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# Combinations and Other Immune Checkpoint Inhibitors/Agonists

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# Disclosures

- Earle A. Chiles Research Institute accepted grants from BMS, MedImmune, Prometheus and Merck to cover costs of clinical trials.
- I am neither employed nor do I have equity interests in any company or entity whose products/drugs will be discussed today.
- Research Support: NIH, Prostate Cancer Foundation, Safeway Foundation, Kuni Foundation, Prometheus Pharmaceuticals
- Speakers Bureau: Prometheus

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# Objectives/Overview

- Understand rationales for combining immunotherapy agents.
- Explore pre-clinical data for immunotherapy combinations.
- Review clinical data on T-cell checkpoint combinations.

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# ~~CTLA-4~~: PD-1: The Brake on T-Cell Activation

T-cell receptor: antigen/MHC

CD28 B7


CTLA-4 B7
PD-1 PD-L1 or PD-L2

Vaccine?

# Why combinations?

- Agents with non-cross reacting mechanisms and toxicities could enhance tumor response.
- Agents with “complimentary” mechanisms could enhance response.
- 1 + 1 = 4
- Post hoc ergo propter hoc

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# What might be complimentary immunotherapy?

- Inhibitor of a T-cell checkpoint + promoter of T-cell proliferation
- Inhibitor of a T-cell checkpoint + promoter of T-cell memory
- Vaccine (source of tumor antigen) + Inhibitor of a T-cell checkpoint
- Adoptive transfer + promoter of T-cell proliferation
- Agent to alter the tumor microenvironment + Immunotherapy X
- . . .

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# How have extant combinations been selected for clinical development?

- Murine tumor models showed anti-tumor activity, therefore we shall test it in humans.
- Hypothesis-driven investigation +/- pre-clinical modeling
- Company A has agents 1, 2 and 3, therefore 1+2+3 tested . . .
- We tried, it worked, any questions?

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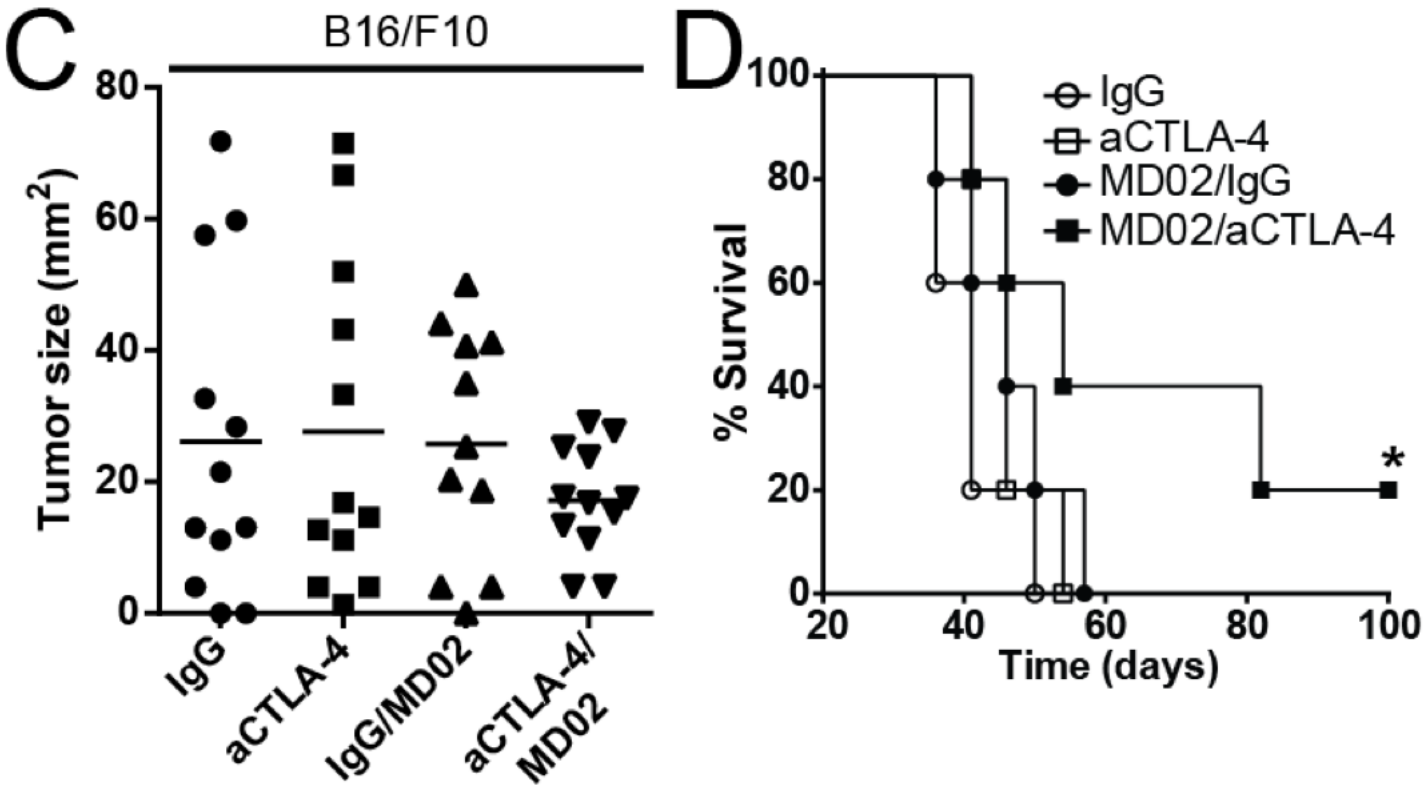
# Murine models:
# Galectin Inhibitor + anti-CTLA-4

