Clinical Pharmacology Considerations for Immuno-oncology Combination Development

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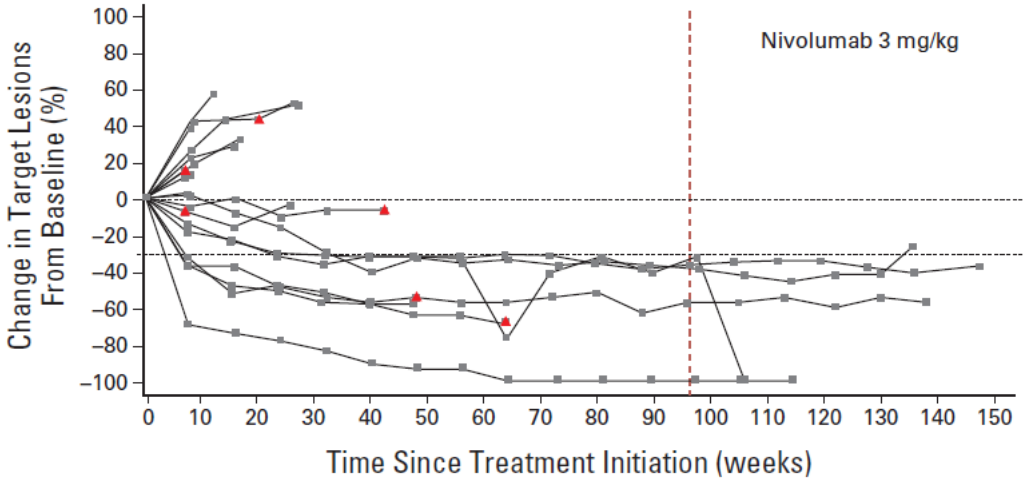
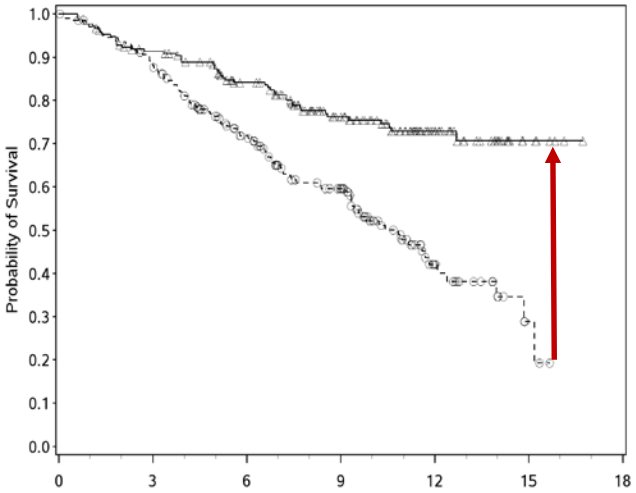
Bristol-Myers Squibb

What is cancer immunotherapy?

Immunotherapy is a type of **cancer** treatment designed to boost the body's natural defenses to fight the **cancer**





Red triangles: New lesions

Nivolumab (events: 50/210), median and 95% CI : NA

Dacarbazine (events 96/208), median and 95% CI : 10.84 (9.33, 12.09)

Characteristics of tumor-response to I-O Agents

- **Patients who do not progress tend to have durable disease control**
- **Unconventional responses: reduction in target tumor burden despite appearance of new lesions**

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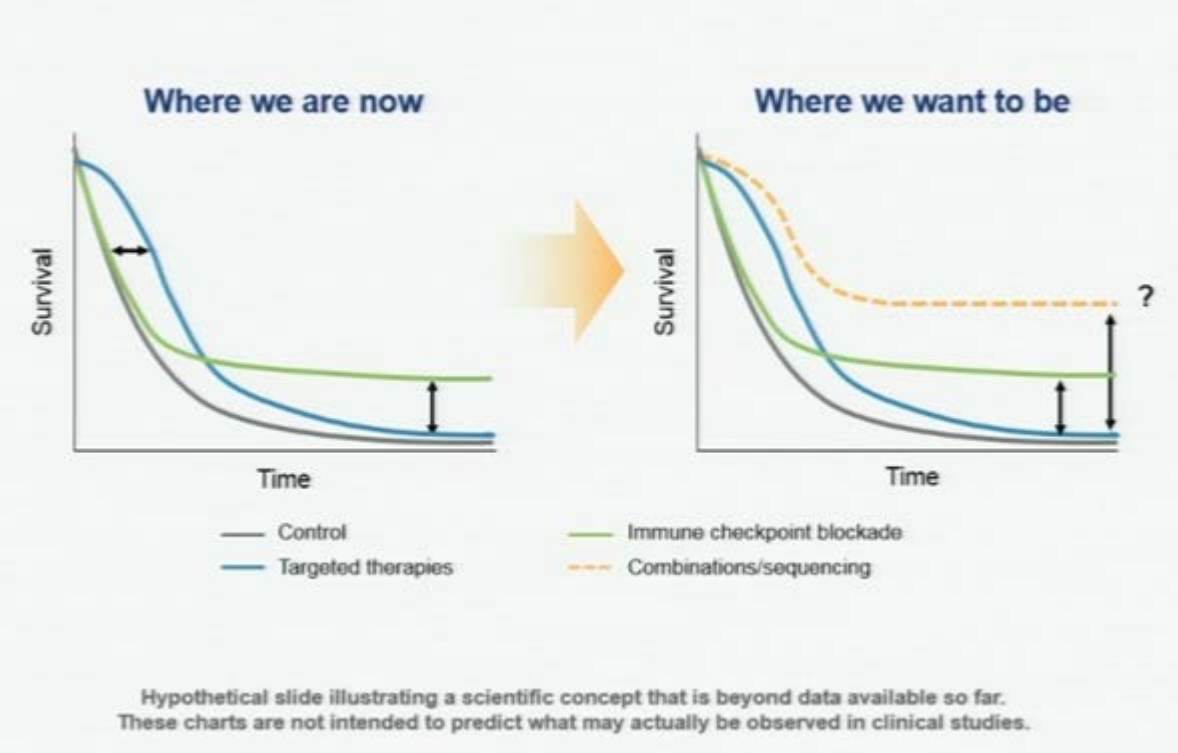
Topalian et al. J Clinical Oncology 2013; 32-1020-30, Robert et al. N Engl J Med 2015;372:320-30

