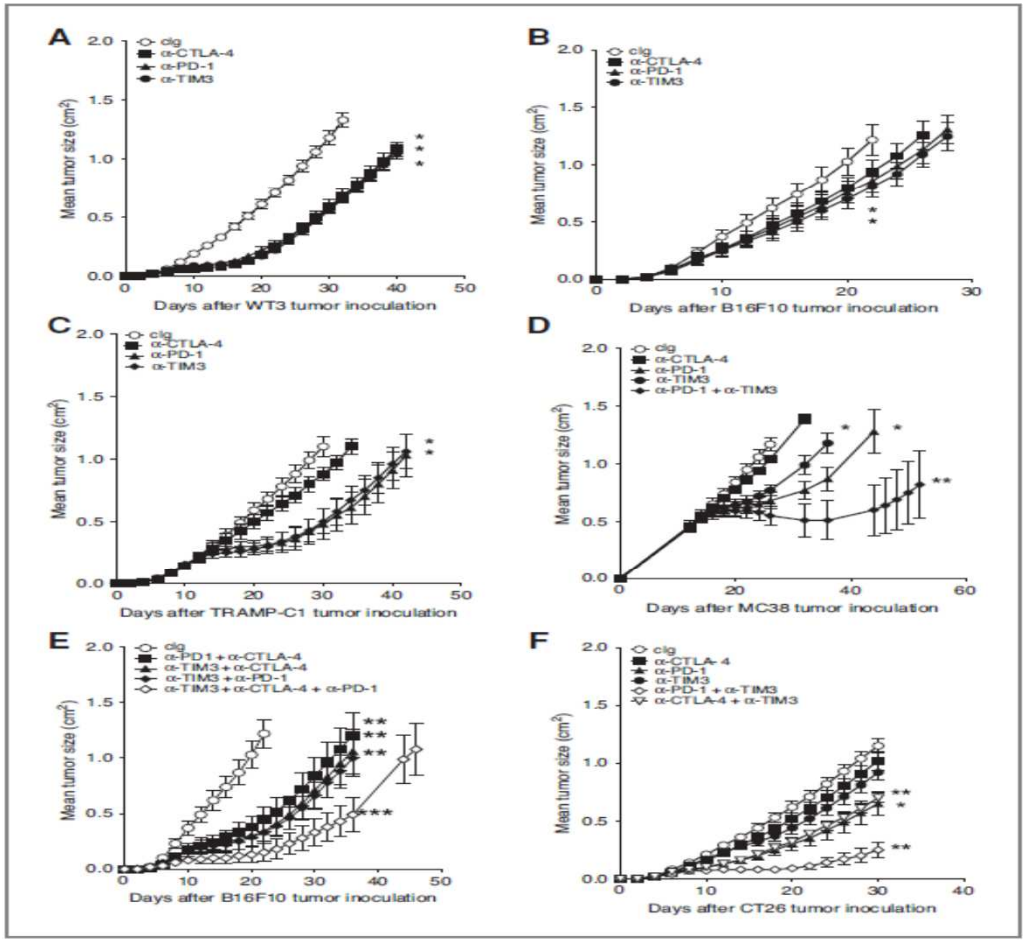
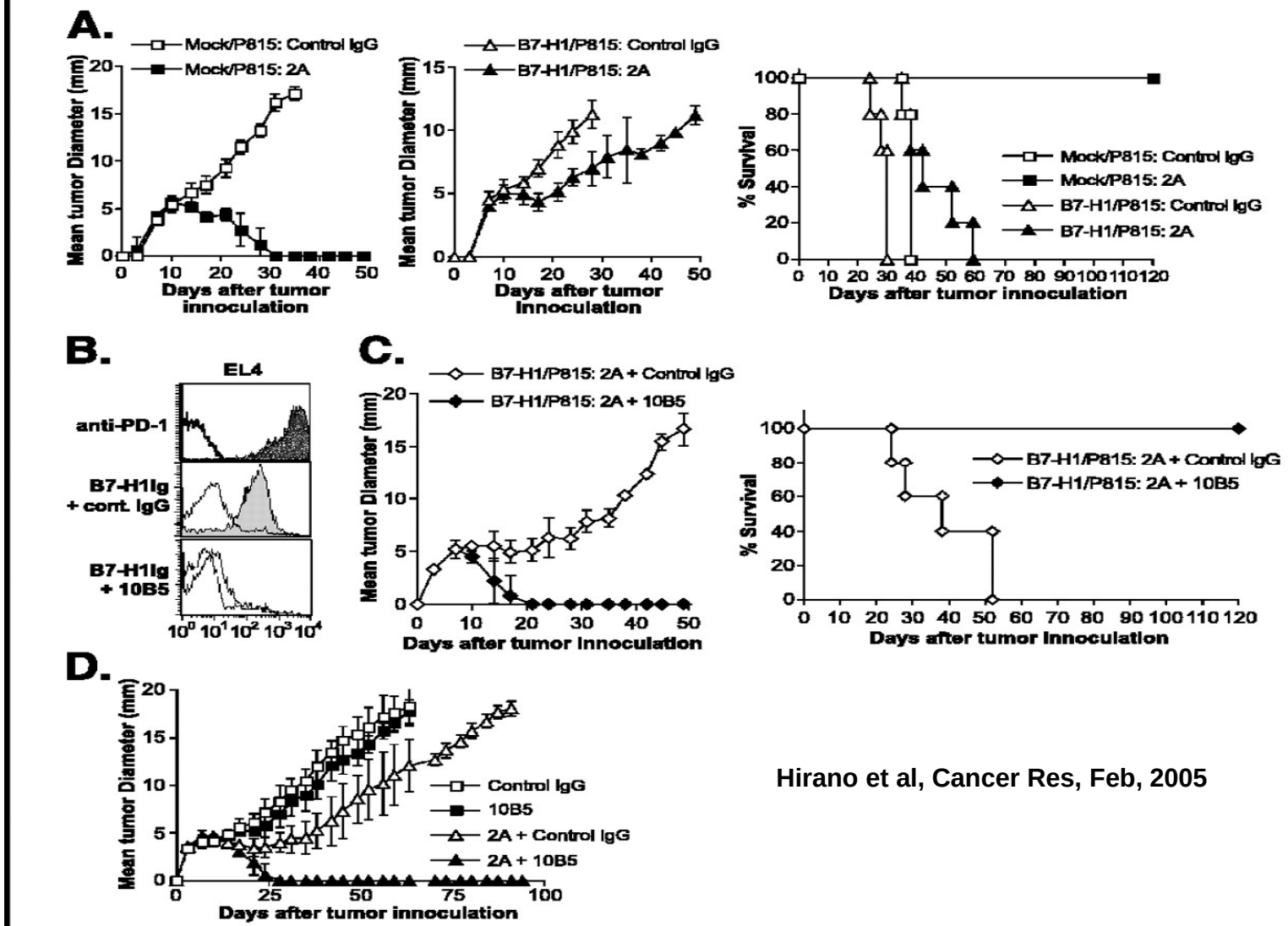