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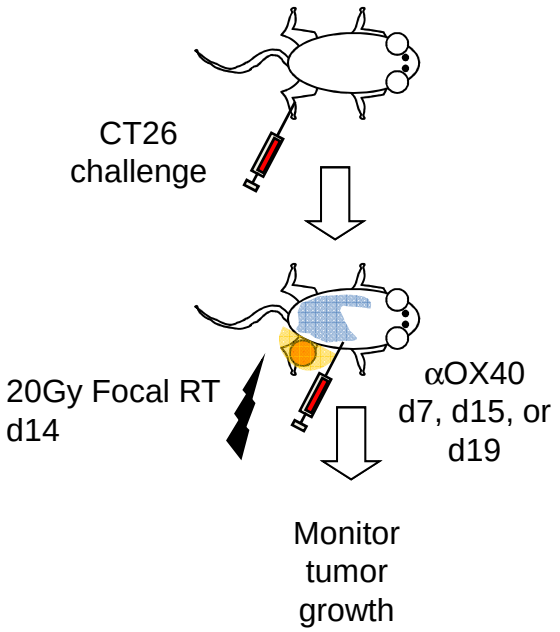
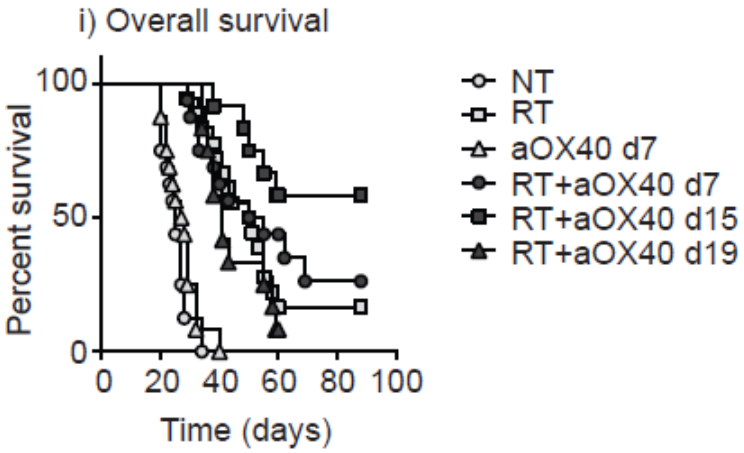
# Murine Models: Radiation + anti-OX40 in CT-26

**Experimental design**




**Tumor growth and survival**

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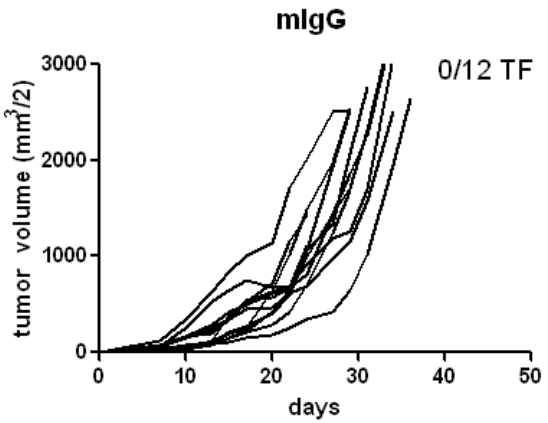
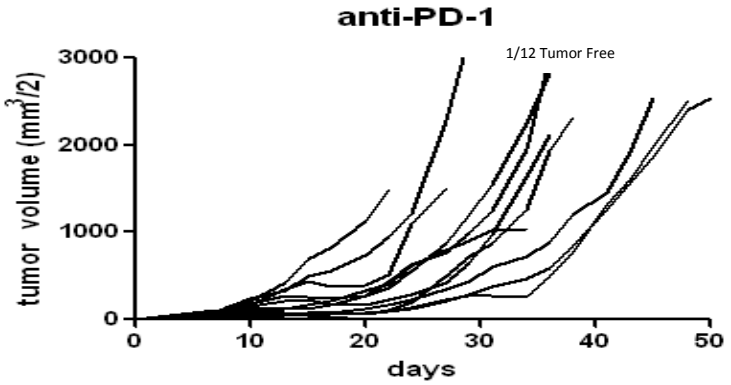
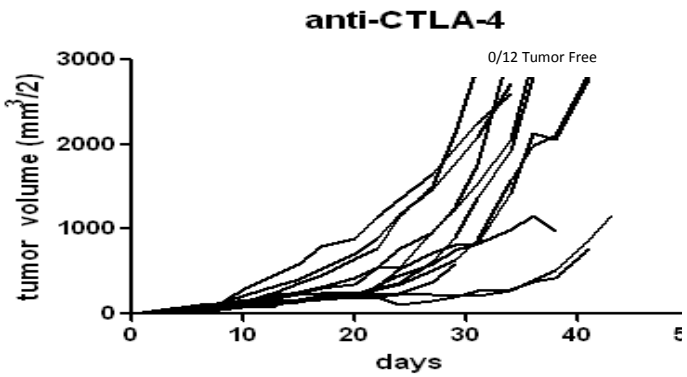
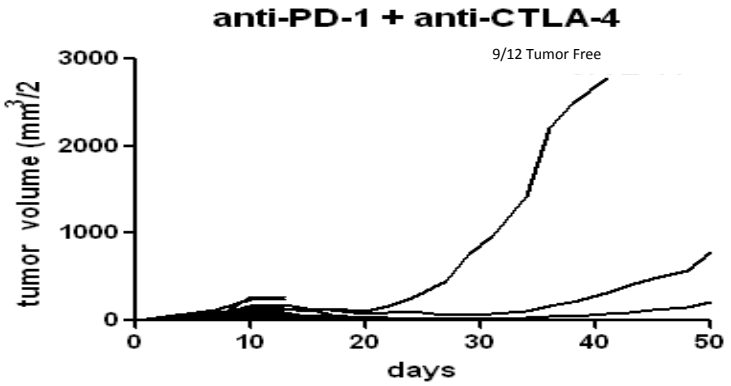
# Murine Models:
# Anti-CTLA-4 and anti-PD1

