Challenges in Distinguishing Clinical Signals to Support Development Decisions: Case Studies

David Feltquate MD, PhD

Head of Early Clinical Development, Oncology

Bristol-Myers Squibb, Princeton, NJ

Challenges in Distinguishing Clinical Signals to Support Development Decisions: Case Studies

- What clinical features are associated with a true signal
- What are potential pitfalls
- Case studies
  - Monotherapy
    - Big Signal
    - False Negative
    - Biomarker-enriched
  - Combinations

Case Study 1: Big Signal
PD-1/PD-L1 Pathway

- PD-1/PD-L1 checkpoint pathway important for T-cell inhibition; postulated to be important pathway for tumor immune evasion
- Inhibitors of the pathway lead to T-cell activation

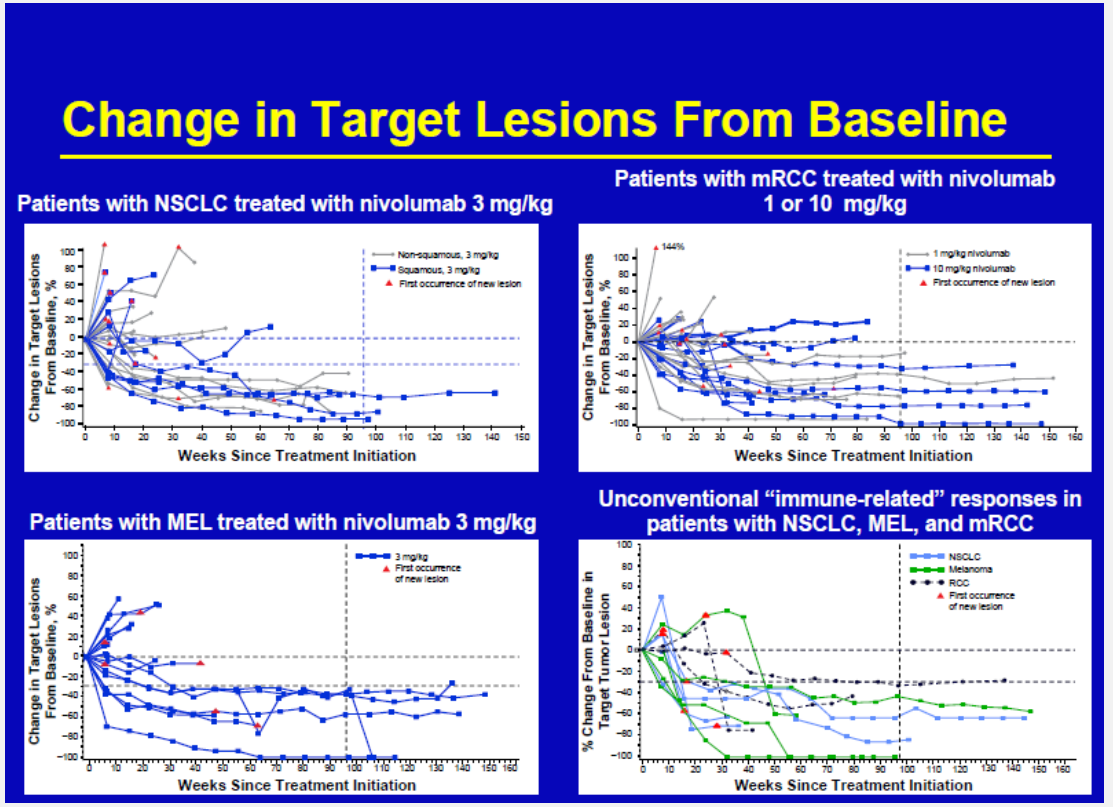
- 20-30% ORR in previously treated MEL (~100 pts), RCC (~30 pts), and NSCLC (~100 pts)
- Durable responses; Pseudoprogression

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.



Case Study 1: Big Signal
PD-1/PD-L1 Pathway

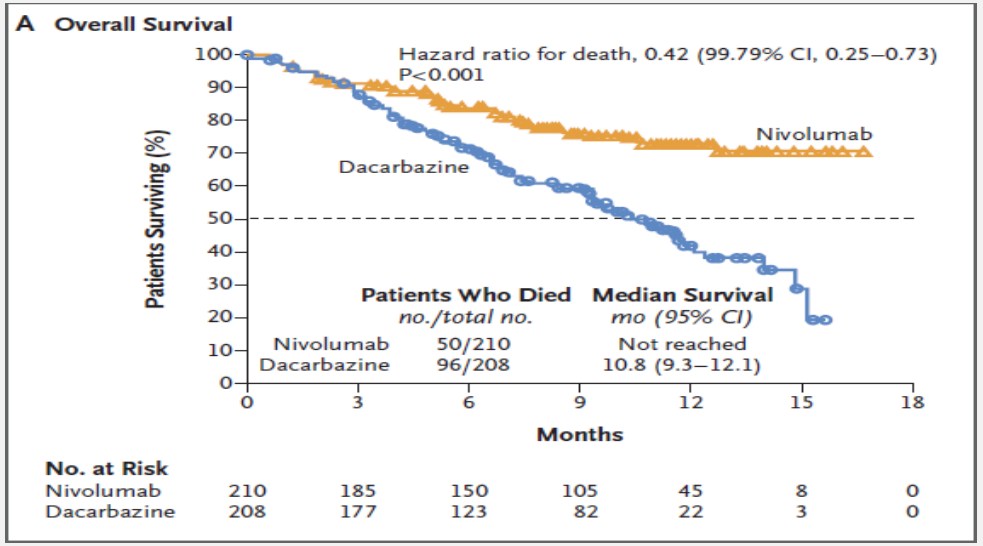
Big signal led to multiple Phase 3 studies with a variety of PD-1/PD-L1 agents confirming benefit in several tumor types….