Combinations may improve efficacy

Combination therapy to block more than one immunomodulatory pathway may further enhance the anti-tumor efficacy of each individual treatment



Sharma P., Allyson JP. Cell 2015, 161: 205-214

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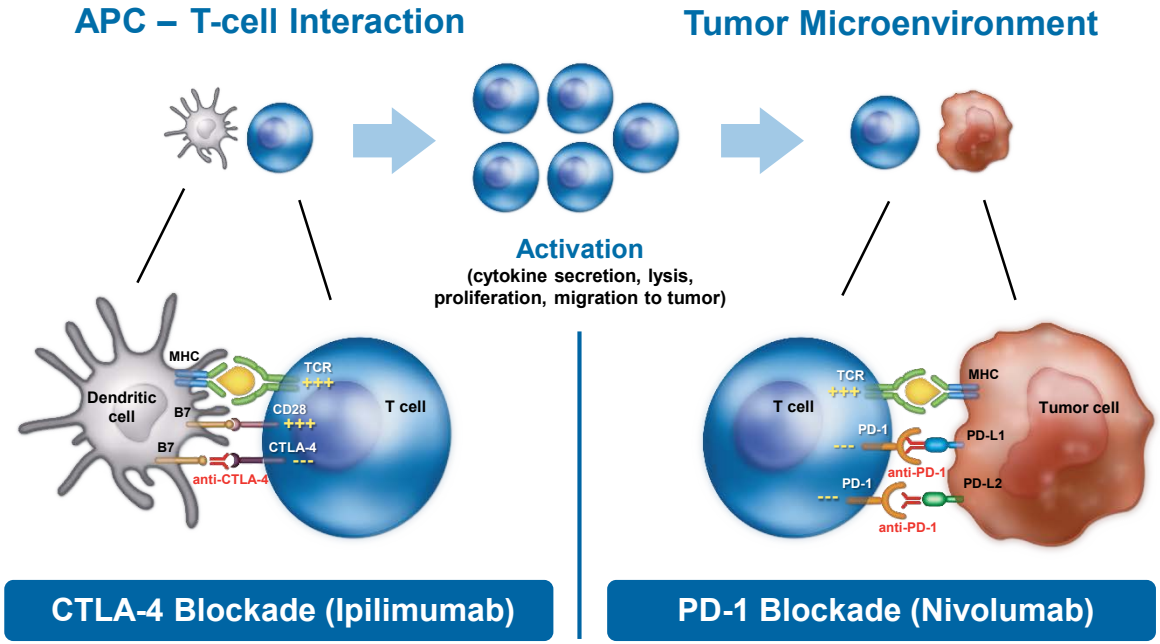
Biologic Rationale for Combined PD-1 and CTLA-4 Blockade

Ipilimumab (IPI) monotherapy in melanoma improves OS (~20% of treated patients alive ≥3 years)[1]

Phase III studies of nivolumab (NIVO) monotherapy in advanced melanoma:[2,3]

- 1-year OS rate of 73% and ORR of 40% in untreated melanoma (BRAF wild-type)
- ORR of 32% after progression on IPI, or IPI and a BRAF inhibitor if BRAF mutation-positive



1. Schadendorf et al. *J Clin Oncol* 2015 Feb 9 [Epub ahead of print]; 2. Robert et al. *N Engl J Med* 2015;372:320-330; 3. Weber et al. *Lancet Oncol* 2015;16:375-384.

Nivo + Ipi combination: Melanoma experience (CA209004)

Monotherapy experience in melanoma

Ipilimumab (mg/kg Q3W)

0.3	1	3	10

Nivolumab (mg/kg Q2W)

0.1	0.3	1	3	10

Activity: Nivo > Ipi
Tolerability: Nivo > ipi

Combination study design

Nivo+ipi treatment (mg/kg, Q3W)	Activity/tolerability
Nivo 10 + Ipi 10	Not enrolled
Nivo 10 + Ipi 3	Not enrolled
Nivo 3 + Ipi 3	DLT
Nivo 3 + Ipi 1	Synergistic activity and tolerable
Nivo 1 + Ipi 3	Synergistic activity and tolerable
Nivo 0.3 + Ipi 3	No synergistic activity

