IMMUNO-ONCOLOGY

CHALLENGES IN DEVELOPING NOVEL-NOVEL COMBINATIONS

Characterizing The Contribution of Monotherapy Components

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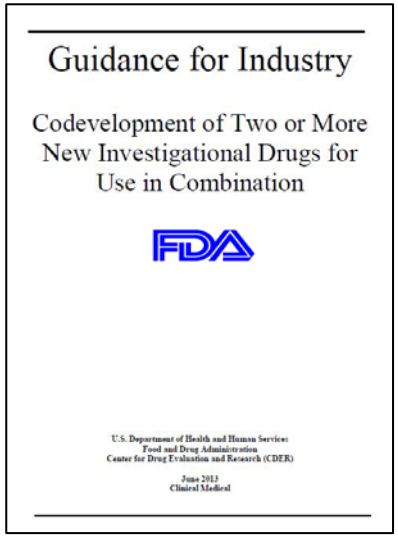
CURRENT REGULATORY VIEW ON NOVEL-NOVEL COMBINATIONS

- **Contribution of Components (CoC): Requirement for demonstrating the contribution of each agent to the activity of the combination to the extent possible and needed**
  - Depends on the level of enhanced activity expected with the combination vs individual monotherapy components



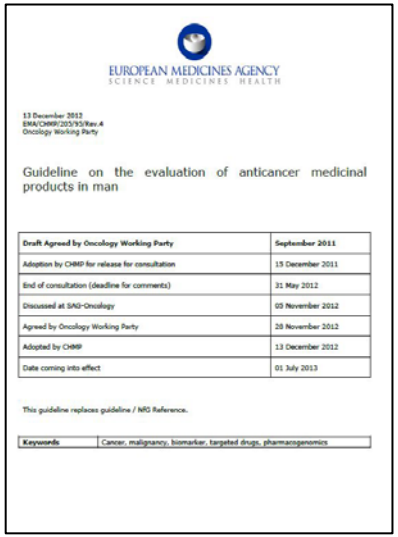
Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

FDA

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2013
Clinical Medical



EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

13 December 2012
EMA/CHMP/205953/Rev.4
Oncology Working Party

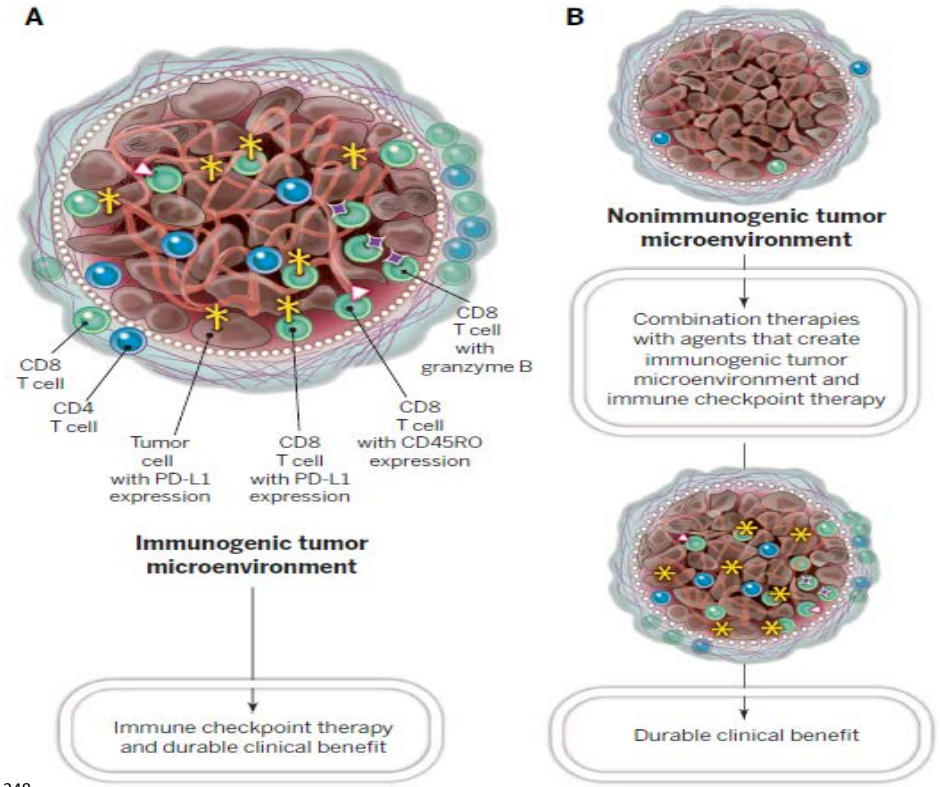
Guideline on the evaluation of anticancer medicinal products in man