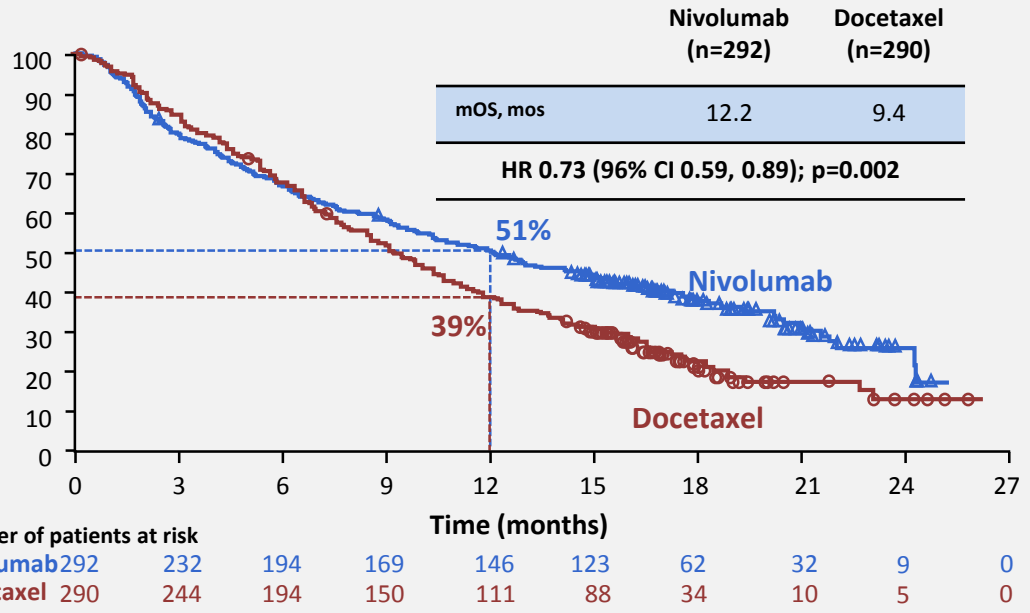
NSCLC	(nivolumab, pembrolizumab, atezolizumab)
Melanoma	(pembrolizumab, nivolumab)
RCC	(nivolumab)
SCCHN	(nivolumab)
Bladder	(pembrolizumab)
Gastric	(nivolumab)

…and meaningful benefit* in many tumor types with single arm data

SCCHN	(pembrolizumab)
Bladder	(atezolizumab, nivolumab, durvalumab)
Hodgkins	(nivolumab, pembrolizumab)
MSI-H CRC	(pembrolizumab)
Merkel Cell	(avelumab)