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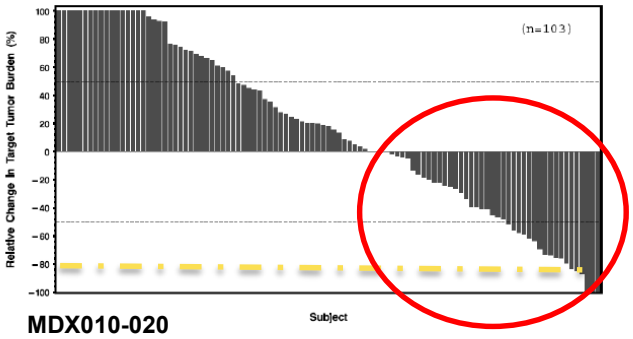
Agrawal et al, SITC-2015; P-141, Sznol et al. ECC-2013; abstr. 3734, Wolchok et al. N Engl J Med 2013, 369:122-33

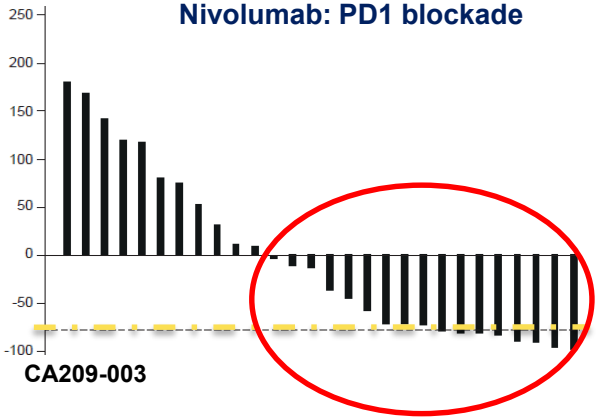
Proof of principle for I-O combinations: Percent Change in Tumor Burden

Ipilimumab: CTLA4 blockade



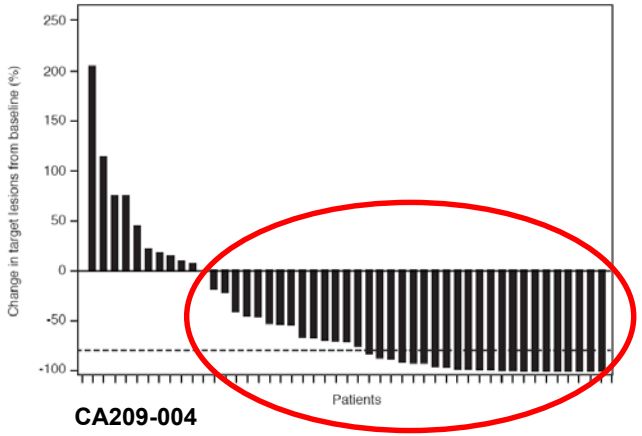
MDX010-020

Nivolumab: PD1 blockade



CA209-003

Ipilimumab + Nivolumab



CA209-004

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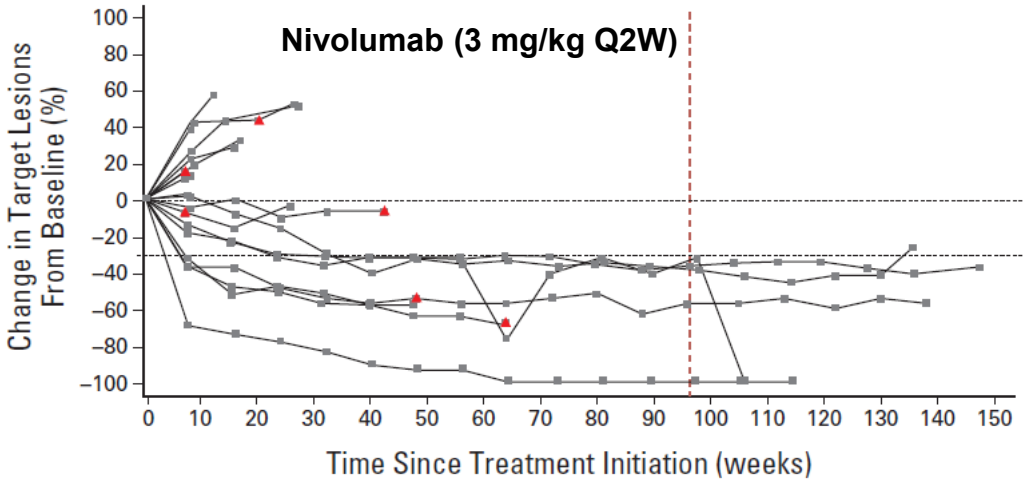
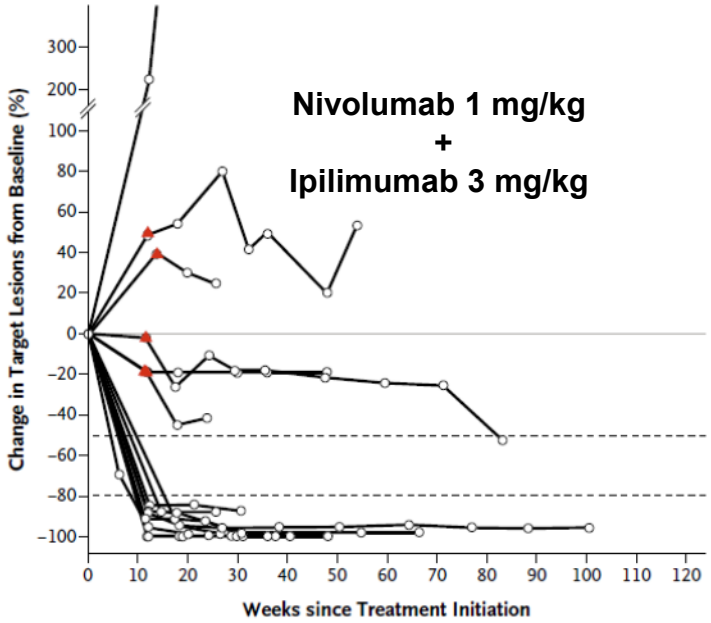
Time-Profile of Target Tumor Burden: Metastatic Melanoma Patients Treated with Nivolumab ± Ipilimumab