Draft Agreed by Oncology Working Party	September 2011
Adoption by CHMP for release for consultation	15 December 2011
End of consultation (deadline for comments)	31 May 2012
Discussed at SAG-Oncology	05 November 2012
Agreed by Oncology Working Party	28 November 2012
Adopted by CHMP	13 December 2012
Date coming into effect	01 July 2013

This guideline replaces guideline / NfG Reference.

Keywords	Cancer, malignancy, biomarker, targeted drugs, pharmacogenomics

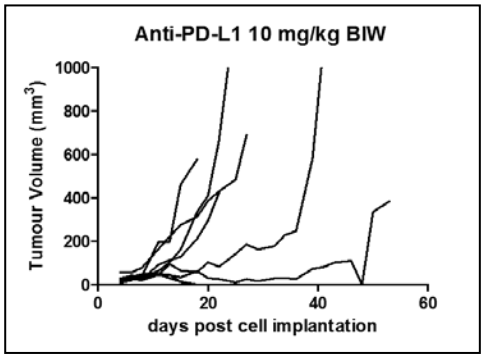
COMBINATIONS CAN CONVERT NON-IMMUNOGENIC TUMORS TO IMMUNOGENIC

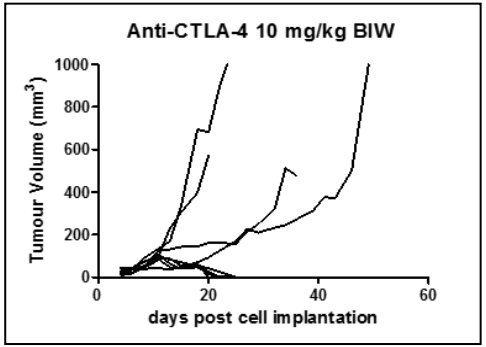


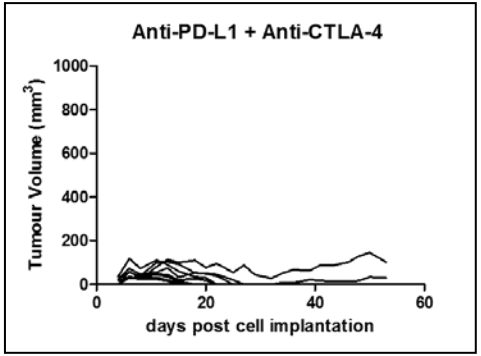
Padmanee Sharma and James P. Allison SCIENCE 2015 • VOL 348