MC38 Colon Cancer
Antibody Rx Only [1, 2]

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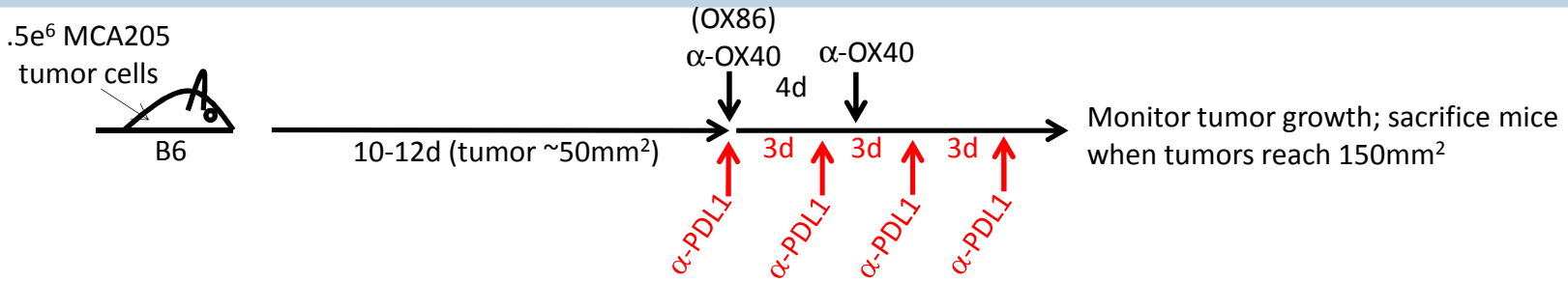
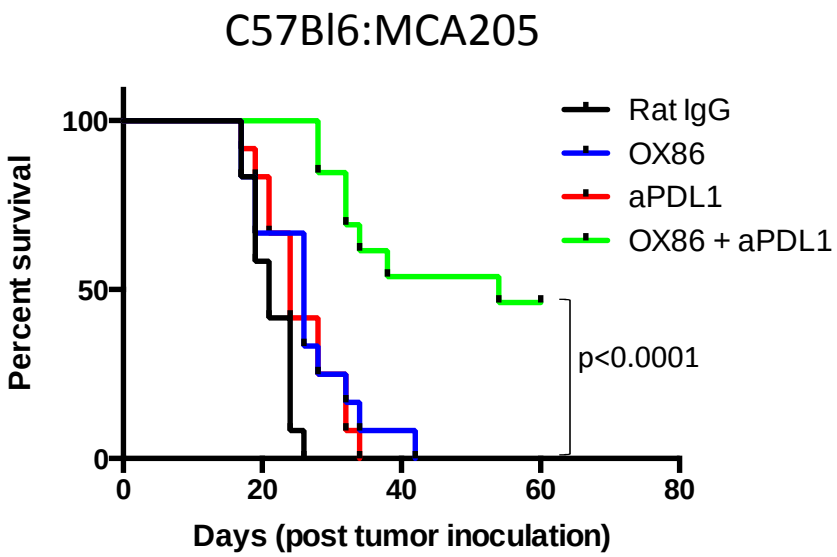
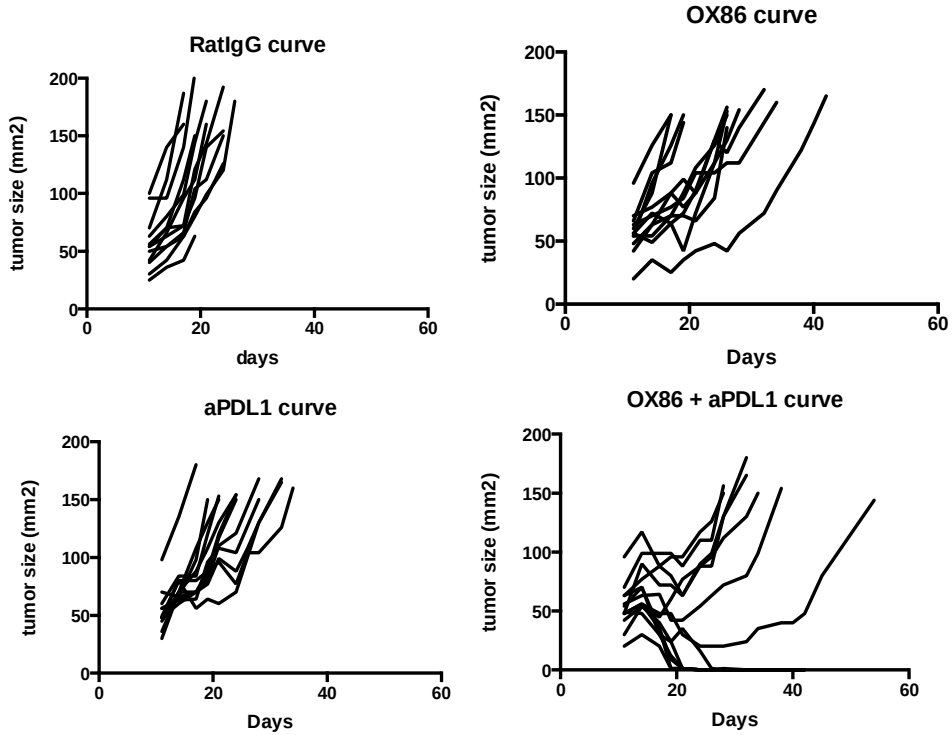
# Murine Models: α-PDL1 and α-OX40