Topalian SL, et al. (2013), *Journal of Clinical Oncology*, *32*(10), 1020–1030



Wolchok JD, et al. (2013). New England Journal of Medicine, 369(2), 122–33.

- **Distinct patterns of response particularly evident with combination therapy**
- **% of patients with > 80% tumor reduction (depth of response) was used for dose selection of combination**
- **N1+ I3 dose was selected based on maximum activity and acceptable tolerability**

Red triangles: New lesions

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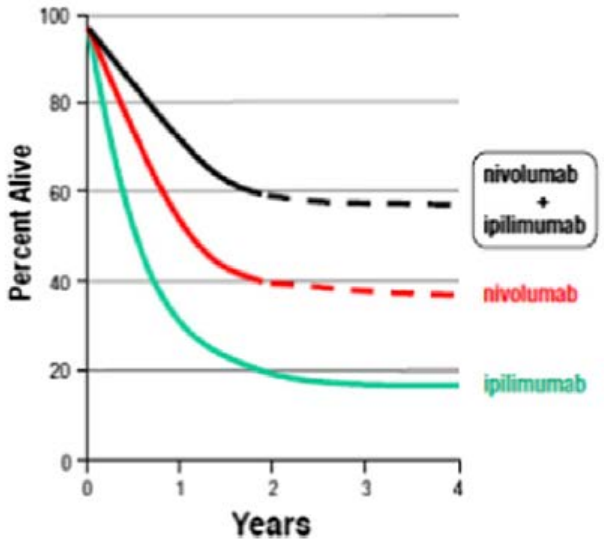
Concept of "Clinical Cure" with I-O combinations in Melanoma



Overall Survival Rates

N	1-year	2-year	Ref.
53	85%	79%	Sznol M et al. ASCO 2014
107	63%	48%	Hodi FS et al. ASCO 2014
137	44%	22%	Hodi FS et al. NEJM 2010

The 5-year survival rate was 18.2% (95% CI, 13.6% to 23.4%) for patients treated with ipilimumab plus dacarbazine versus 8.8% (95% CI, 5.7% to 12.8%) for patients treated with placebo plus dacarbazine (*P* = .002).

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Nivo + Ipi combination: NSCLC experience (CA209012)

Monotherapy experience in NSCLC

Ipilimumab (mg/kg Q3W)

3 mg/kg with chemo combination not active

Nivolumab (mg/kg Q2W)

0.1	0.3	1	3	10

Nivo+ipi treatment	Activity/tolerability
Nivo1 + Ipi3, Q3W X 4 cycles	DLT
Nivo3 + Ipi1, Q3W X 4 cycles	DLT
Nivo1 + Ipi1, Q3W X 4 cycles	No synergistic activity
Nivo1, Q2W + Ipi1, Q6W	No synergistic activity
Nivo3, Q2W + Ipi1, Q12W	Synergistic activity and tolerable
Nivo3, Q2W + Ipi1, Q6W	Synergistic activity and tolerable

Higher nivo exposure with low ipi exposure results in optimal benefit-risk profile

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NSCLC: Non small cell lung cancer