PRECLINICAL DATA INDICATES POTENTIAL SYNERGY OF PD-L1/CTLA-4 COMBINATION

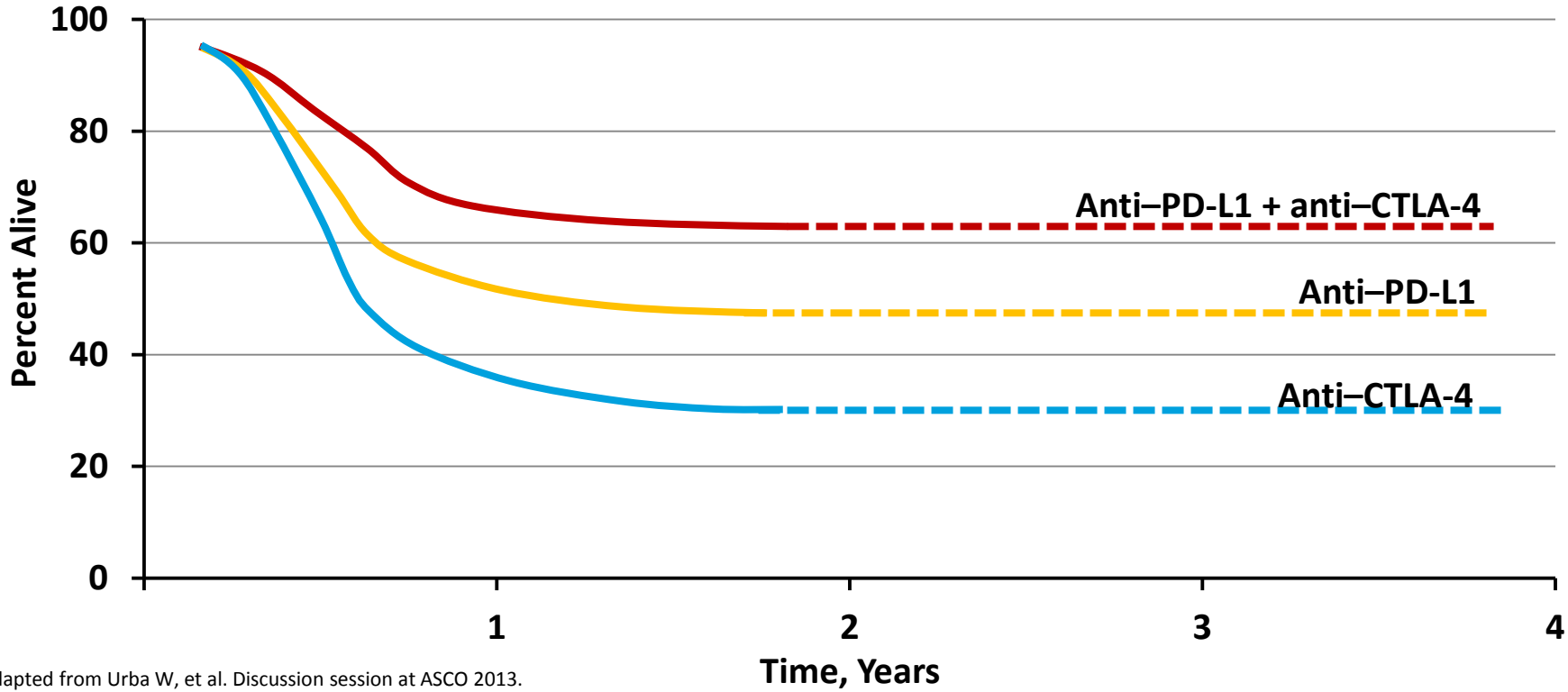
Tumor Volume vs Time After Tumor Cell Implantation







POTENTIAL LONG-TERM SURVIVAL WITH IO MONOTHERAPY OR COMBINATION



Adapted from Urba W, et al. Discussion session at ASCO 2013.