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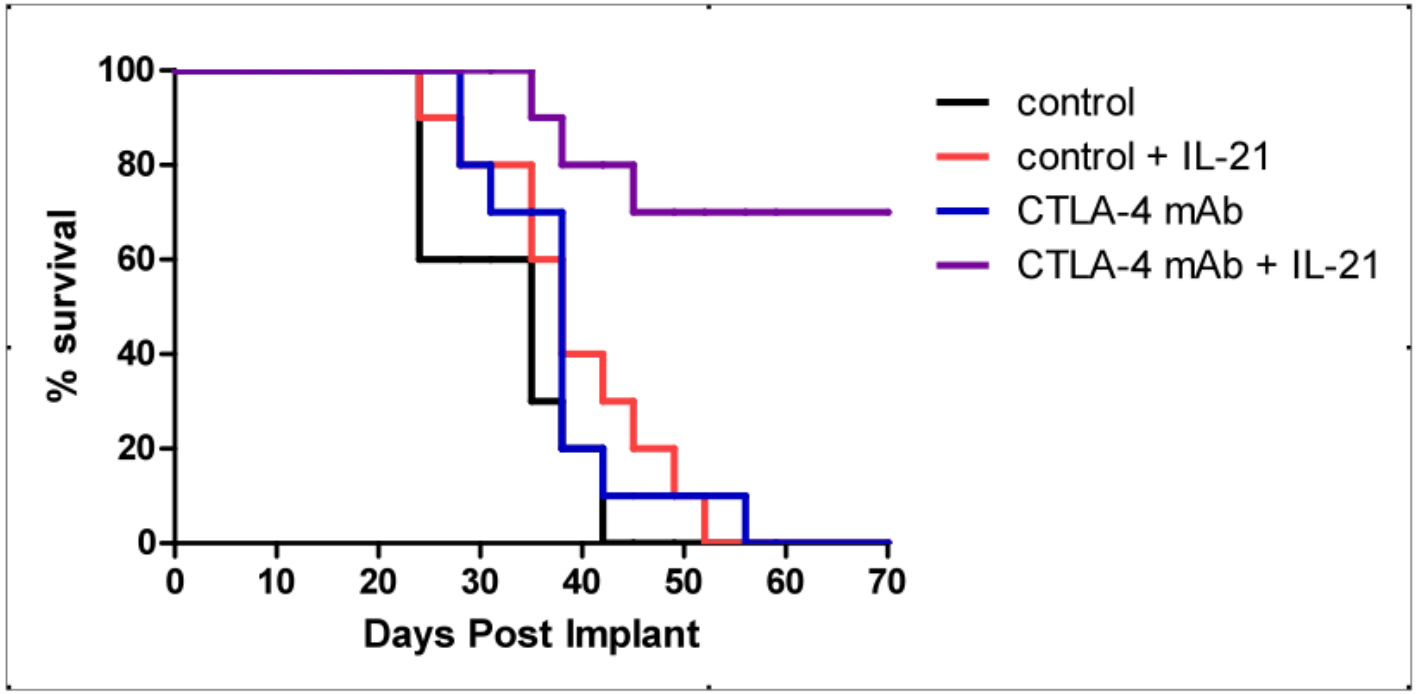
# Murine Models:
# IL-21 + Anti-CTLA4 in MC-38