Agrawal et al, SITC-2015; P-141 , Rizvi NA. WCLC 2015. ORAL02.05

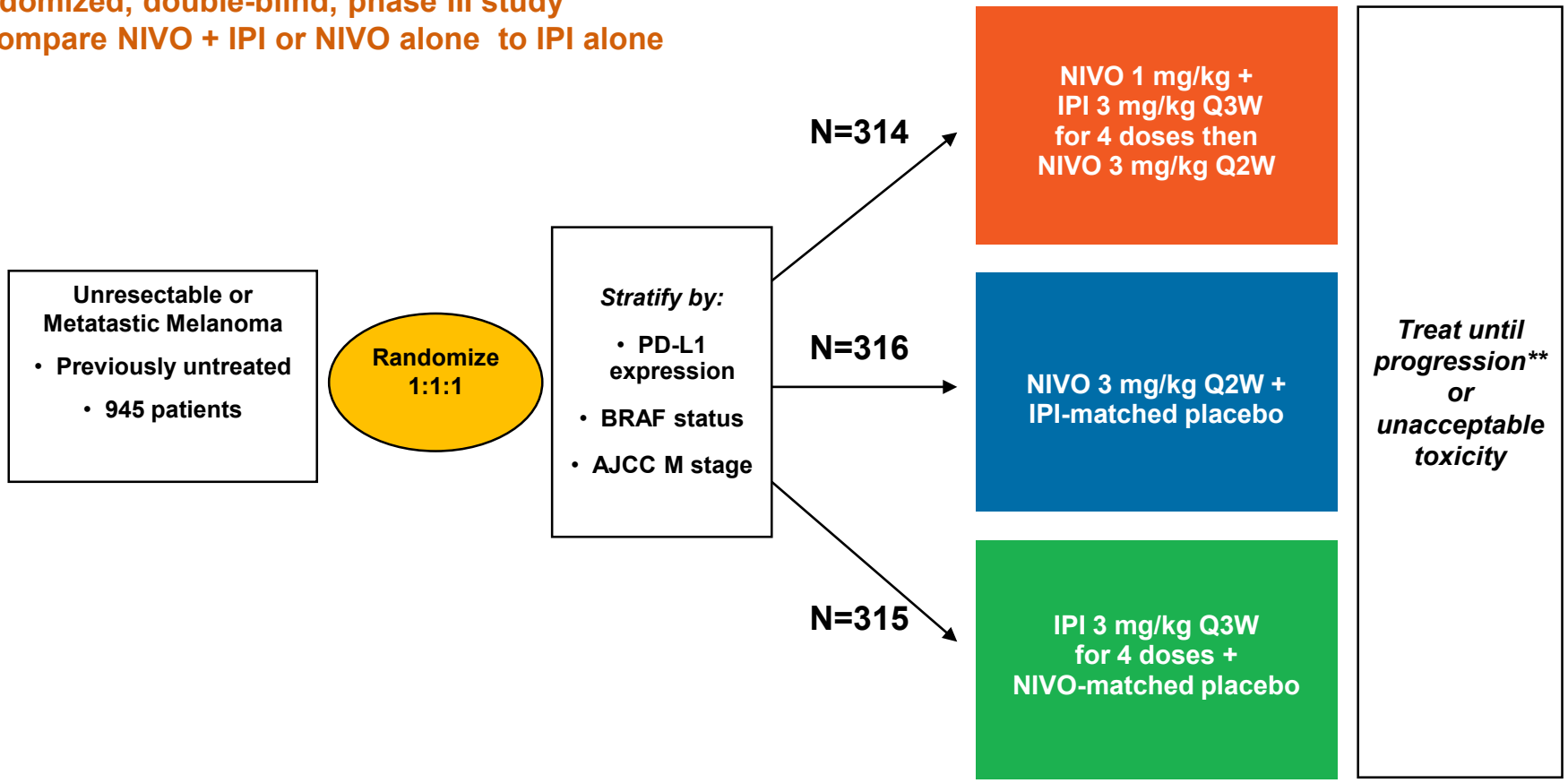
Considerations for combination trial design

- Dose cohorts based on expression levels of relevant targets in tumor types
- Differences in activity and tolerability by tumor type
- Dose de-escalation for either compounds
- Close monitoring of safety
- Novel study design to screen multiple combinations with speed
- Early surrogate endpoints for decision making
- PK and biomarker to understand contribution to efficacy and/or safety
- Patient selection for maximizing benefit from monotherapy vs. combination

Determining contribution of each component

CA209067 study design

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



Wolchok et al. ASCO 2015. LBA1

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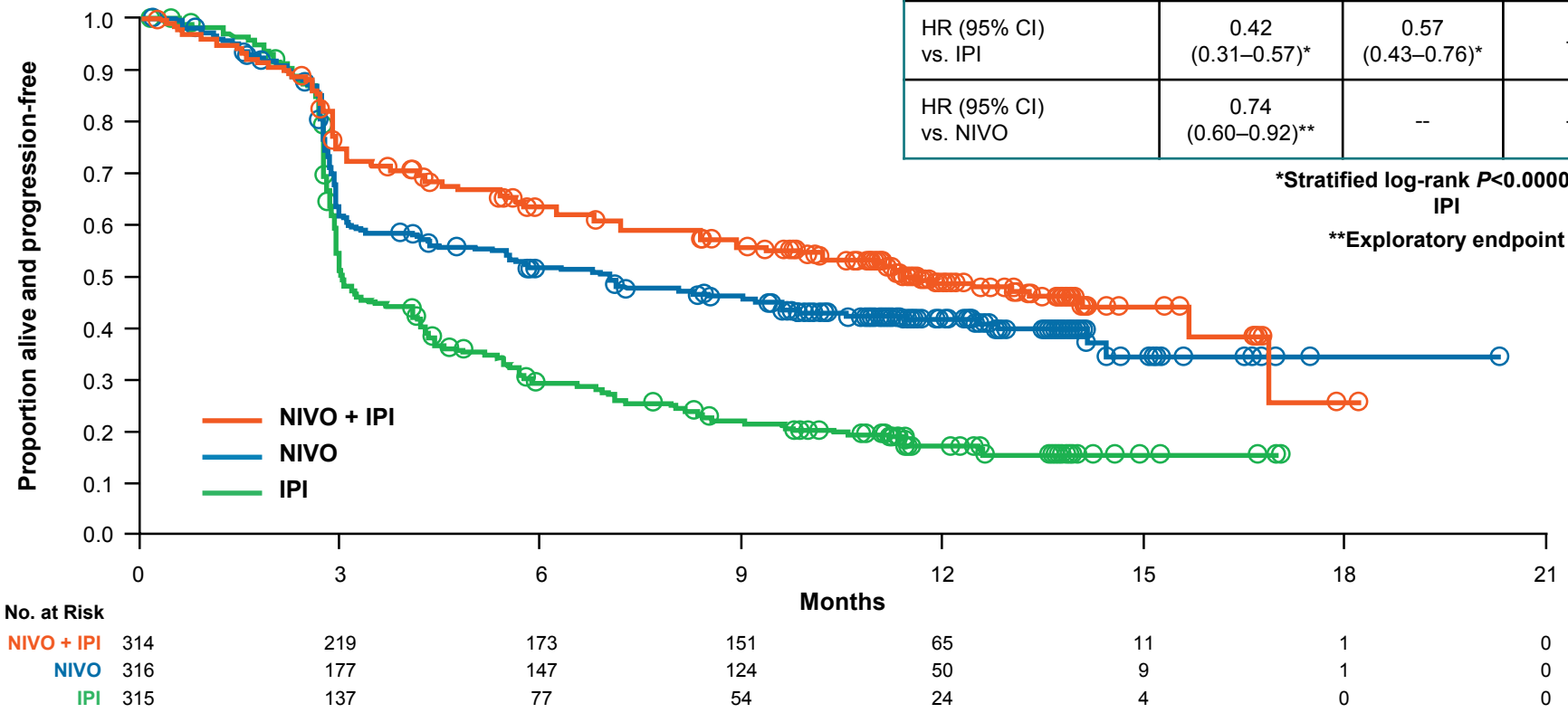
Efficacy: Progression-free-survival