*FDA approval or Breakthrough Status



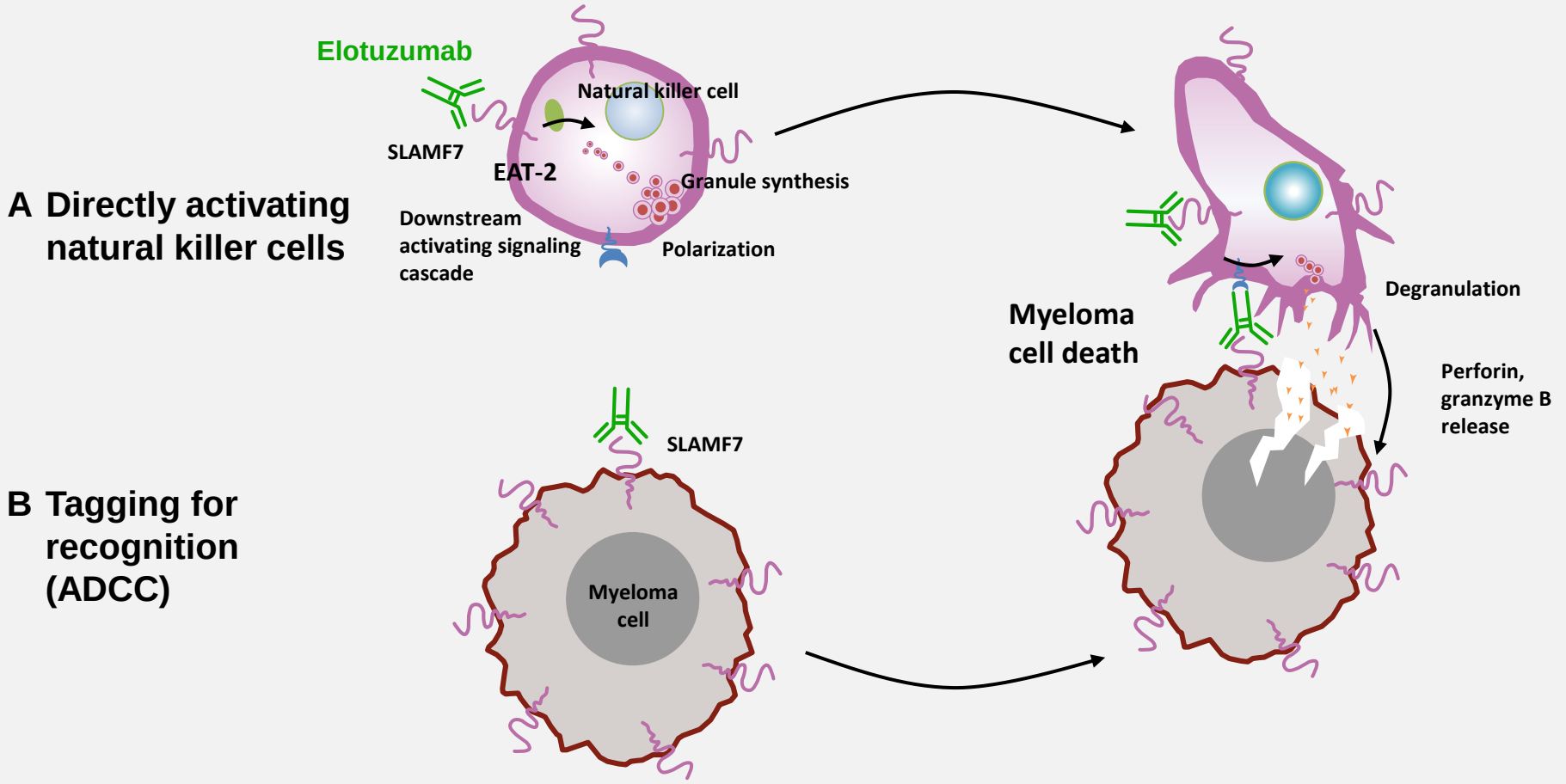


Robert, C. et al., n engl j med 372;4 nejm.org january 22, 2015

Case Study 2a: False Negative Signal

Single Agent Elotuzumab in Multiple Myeloma

- Elotuzumab is an immunostimulatory monoclonal antibody that recognizes SLAMF7 (CS-1), a protein highly expressed by myeloma and natural killer cells[1]
- Elotuzumab causes myeloma cell death potentially via a dual mechanism of action[2]



1. Hsi ED et al. *Clin Cancer Res* 2008;14:2775–84; 2. Collins SM et al. *Cancer Immunol Immunother* 2013;62:1841–9.
ADCC=antibody-dependent cell-mediated cytotoxicity; SLAMF7=signaling lymphocytic activation molecule F7

Case Study 2a: False Negative Signal

Single Agent Elotuzumab in Multiple Myeloma

- Study 1701: Phase 1 dose escalation study of single agent elotuzumab
- No objective responses were observed; Stable disease observed in 9 of 34 patients (26.5%)
- Elotuzumab added to lenalidomide and bortezomib in separate Phase 1 studies
- Led to Confirmatory Phase 3 study (ELOQUENT-2)

Response at Day 56

EBMT Response	Cohort 1 0.5 mg/kg (n=3)	Cohort 2 1.0 mg/kg (n=4)	Cohort 3 2.5 mg/kg (n=6)	Cohort 4 5 mg/kg (n=4)	Cohort 5 10 mg/kg (n=3)	Cohort 6 20 mg/kg (n=14)	Total (N=34)
Complete	0	0	0	0	0	0	0
Partial	0	0	0	0	0	0	0
SD (no change)	1	0	1	1	2	4	9 (26.5%)
PD	1	4	4	2	1	0	25 (73.5%)

EBMT = European Group for Blood and Marrow Transplant; PD = progressive disease; SD = stable disease

Zonder JA et al. Presented at the Annual Meeting of the American Society of Hematology, 2008: Abstract 2773; Zonder JA et al. *Blood.* 2011 (published ahead of print).

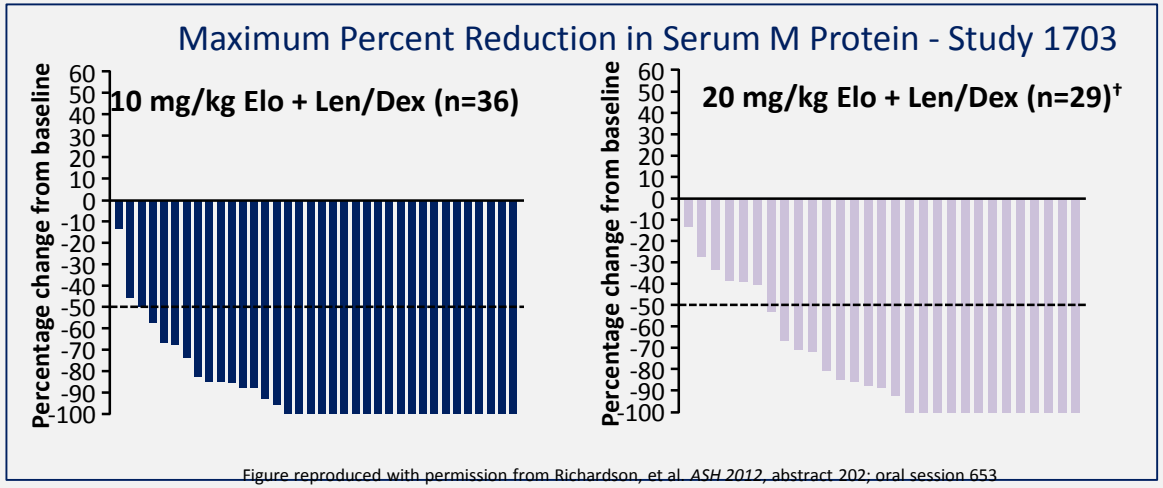
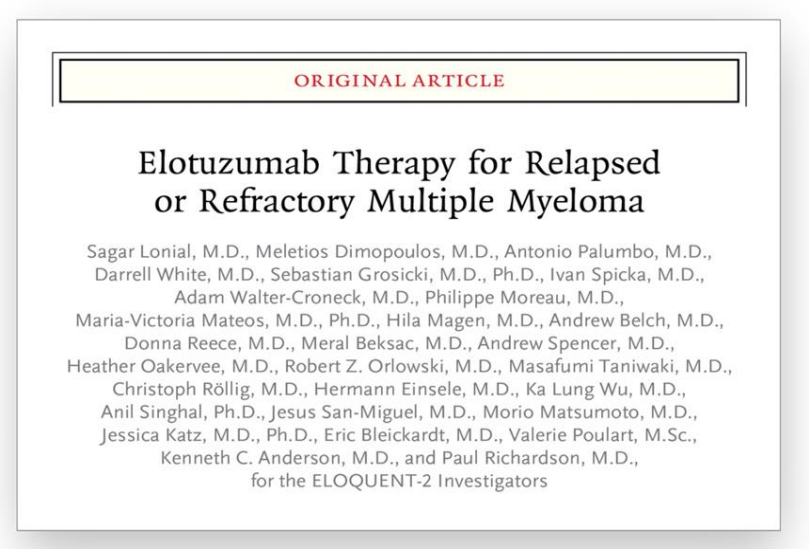