DOSE SELECTION DESIGN FOR DURVALUMAB + TREMELIMUMAB IN ADVANCED NSCLC

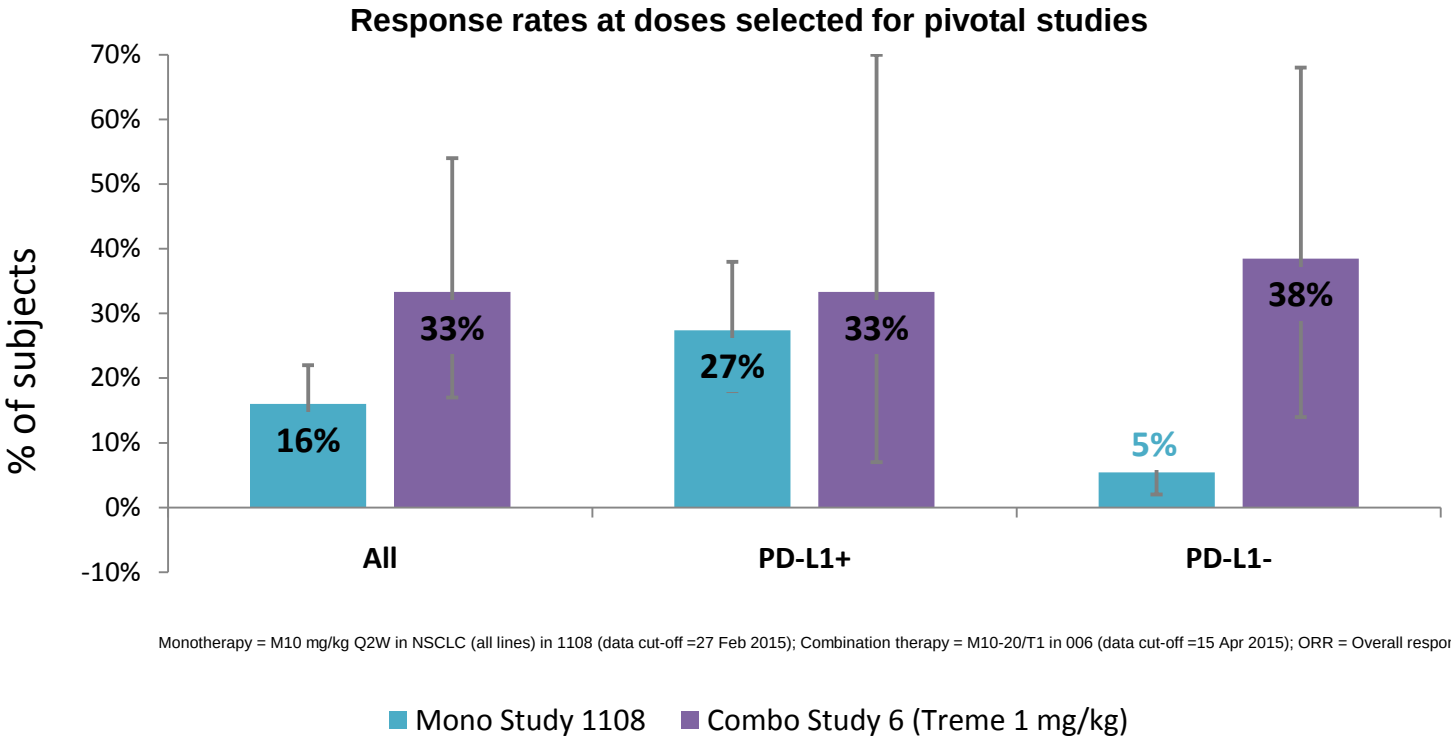
Study 006 Design: Zone-based dose escalation and Phase Ib expansion phase

Population: Stage III-IV NSCLC patients who have failed systemic therapy (no restrictions on number of prior therapies)

1st endpoint:	2nd endpoint:	Exploratory endpoints:
Safety (28-day DLT period)	Efficacy (RECIST response Q8 wks)	Peripheral pharmacodynamics, tumour PD-L1 status

*DLT, dose-limiting toxicity

COMBINATION CAN POTENTIALLY ADDRESS SUBPOPULATIONS IN AREAS OF UNMET MEDICAL NEED



Monotherapy = M10 mg/kg Q2W in NSCLC (all lines) in 1108 (data cut-off =27 Feb 2015); Combination therapy = M10-20/T1 in 006 (data cut-off =15 Apr 2015); ORR = Overall response rate

Rizvi N, et al. Oral presented at the 30th Society for Immunotherapy of Cancer Annual Meeting, National Harbour, MD, USA, 4–8 November 2015 (Oral 477; Abstract P193

TREME DOSE SELECTION KEY TO OPTIMIZING B/R OF COMBINATION

- Related Grade 3/4 AEs and discontinuations due to related AEs were lowest in the 1 mg/kg Q4W tremelimumab cohorts
- AEs did not appear related to dose or schedule of durvalumab

	M10-20 Q4/2W T1 mg/kg n=56	M10-20 Q4/2W T3 mg/kg n=34	M15 Q4W T10 mg/kg n=9
Related AE	35 (63%)	30 (88%)	8 (89%)
Related G3/4 AE	16 (29%)	18 (53%)	7 (78%)
Related death	1 (2%)	1 (3%)	0
Related serious AE	10 (18%)	17 (50%)	7 (78%)
Related AE leading to discontinuation	4 (7%)	12 (35%)	4 (44%)