	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 (95% CI) vs. IPI	0.42 (0.31–0.57)*	0.57 (0.43–0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60–0.92)**	--	--

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

**Exploratory endpoint



No. at Risk								
NIVO + IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

Wolchok et al. ASCO 2015. LBA1

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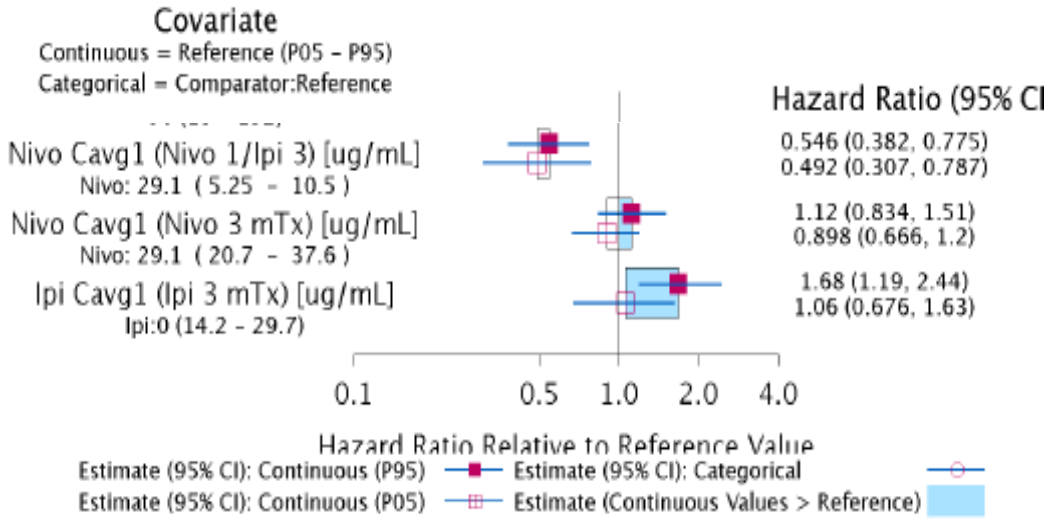
Determining contribution of each component

Exposure-Efficacy (PFS) Analysis



reference: median Cavg1 at nivo 3 mg/kg monotherapy

Cavg1 produced in combination therapy associated with improved PFS relative to monotherapy of nivo and ipi due to synergistic effect

PFS: Progression Free Survival

Feng et al. ACoP 2015. T-56

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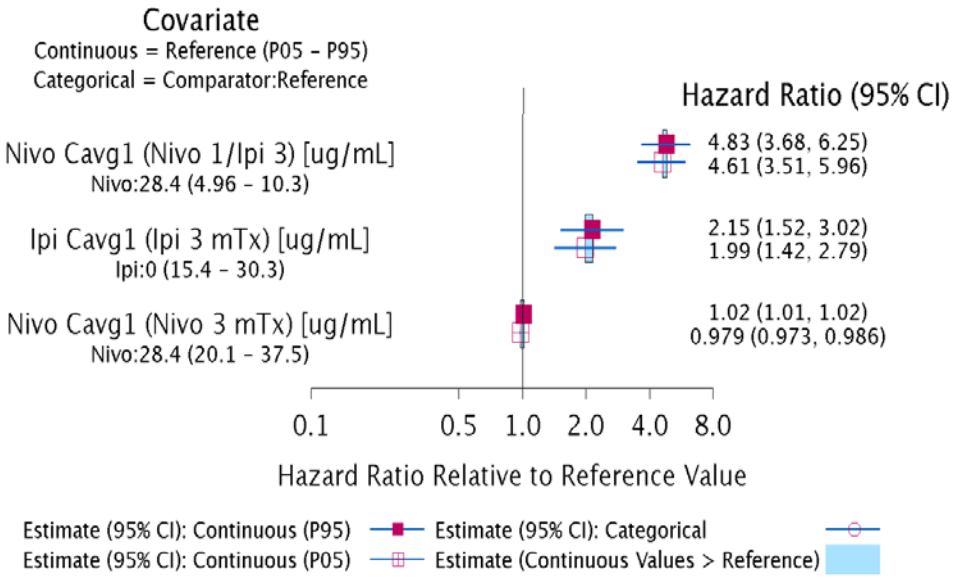
Determining contribution of each component