Figure reproduced with permission from Richardson, et al. *ASH 2012*, abstract 202; oral session 653

1. Richardson PG et al. *Blood* 2014;124:302

ELOQUENT-2: Primary Analysis

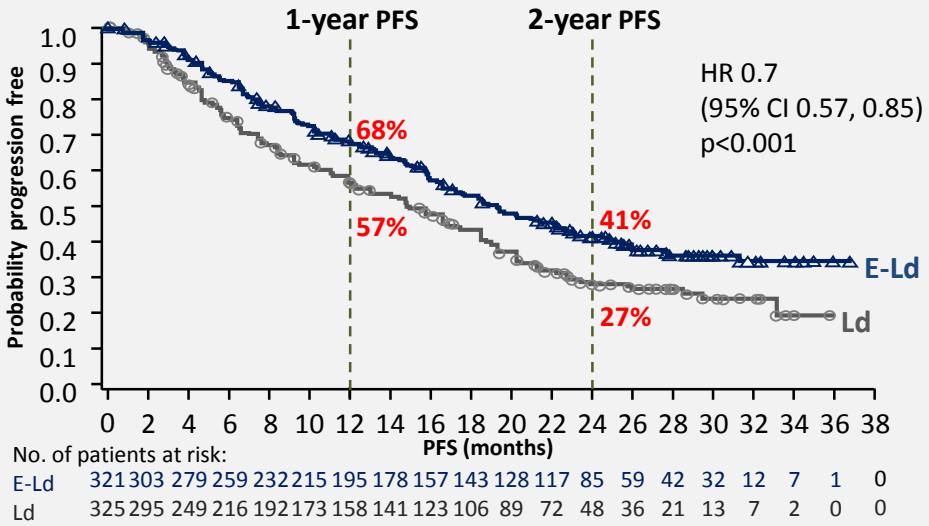


ORIGINAL ARTICLE

Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma

Sagar Lonial, M.D., Meletios Dimopoulos, M.D., Antonio Palumbo, M.D., Darrell White, M.D., Sebastian Grosicki, M.D., Ph.D., Ivan Spicka, M.D., Adam Walter-Croneck, M.D., Philippe Moreau, M.D., Maria-Victoria Mateos, M.D., Ph.D., Hila Magen, M.D., Andrew Belch, M.D., Donna Reece, M.D., Meral Beksac, M.D., Andrew Spencer, M.D., Heather Oakervee, M.D., Robert Z. Orlowski, M.D., Masafumi Taniwaki, M.D., Christoph Röllig, M.D., Hermann Einsele, M.D., Ka Lung Wu, M.D., Anil Singhal, Ph.D., Jesus San-Miguel, M.D., Morio Matsumoto, M.D., Jessica Katz, M.D., Ph.D., Eric Bleickardt, M.D., Valerie Poulart, M.Sc., Kenneth C. Anderson, M.D., and Paul Richardson, M.D., for the ELOQUENT-2 Investigators

Co-primary endpoint: PFS



From *N Engl J Med*, Lonial S et al, Elotuzumab therapy for relapsed or refractory multiple myeloma, 373, 621–31.

Co-primary endpoint: ORR	E-Ld	Ld
%	79	66
95% CI	74, 83	60, 71

ELOQUENT-2 demonstrated clinical benefits of E-Ld compared with lenalidomide and dexamethasone (Ld) alone[1]

1. Lonial S et al. *N Engl J Med* 2015;373:621–31.

Case Study 2b: False Negative Signal

Single agent PD-1 inhibition in Multiple Myeloma

- Phase 1 study of nivolumab in several hematologic malignancies (CA209-039)
- Single agent nivolumab active in HL, FL, DLBCL, T-cell lymphoma
- No responses in Myeloma

	Objective Response Rate, n (%)	Complete Responses, n (%)	Partial Responses, n (%)	Stable Disease n (%)
B-Cell Lymphoma* (n=29)	8 (28)	2 (7)	6 (21)	14 (48)
Follicular Lymphoma (n=10)	4 (40)	1 (10)	3 (30)	6 (60)
Diffuse Large B-Cell Lymphoma (n=11)	4 (36)	1 (9)	3 (27)	3 (27)
T-Cell Lymphoma† (n=23)	4 (17)	0 (0)	4 (17)	10 (43)
Mycosis Fungoides (n=13)	2 (15)	0 (0)	2 (15)	9 (69)
Peripheral T-Cell Lymphoma (n=5)	2 (40)	0 (0)	2 (40)	0 (0)
Multiple Myeloma (n=27)	0 (0)	0 (0)	0 (0)	18 (67)
Primary Mediastinal B-Cell Lymphoma (n=2)	0 (0)	0 (0)	0 (0)	2 (100)