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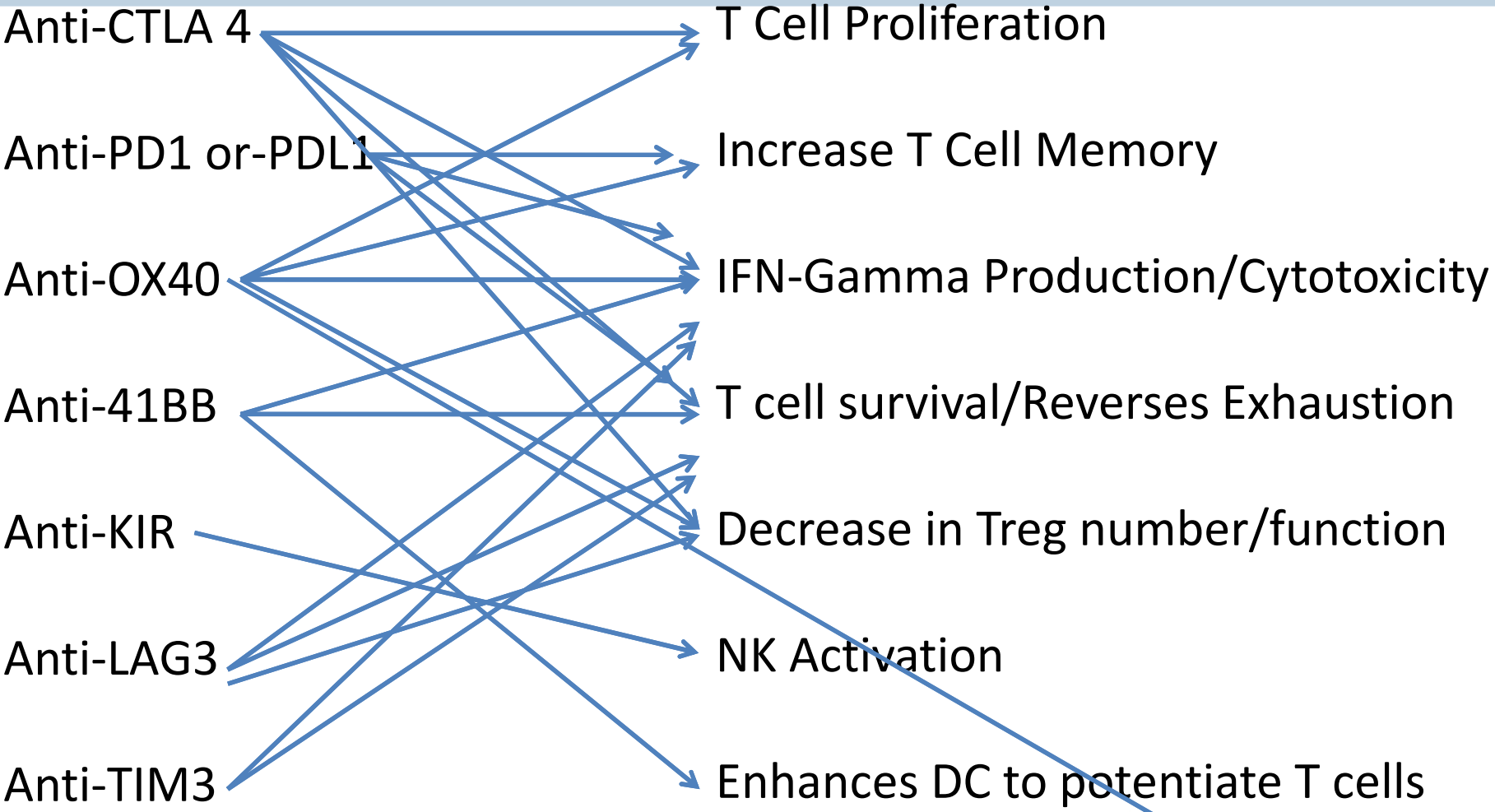
# Biological Effects of Some Immunotherapeutics

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# 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]