Figure 6. Comparative effect of anti-TIM3 against experimental tumors. Groups of B6 mice ($n = 5$) were inoculated subcutaneously with (A) WT3 (5×10^5), (B and E) B16F10 (1×10^5), (C) TRAMP-C1 (5×10^5), (D) MC38, and (F) CT26. On days 3, 7, 11, and 15 (A, B, E, and F), days 10, 14, 18, and 22 (C), or days 14, 18, 22, and 26 (D) after tumor inoculation, mice were intraperitoneally treated with either cIg, anti-TIM3, anti-CTLA-4, anti–PD-1, or their combination (100 μg) as indicated. Tumor sizes are represented as the mean ± SEM. A–D and F, statistical differences in tumor sizes between mice treated with cIg and single mAb therapy were determined by a Mann–Whitney test (*, $P < 0.05$). D–F, statistical differences in tumor sizes between mice treated with single mAb therapy or a dual combination were determined by a Mann–Whitney test (**, $P < 0.05$). E, statistical differences in tumor sizes between mice treated with dual mAb therapy or triple combination were determined by a Mann–Whitney test (***, $P < 0.05$).

Cancer Res; 71(10); 3540–51. ©2011 AACR.



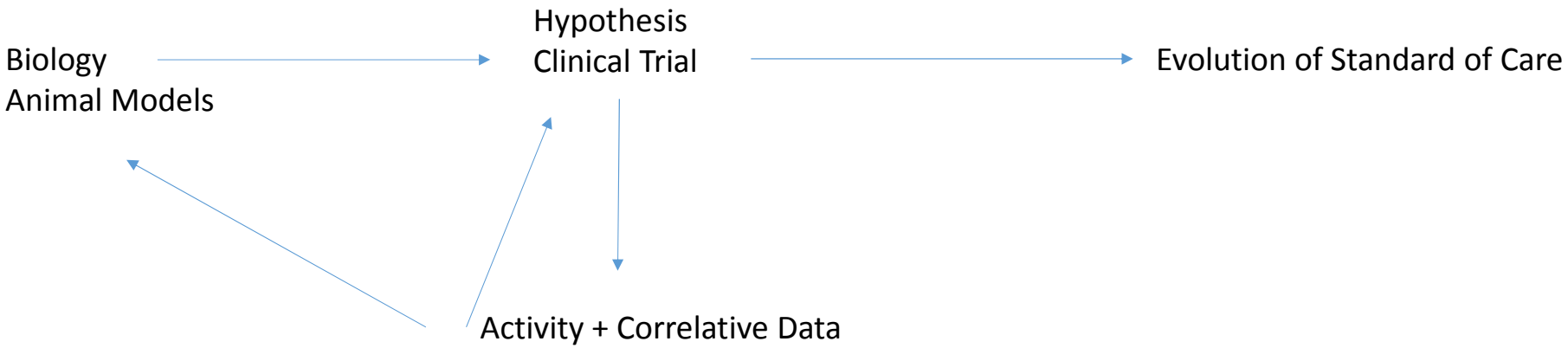
Hirano et al, Cancer Res, Feb, 2005

Challenges in Developing 'Rational' Combinations - Unknowns

- Different 'levels' of microenvironment inflammation
- True interactions between all cells in the microenvironment
- Critical signals required to convert to productive T-cell response in any individual
  - Why does HD Il-2 work (no checkpoint blockade)?
- Critical and non-redundant pathways/signals for T cell activation and function
- State of tumor antigen T cell response in any individual
- Cause for the current state of inflammation (or lack of inflammation) in the microenvironment (in an individual)
- True and complete immunologic effects of any single or combination immune intervention
- Inability to assess real-time evolution of the microenvironment

Considerations in Selecting and Developing Combinations

- Understand the critical biology and pathways
- Understand when the animal models are and are not relevant to human biology
  - Differences in evolution of tumors and tumor host relationship
  - In vitro and tissue correlative studies in humans (PBL, TIL)
- Prioritize based on prior clinical data, human biology, strength of preclinical data