*includes other B-cell lymphoma (n=8)

†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)

Case Study 2b: False Negative Signal

PD-1 agent in Multiple Myeloma

A Phase II Study of Pembrolizumab, Pomalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

Ashraf Badros, Mehmet Kocoglu, Ning Ma, Aaron Rapoport, Emily Lederer, Sunita Philip, Patricia Lesho, Cameron Dell, Nancy Hardy, Jean Yared, Olga Goloubeva and Zeba Singh

	All N=27	Double refractory N=20	High risk cytogenetics N=12
ORR (≥ PR), %	60%	55%	50%
sCR	1	0	0
CR	0	0	0
VGPR	4	2	1
PR	11	9	5
Stable Disease	8 (30%)	6 (30%)	5 (42%)
Progressive disease	3 (10%)	3 (15%)	1 (8%)

- Confirmation of signal currently under evaluation with several PD-1/PD-L1 agents

Key Lesson in both Case Studies:
Some drugs have little single agent activity but are additive or synergistic when combined with drugs targeting other mechanisms

	Pomalidomide plus low-dose dexamethasone (n=302)	High-dose dexamethasone (n=153)
Overall response	95 (31%)	15 (10%)†
Complete or stringent complete response	3 (1%)	0
Very good partial response	14 (5%)	1 (<1%)
Partial response	78 (26%)	14 (9%)
Minor response	23 (8%)	9 (6%)
Stable disease	129 (43%)	70 (46%)
Progressive disease	29 (10%)	41 (27%)
Not estimable	26 (9%)	18 (12%)
Duration of response in patients with at least a partial response (months)	7·0 (6·0–9·0)	6·1 (1·4–8·5)

Case Study 3: Biomarker-based Signal
Anti-PD-1 treatment in patients with MSI-H

- MDX-1106-01 (CA209-001): First-in-Human study of a PD-1 agent (nivolumab)
- Phase 1 Single Ascending Dose study
- 3 long-term responders; MEL, RCC, and CRC
- CRC patient identified later as MSI-H

- MSI-H (mismatch repair defect) associated with very high mutational load and TILs

Published OnlineFirst on November 20, 2012; DOI:10.1158/1078-0432.CCR-12-2625

Clinical Cancer Research

Cancer Therapy: Clinical

Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody

Evan J. Lipson[1], William H. Sharfman[1,3], Charles G. Drake[1,2], Ira Wollner[6], Janis M. Taube[3,4], Robert A. Anders[4], Haiying Xu[4], Sheng Yao[1,3], Alice Pons[1], Lieping Chen[1,3], Drew M. Pardoll[1], Julie R. Brahmer[1], and Suzanne L. Topalian[5]

Table 2. Treatment Characteristics and Clinical Response to Therapy

Dose (mg/kg)	No. of Patients	Total No. of Doses					Best Response (duration in months)*
		1	2	3	5	11	
0.3	6	6	0	0	0	0	N/A
1	6	3	1	1	1	0	1 MXR (1)
3	6	3	0	2	1	0	1 CR (21+)†
10	21	15	1	4	0	1	2 PR (3+, 16+)‡§ 1 MXR (1)
Total	39	27	2	7	2	1	1 CR, 2 PR, 2 MXR

Abbreviations: N/A, not applicable; MXR, mixed response defined as regression in some lesions but concomitant progression in others; CR, complete response; PR, partial response.

*CR and PR by Response Evaluation Criteria in Solid Tumors 1.0 criteria.

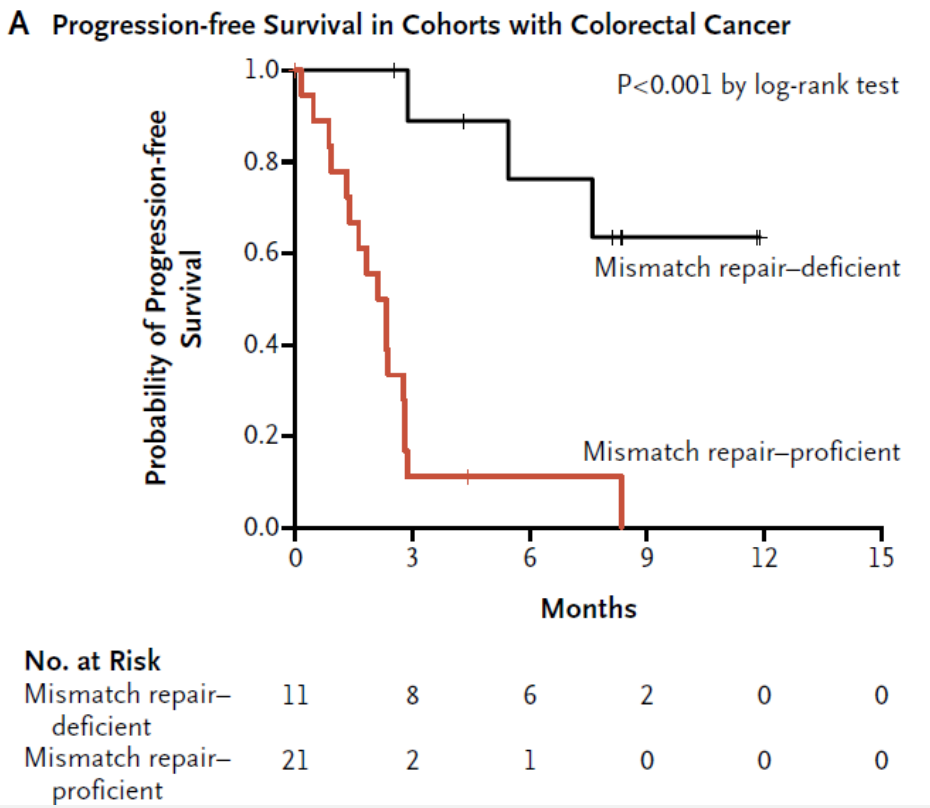
†This patient with stage IV colorectal cancer had previously shown progressive disease after receiving chemotherapy regimens including bevacizumab and cetuximab.