SUMMARY

- Biology of the combination is complex
- Preclinical data may support scientific hypothesis for synergistic effect
  - Where appropriate & relevant animal models or systems can be identified
- Monotherapy dose may differ from that used in combination
  - Impact on evaluating CoC
- Clinical activity & tolerability burden of combination drive B/R optimization through dose selection
- Combinations may address unmet need not fulfilled by monotherapies
  - Challenge with extent of monotherapy data to be generated in these areas

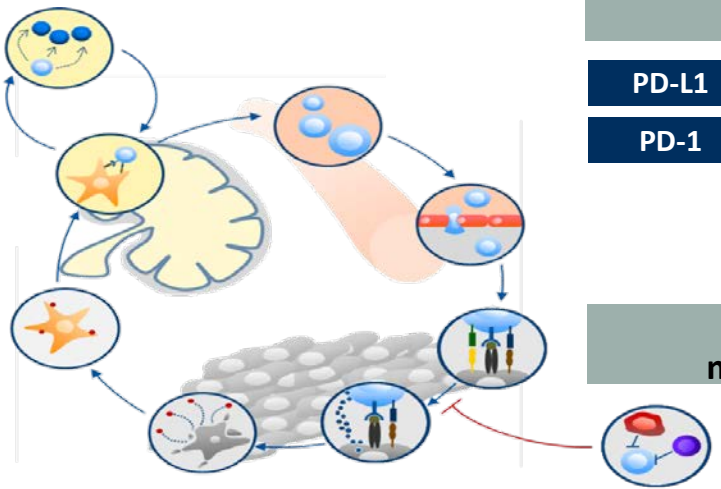
COMBINATIONS HAVE POTENTIAL TO ADDRESS DIFFERENT ESCAPE MECHANISMS

Optimising T-cell function and memory

- PD-L1
- CTLA-4
- OX40
- PD-1
- CART
- TIM-3

Antigen presentation

- Chemo
- Oncolytic virus
- NKG2A
- Radio-therapy
- TKI
- ADC
- Vaccines



Inhibition by micro-environment

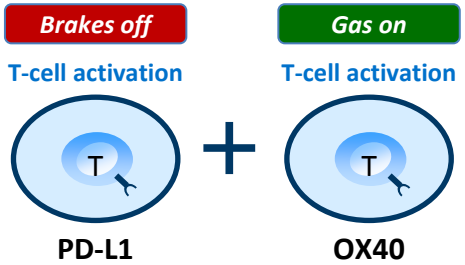
- IDO
- CCR4
- STAT3
- CXCR2

Haematology

ADC, antibody-drug conjugate; CART, chimeric antigen receptor T-cell therapy; IDO, indoleamine 2,3-dioxygenase; TKI, tyrosine-kinase inhibitor

Chen DS and Mellman I. *Immunity* 2013;39(1):1–10

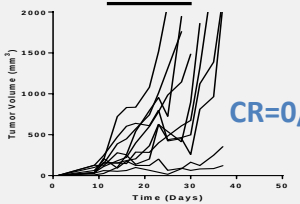
THE PROMISE OF COMBINATIONS BEYOND CTLA-4 + PD-L1



PD-L1 + OX40 and CTLA-40 + OX40

Pre-clinical[1] data with PD-L1

PD-L1



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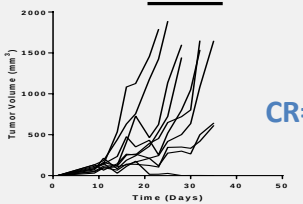
OX40



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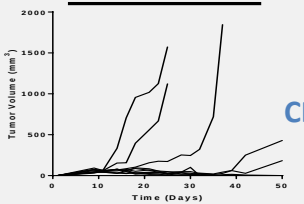
PD-L1 + OX40



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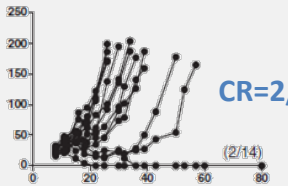
Pre-clinical[1] data with CTLA-4