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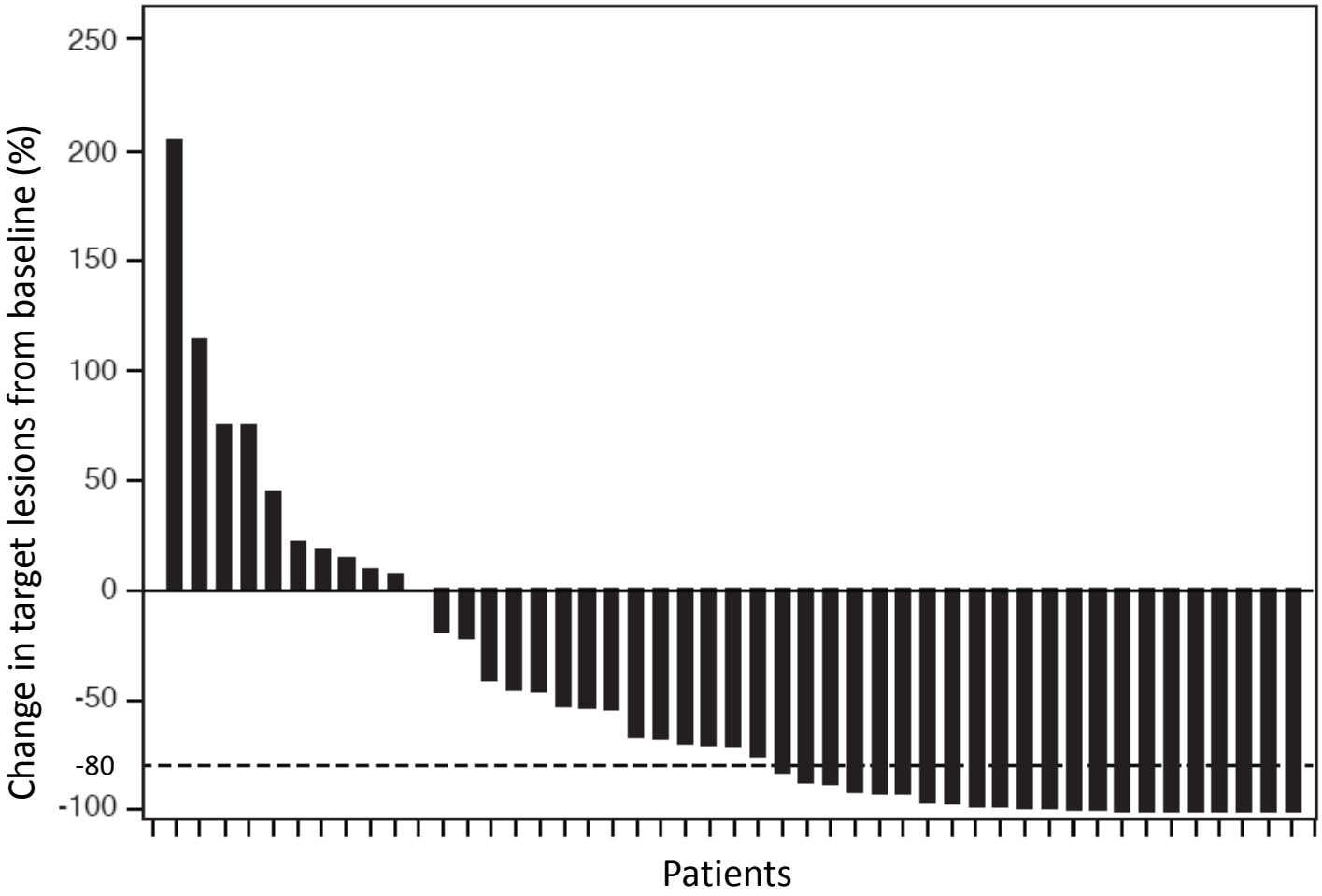
# Best Responses in All Evaluable Patients in Concurrent Cohorts




**After ~13 months of follow-up, for all concurrent cohorts, 90% of all responding patients continue to respond as of Feb 2013.**