‡PR duration of 3+ months was preceded by an MXR in this patient with melanoma lasting 20 months. Previous therapies that were ineffective included high-dose interleukin-2 and temozolomide.

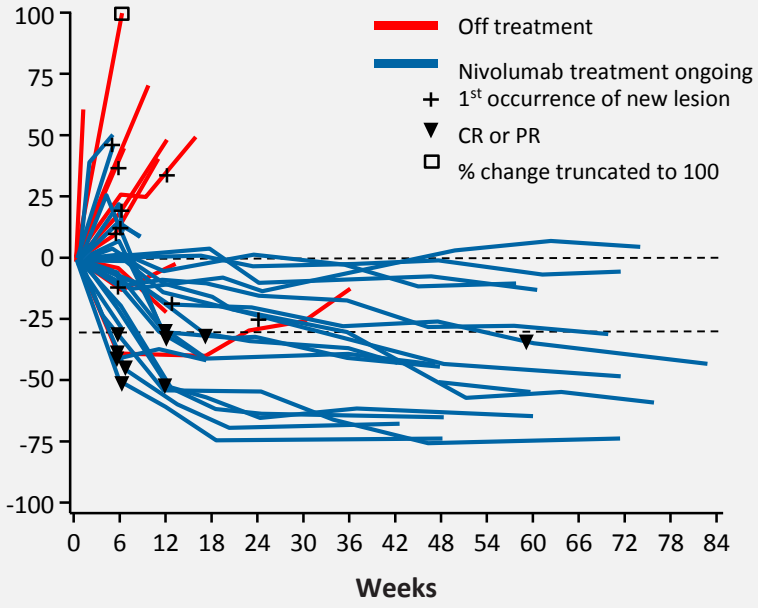
§PR duration of 16+ months was preceded by an MXR in this patient with renal cell carcinoma lasting 4 months. Previous therapies that were ineffective included sunitinib, sorafenib, and an experimental histone deacetylase inhibitor.

Case Study 3: Biomarker-based Signal
Anti-PD-1 treatment in patients with MSI-H

JHU Investigator-sponsored Phase 2a study in MSI-H and MSS CRC
Pembrolizumab



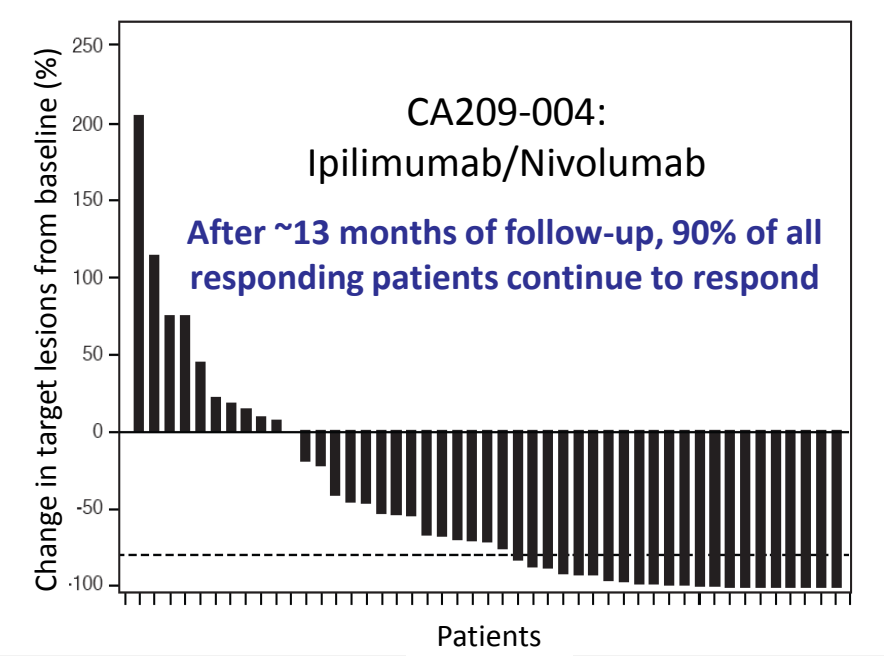
CA209-142: Phase 2 study in previously treated metastatic MSI-H CRC
Nivolumab