- Study the combinations in potentially responsive and non-responsive tumors (don't make premature decisions or unsubstantiated assumptions)
- Target activity endpoint to the appropriate patient population (stratify)
- Goal is durable CR/near CR through conventional or unconventional activity
- Use all activity information to make go- no-go decision to randomized trials
  - Kinetics, depth, duration
- Place toxicity in appropriate context
- Collect tissue and blood at baseline
- Study PD effects of combination in blood and tumor


Biology
Animal Models
Hypothesis
Clinical Trial
Evolution of Standard of Care
Activity + Correlative Data

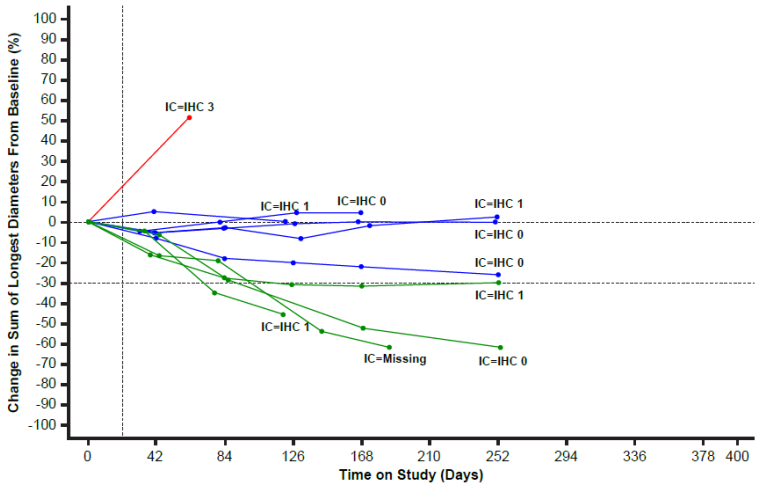
Anti-CTLA-4 → Increased ICOS+ T cells
Increased ALC
Increased tumor T cell infiltrate
Expands T-cell repertoire
Proliferative gene signature
Depletes intratumoral Treg?
Increased serologic responses

Anti-PD-1 → Enhanced expression of genes controlling function

MPDL3280A + Bevacizumab: Summary of Phase Ib Results

Safety and efficacy of patients with 1L clear cell RCC in Arm A

- Safety
  - 100% of patients (n = 35) experienced an all-grade AE, with 49% experiencing a G3-4 AE
  - 1 MPDL3280A treatment-related AE occurred (1 case of neutropenia in Arm A)
  - No Grade 4 AEs or deaths related to MPDL3280A
- Efficacy
  - 4 out of 10 patients (2 IHC 1, 1 IHC 0, 1 IHC unknown) demonstrated an objective response per RECIST v1.1
  - ORR = 40%; SD = 50%



See Lieu et al., abstract 1049O, presented Saturday.

Unconfirmed best responses by RECIST v1.1.
Patients dosed by Apr 7, 2014; data cutoff Jul 7, 2014.
IHC 3: ≥ 10% of ICs are PD-L1+; IHC 2: ≥ 5% and < 10% of ICs are PD-L1+. IHC 1: ≥ 1% and < 5% of ICs are PD-L1+; IHC 0: < 1% ICs are PD-L1+.

Biological Goal of Immunotherapy Combinations

- Induce Ag-specific T cells (not present before)
  - Vaccine, Release Ag with RT/targeted agent/chemoRx
- Provide more Ag-presenting cells (FLT3, GM-CSF)
- 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), ACT
- 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**
  - Anti-CTLA-4, anti-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), CD3-Ag conjugates, ACT
- **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 (B7-H3, B7-H4), KIR, HLA-G, CD200, TIm3, LAG3)
- Restore tumor Ag presentation

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