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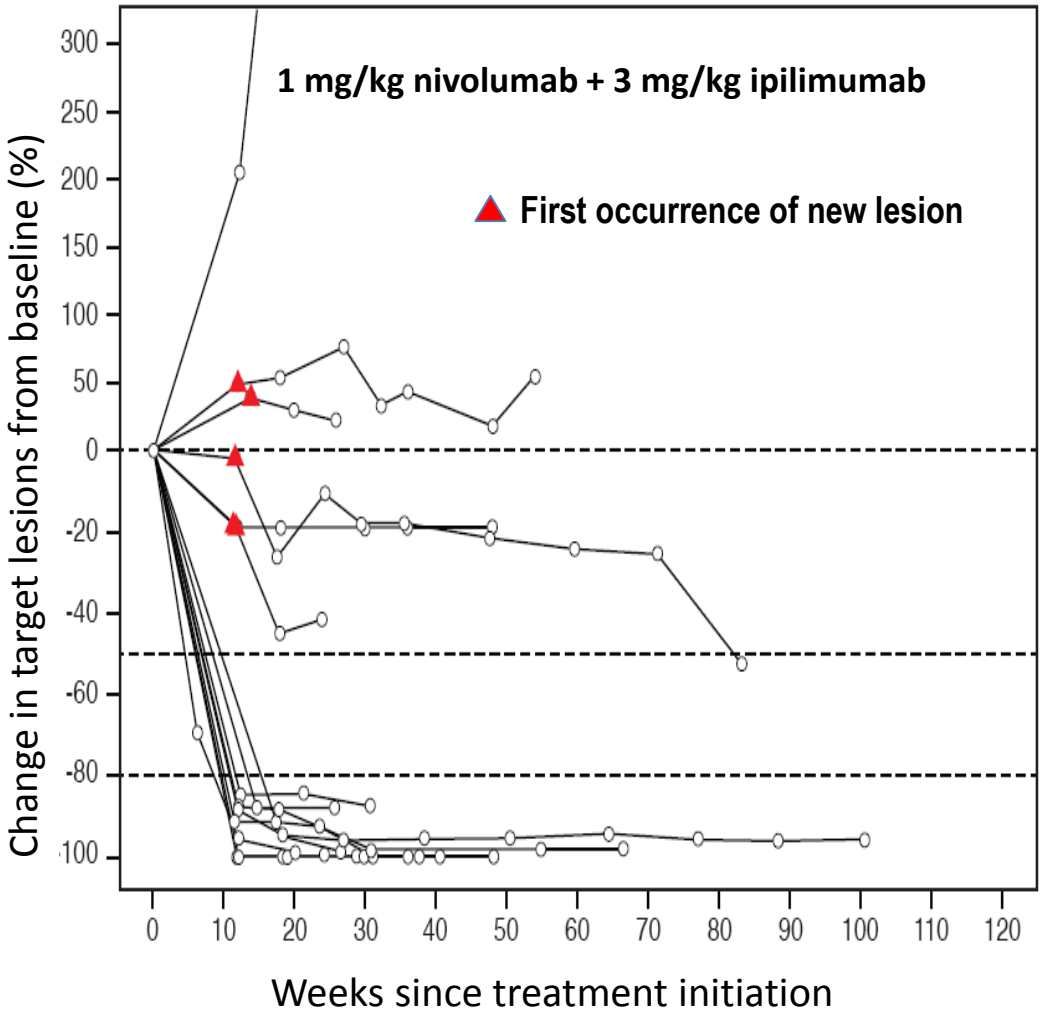
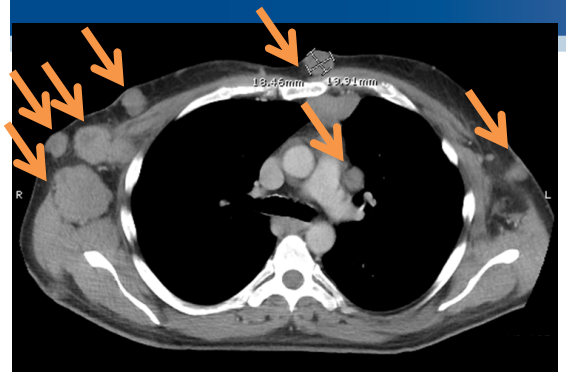
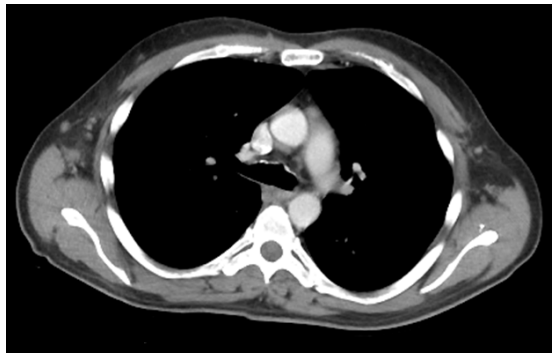
# Rapid and Durable Changes in Target Lesions