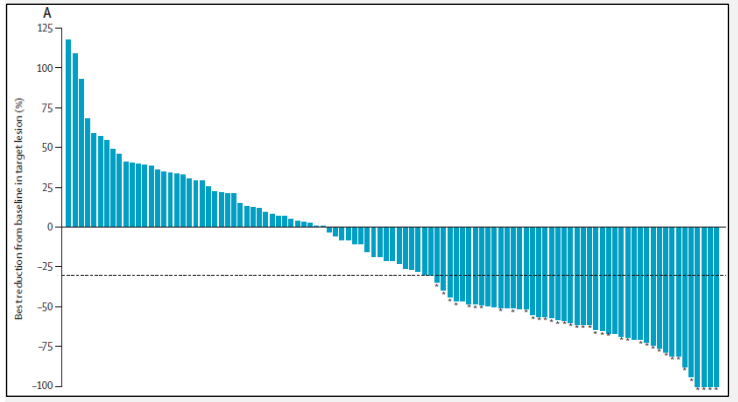
Case Study 4: Signals with Combination Regimens
Ipilimumab/Nivolumab

- Phase 1 study of ipilimumab/nivolumab in patients with treatment naïve MEL
- Greater ORR (and CRs); greater proportion with "deep responses"; durable; greater toxicity

- Led to confirmatory trials CA209-069 and CA209-067

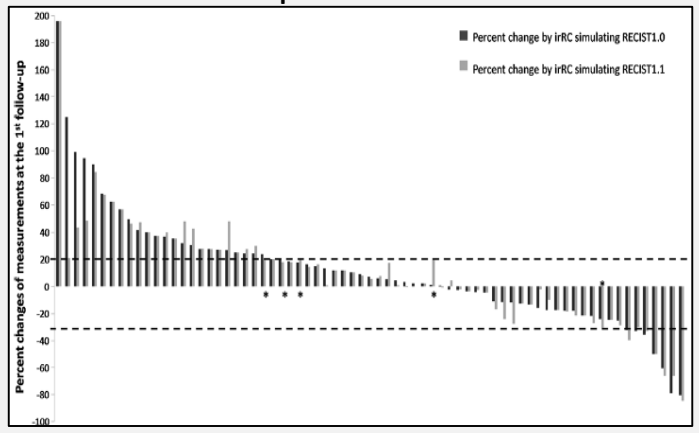


CA209-066: Nivolumab



Weber J. et al. Lancet Oncol 2015 Published Online March 18, 2015
http://dx.doi.org/10.1016/ S1470-2045(15)70076-8

Single Institution Experience
Ipilimumab



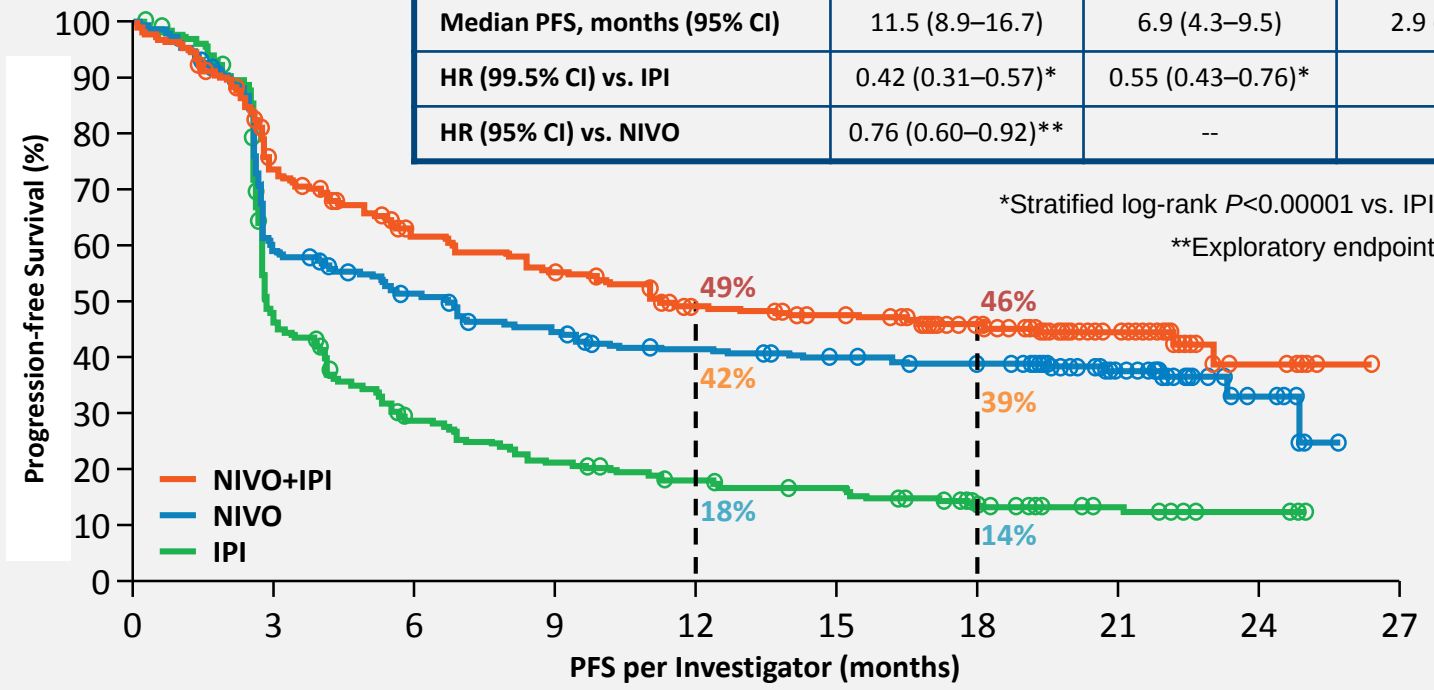
Nishino et al. Journal for ImmunoTherapy of Cancer 2014, 2:17
Page 2 of 12
http://www.immunotherapyofcancer.org/content/2/1/17