CTLA-4



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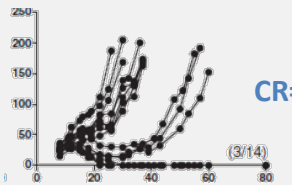
OX40



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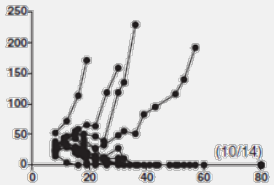
CTLA-4 + OX40



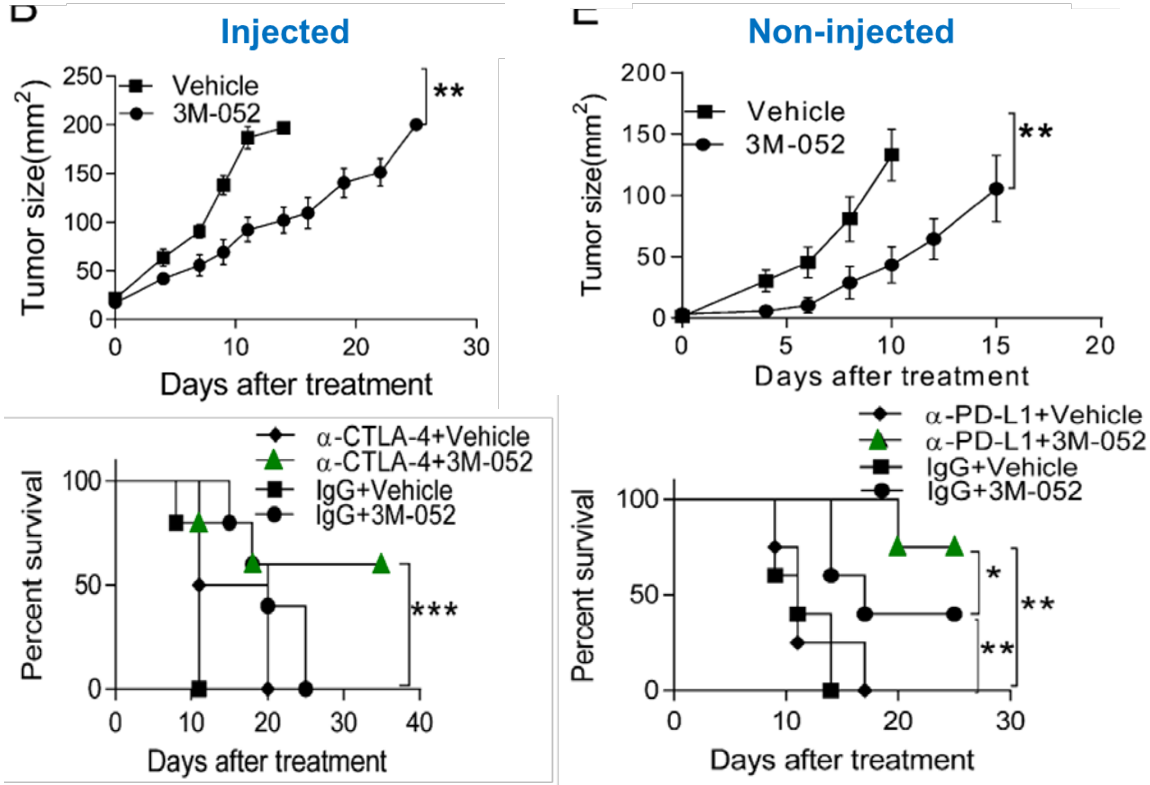
CR=10/14

1 Mouse model used in experiments, CR = complete response, McGlinchey et al. Poster AACR 2014

TLR7/8 AGONIST IN COMBINATION WITH CTLA-4 AND PD-L1

Gas on

Triggers Innate Immunity + Promotes Adaptive Immune Response

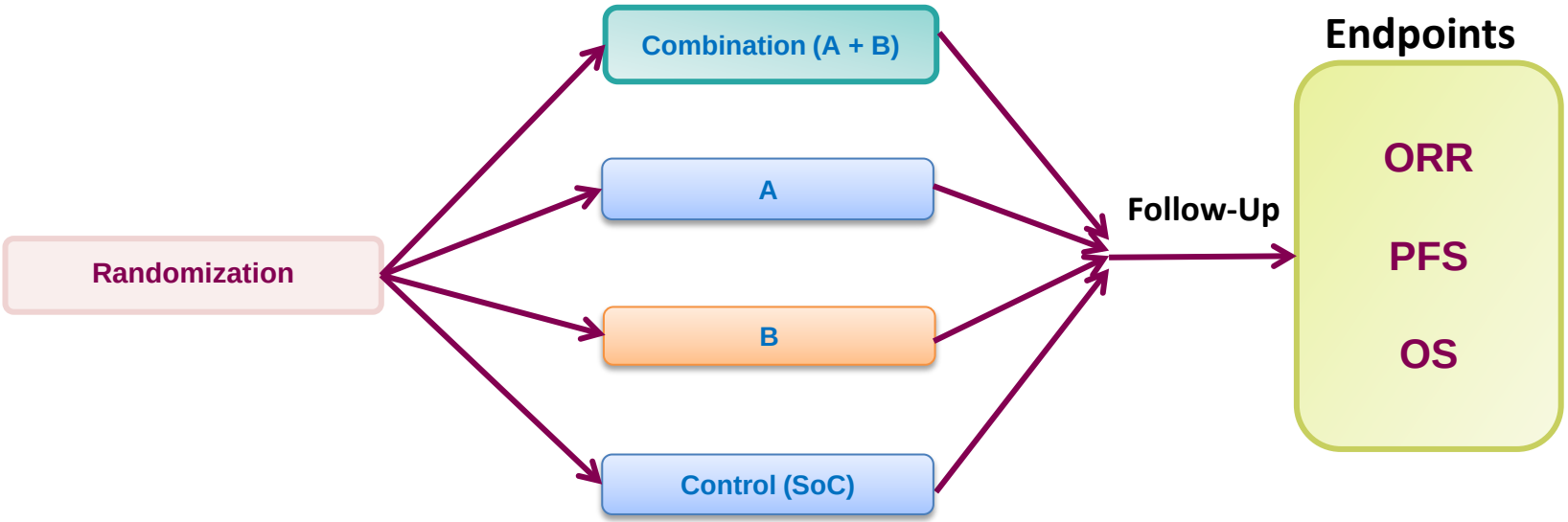


Evidence of Abscopal Effect

Potential Synergy with Checkpoint Inhibitors

Singh M *et al* J Immunol 2014;193:4722-4731

CONTRIBUTION OF COMPONENTS: 4-ARM PHASE II OR III TRIAL



- Characterizing CoC in purist form through randomized controlled 4-arm design
- Ideally, conducted within context of Phase II

CHALLENGES WITH ADDRESSING COC FOR IMMUNOTHERAPIES

- Complex study designs requiring large sample size and longer duration of follow-up
- May be difficult to enroll monotherapy arms
  - If no preliminary evidence of activity (e.g. anti-CTLA4 in NSCLC)
- Challenging to drop arms early based on surrogate endpoints
- Dose-selection for monotherapy vs combination
- How much evidence is enough?
  - Need to generate data across tumor types and lines of therapy within tumor?
- Regulatory expectations across global & regional health authorities

POSSIBLE SOLUTIONS TO CONSIDER

- Relying more on small randomized Phase II trials or on single-arm activity
- Adaptive designs
  - Introducing flexibility in level of evidence required to drop a monotherapy arm
    - Seamless Phase II/III designs
    - Working with regulators to define acceptable thresholds for dropping arms
    - Opportunities to share data with health authorities before making decisions
- Conducting 3-arm trials with only one monotherapy component
  - Understanding the contribution of one-arm relative to the combination may be enough in many situations
- Further clarifying regulatory hurdle on level of evidence required
  - A “pyramid” approach of gathering more data in Phase I & II versus III
  - Alignment across global regulatory authorities on expectations for CoC

PROPOSED FRAMEWORK – EVALUATING TOTALITY OF DATA