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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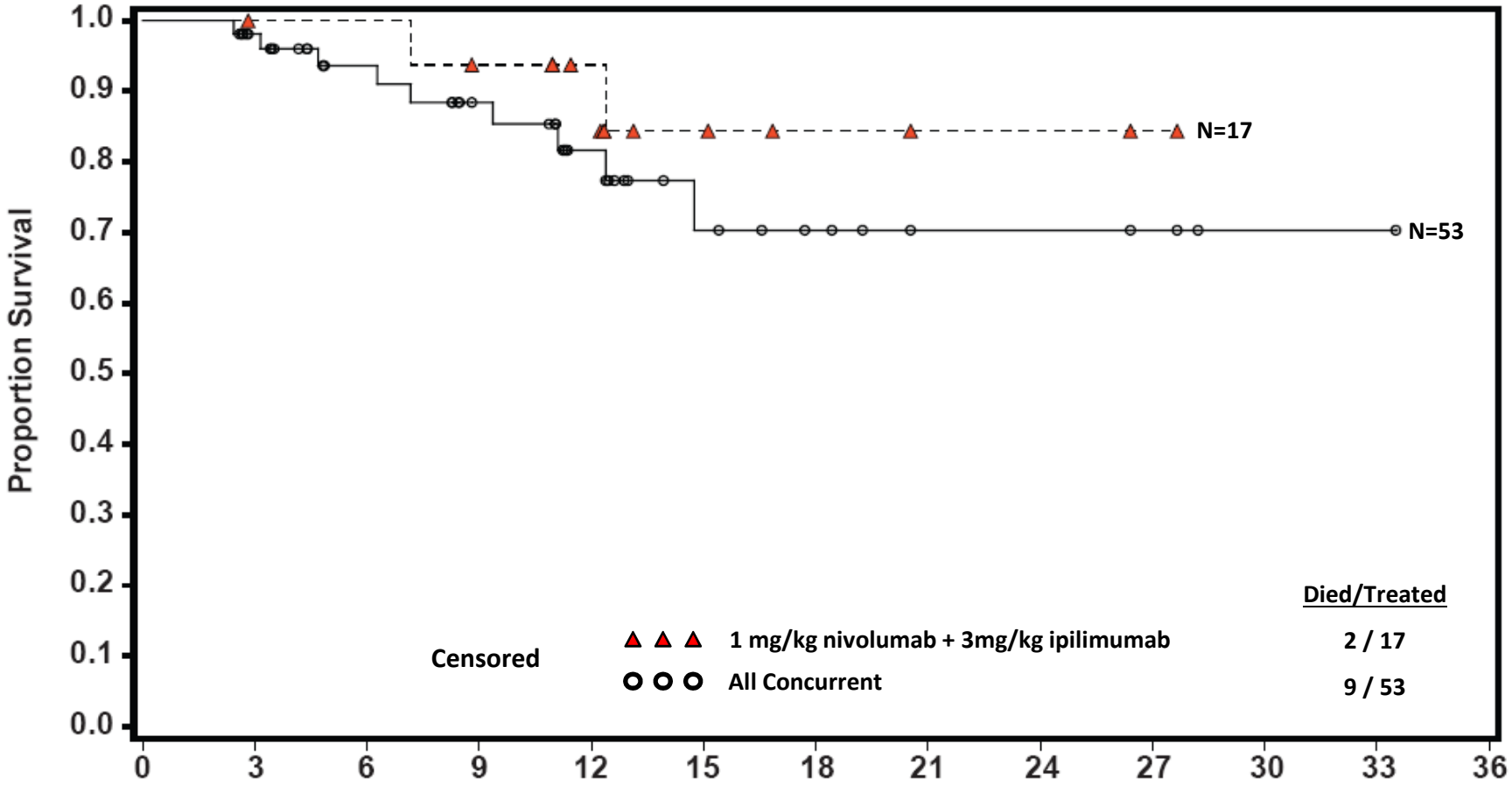
# Ongoing survival of patients treated with concurrent regimens




**Subjects 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 |

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# Results Updates

| Nivo + IPI Regimen | 1-year OS (%) | 2-year OS (%) | Median OS (mo) | Median PFS (Weeks) |
|---|---|---|---|---|
| Concurrent [53] | 85 | 79 | 40 | 27 |
| 0.3 + 3 [14] | 57 | 50 | 27 | 13 |
| 1 + 3 [17] | 94 | NC | NR | 58 |
| 3 + 1 [16] | 94 | NC | NR | 34 |
| 3 + 3 [6] | 100 | NC | NR | 34 |

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# Primary Analysis of a Phase 1B Multicenter Trial to Evaluate the Safety and Efficacy of T-VEC and Ipilimumab in Previously Untreated Unresected Stage IIIB-IV Melanoma

Puzanov et al.

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# Background

- Hypothesis: Priming an immune response with T-VEC will enhance ipilimumab-induced anti-melanoma activity.
- Primary Objective = Objective Response

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# Treatment Plan

- T-VEC given IT on weeks 1 and 4, then every 2 weeks thereafter.
  - T-VEC continued until all SQ lesions disappeared, DLT or progressive disease
- Ipi (3 mg/kg IV q3 weeks x 4 doses) started at week 6.

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# Results

- 19 patients enrolled
- 10 had stage IV (M1b/c) disease
- Grade 3/4 adverse events occurred in 32% (hypophysitis, diarrhea, or adrenal insufficiency attributed to Ipi)

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# Results Continued

- ORR = 57% (6 CR, 5PR)
  - 6 patients had stable disease
- Peripheral blood CD8 T cells increased 1.8 fold after T-VEC and 2.9 fold after Ipi (+ T-VEC)
- Median time to response was 2.9 months

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# Cautionary Tales from Combination Trials

- The combination of ipilimumab and vemurafenib resulted in grade 3 hepatic toxicity.
- The combination of IL-21 + ipilimumab showed no convincing synergy (ORR << 10%).
- PD1 expression touted as a biomarker for response to anti-PD-1, now ???
- Gp100 vaccine + ipilimumab showed lower ORR compared to ipilimumab + placebo (5.7 vs 10.9%)
- . . .

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# Selected Combination Immunotherapy Trials at EACRI

- Anti-KIR + Anti-PD1
- Anti-LAG3 + Anti-PD-1
- GRMD-02 + Ipilimumab
- Anti-OX40 (aka MEDI6469) + SBRT
- MEDI6469 + tremilimumab or MEDI-4736 or rituximab
- IL-2 + Ipilimumab
- IL-2 + SBRT
- CVA-21 + Ipilimumab (coming soon)
- . . .

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# Questions for the Future (and present)

- What is the best sequence of immunotherapies?
- Will the best combination be individualized? (e.g. “personalized immunotherapy” based on immunoscore or similar)
- How have prior treatments influenced the results of extant clinical trials?
- Are the mechanisms observed in pre-clinical work relevant to patient responses?
- What is the best timing of agents?
- . . .

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