Case Study 4: Signals with Combination Regimens
Ipilimumab/Nivolumab

	NIVO + IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median PFS, months (95% CI)	11.5 (8.9–16.7)	6.9 (4.3–9.5)	2.9 (2.8–3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31–0.57)*	0.55 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.76 (0.60–0.92)**	--	--

*Stratified log-rank *P*<0.00001 vs. IPI

**Exploratory endpoint



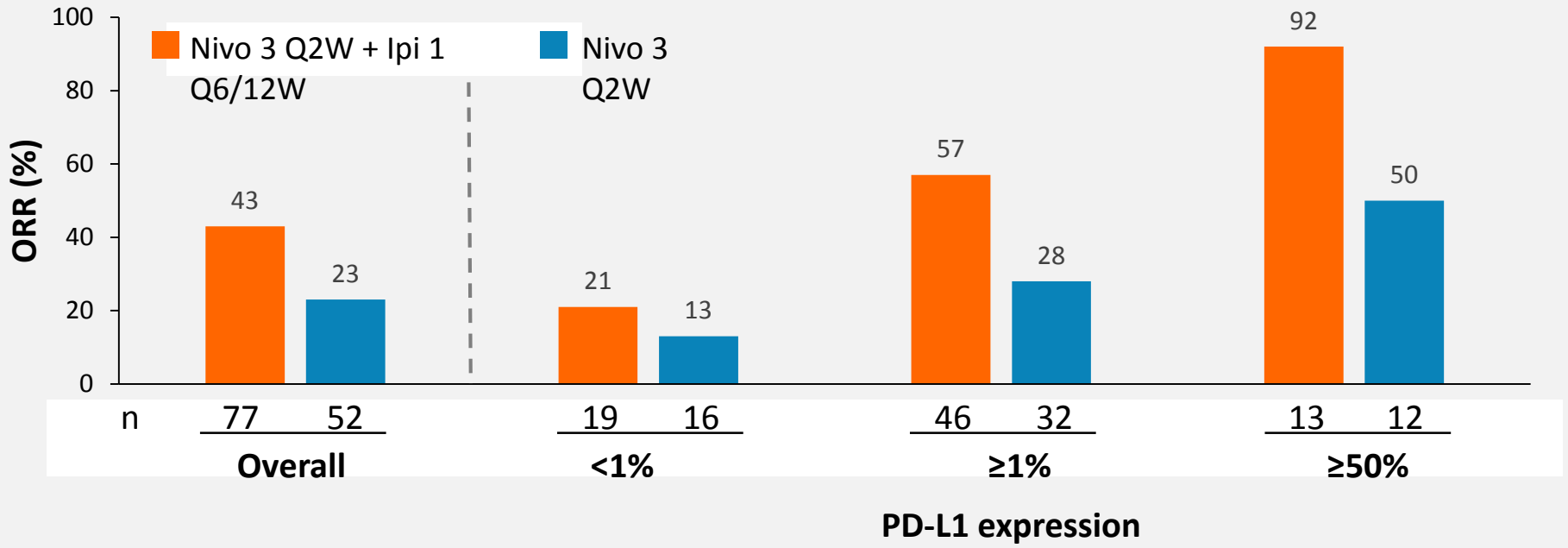
Number of patients at risk:

Nivolumab + Ipilimumab	314	219	174	156	133	126	103	48	8	0
Nivolumab	316	177	148	127	114	104	94	46	8	0
Ipilimumab	315	137	78	58	46	40	25	15	3	0

Case Study 4: Signals with Combination Regimens

CheckMate 012: First-Line Nivolumab ± Ipilimumab in NSCLC

Will this signal with Ipi/Nivo translate into confirmed benefit in a randomized study?
In all-comers? In PD-L1 ≥1%; PD-L1 ≥50%?



Based on a September 2016 database lock; [a]3 determined radiographically per RECIST v1.1 and 3 identified by pathologic evaluation

Case Study 4: Signals with Combination Regimens
Nivolumab + Lirilumab (anti-KIR)

- Lirilumab is a fully human IgG4 mAb that blocks inhibitory KIRs on NK cells and promotes NK-cell activation and tumor cell death
- CA223-001: Phase 1b study evaluating safety and clinical activity of lirilumab combined with nivolumab
- Potential signal was identified in a previously treated **SCCHN** expansion cohort

Will this signal with Liri/Nivo in patients with PD-L1+ SCCHN tumors translate into confirmed benefit in a randomized study?

	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab	CheckMate 141 (Phase 3)[1,2] Nivolumab Monotherapy
ORR, n/N (%)	**7/29 (24)***	**32/240 (13)**
Complete response	3 (10)*	6 (2.5)
Partial response	4 (14)*	26 (11)
DCR, n/N (%)	15/29 (52)	NR
ORR by PD-L1 expression, n/N (%)†		
<1%	0/9 (0)	9/73 (12)
≥1%	7/17 (41)	15/88 (17)
≥5%	6/11 (54)	12/54 (22)
≥50%	4/7 (57)	7/19 (37)

*Includes unconfirmed responses.

‡Patients at risk, n = 15/41.

1. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print]; 2. BMS data on file.

Conclusions:

- As we move toward seamless drug development, discerning true positive from true negative signals will become even more important
- Adequate sample size, clinically meaningful effects, and a focus on key clinical or biologically defined subsets may decrease chances of acting upon false positive and false negative results.
- Similar principles for monotherapy treatments are expected to apply with combination regimens