Exposure-Safety (AEs leading to discontinuation) Analysis



reference: median Cavg1 at nivo 3 mg/kg monotherapy

- **The hazard of AE-DC/D increased with nivo1/ipi 3**

Wang et al. ACoP 2015. M-61

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Immunogenicity in combination

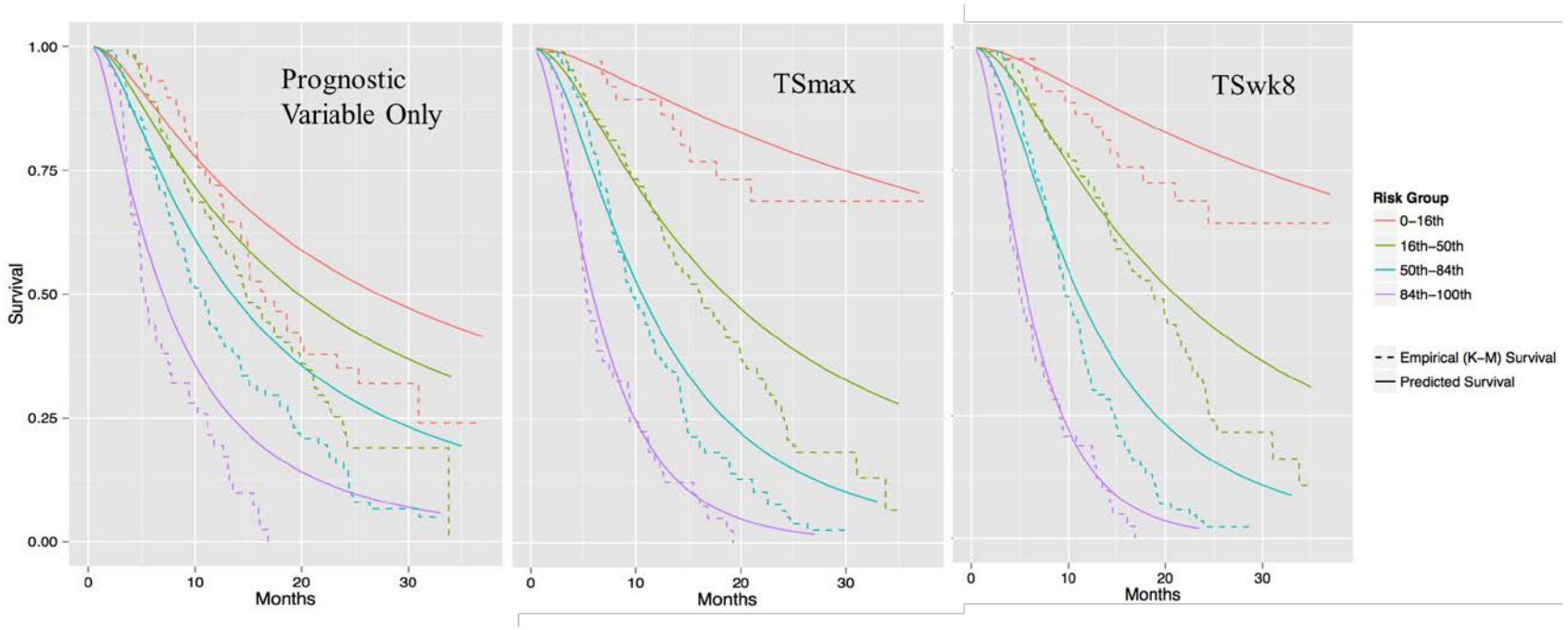
- Both Nivo and Ipi have shown low immunogenicity potential when administered alone
- Theoretically, higher immunogenicity may be possible due to the immunostimulatory mechanisms of these immune checkpoint inhibitors
- The incidence of Nivo immunogenicity was higher combination; however, only a minority of the patients were NAb-positive
- The safety profile for combination regimen was similar in ADA-positive/NAb-positive patients and ADA-negative patients.
- Efficacy profiles were also similar between ADA-positive patients and ADA-negative patients
- Overall, the immunogenic potential of Nivo+Ipi when given in combination was low, with no clear evidence of impact on safety or efficacy

Statkevich et al. ASCPT 2016. PI-126.

Translational approaches to accelerate immunotherapy combination

Leveraging totality of IO data to accelerate dose selection for IO combinations

Early tumor shrinkage is predictive of survival



Suryawanshi et al. ACoP 2015. S-11

Model predicted tumor shrinkage is based on nonlinear mixed-effects mixture-model of TGD

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IO systems pharmacology to predict combination efficacy

Melanoma immuno-oncology pilot PhysioMap: cells, cytokines, and biomarkers

Blood/Plasma

Pilot: circulating immune cells, cytokines, chemokines, RO, therapy A and B

Stage 2: expand immune cells, 3 more therapies (checkpoint inhibitors, agonists)

Transport

Tumor & lymph node

Pilot cell types: CD4: Naïve, Th, Th1, Th2, Th17, Treg, TEM; CD8: Naïve, CTL, TEM; NK, B, DC, M1/M2 Macrophages, MDSC, Cancer

Stage 2 cell types: CD4: TFH , TCM; CD8: TCM; B: Naïve, Plasma (short & long lived), Memory; VEC, LEC, CAF, pDC, N1/N2 Neutrophils, TIE2-Expressing Monocytes, Lymph node fibroblasts

Pilot mediators and markers (21): IL1, IL2, IL4, IL6, IL7, IL10, IL12, IL15, IL17, IL21, IL23, IFNg, TGFb, GMCSF, IDO, ~~Chemokines~~, LDH, tumor associated antigens, antibodies, nivo, ipi

Stage 2 mediators and markers (39): IL18, IFN1, TNFalpha, CXCL8, CXCL9, CXCL12, CCL4, CCL2, CCL5, CCL20, CCL21, CCL22, MCSF, PGE2, ICAM1, VEGFA, VEGFC, Ang2, ECM, MMP

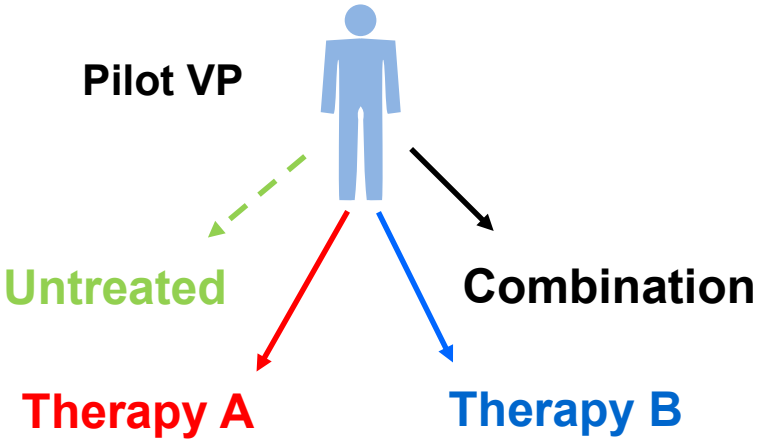
Pilot cell associated markers: MHC, CTLA4, B7, CD28, PD-1, PD-L1, PD-L2 FoxP3, Granzymes

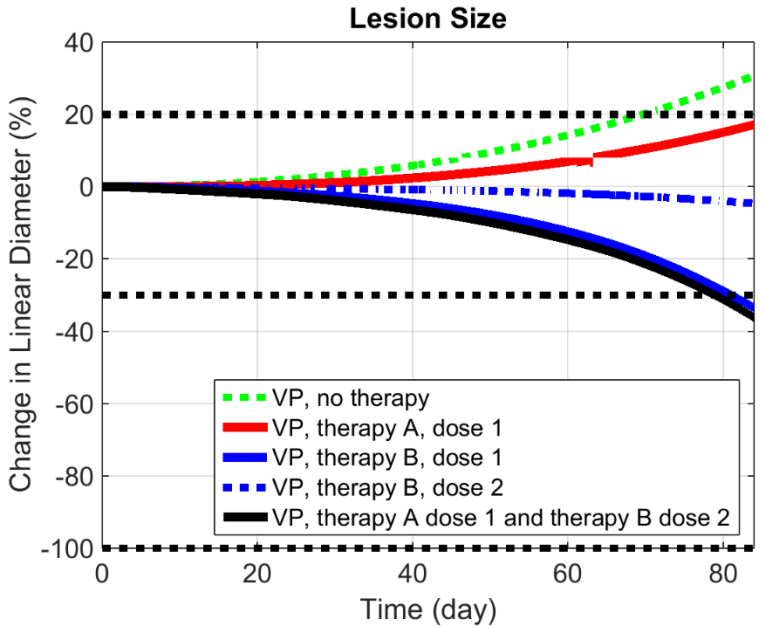
Stage 2 cell associated markers: LAG3, sLAG3, CD137, CD137L, GITR, GITRL

Some of the new processes in Stage 2: hypoxia, vessel and ECM density (metastatic potential), cancer and immune migration to the lymph node, adaptive immune response in the lymph node

Schmidt B. ASCPT 2016

Pilot virtual patient: Lesion response to combination therapies





- Different IO therapies tested in same VP
- Note the simulated increased response for the combination relative to monotherapies at the same concentrations
- Alternate VPs will facilitate exploring phenotypes that may have greater benefit from the combination

Schmidt B. ASCPT 2016

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Future directions in optimizing cancer immunotherapy combination regimen

- Establishing optimal regimen: sequencing, concurrent
- Dosing frequency
- Duration of treatment/number of combination doses
- Triple combinations
- Combinations with multiple treatment modalities

Acknowledgements

- Patients enrolled in clinical trials
- Clinical Pharmacology and Pharmacometrics group at Bristol-Myers Squibb
- Nivolumab and ipilimumab clinical development teams

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