Master Protocols for Immunotherapy Combinations

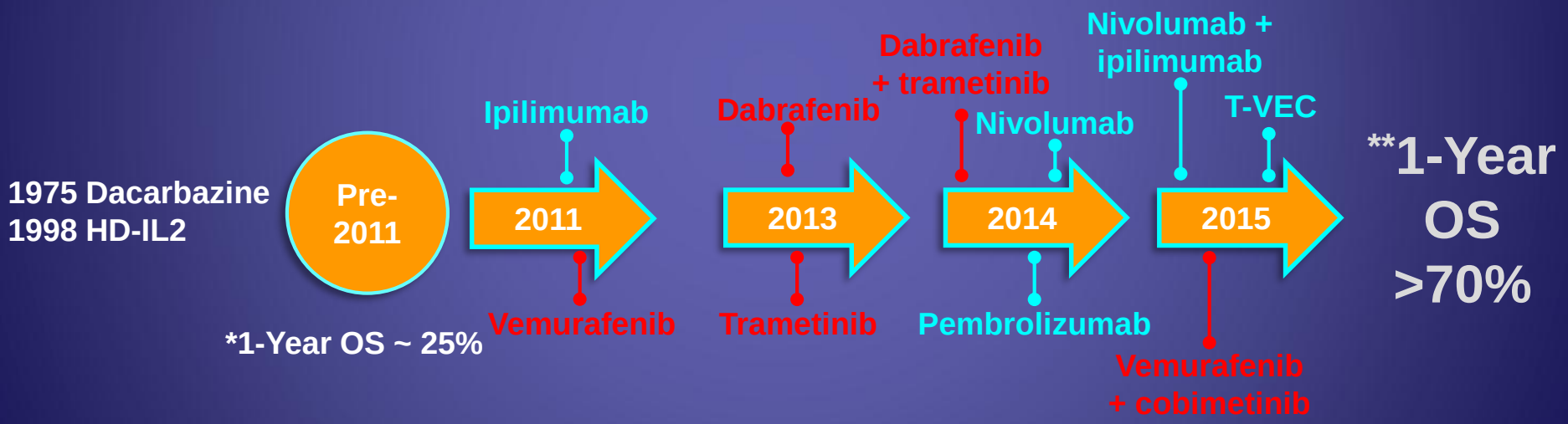
Ahmad Tarhini, MD, PhD

Professor of Medicine, CCLCM, CWRU
Director, Melanoma and Skin Cancer Program
Director, Center for Immuno-Oncology Research
Cleveland Clinic Taussig Cancer Institute
Case Comprehensive Cancer Center

Disclosures

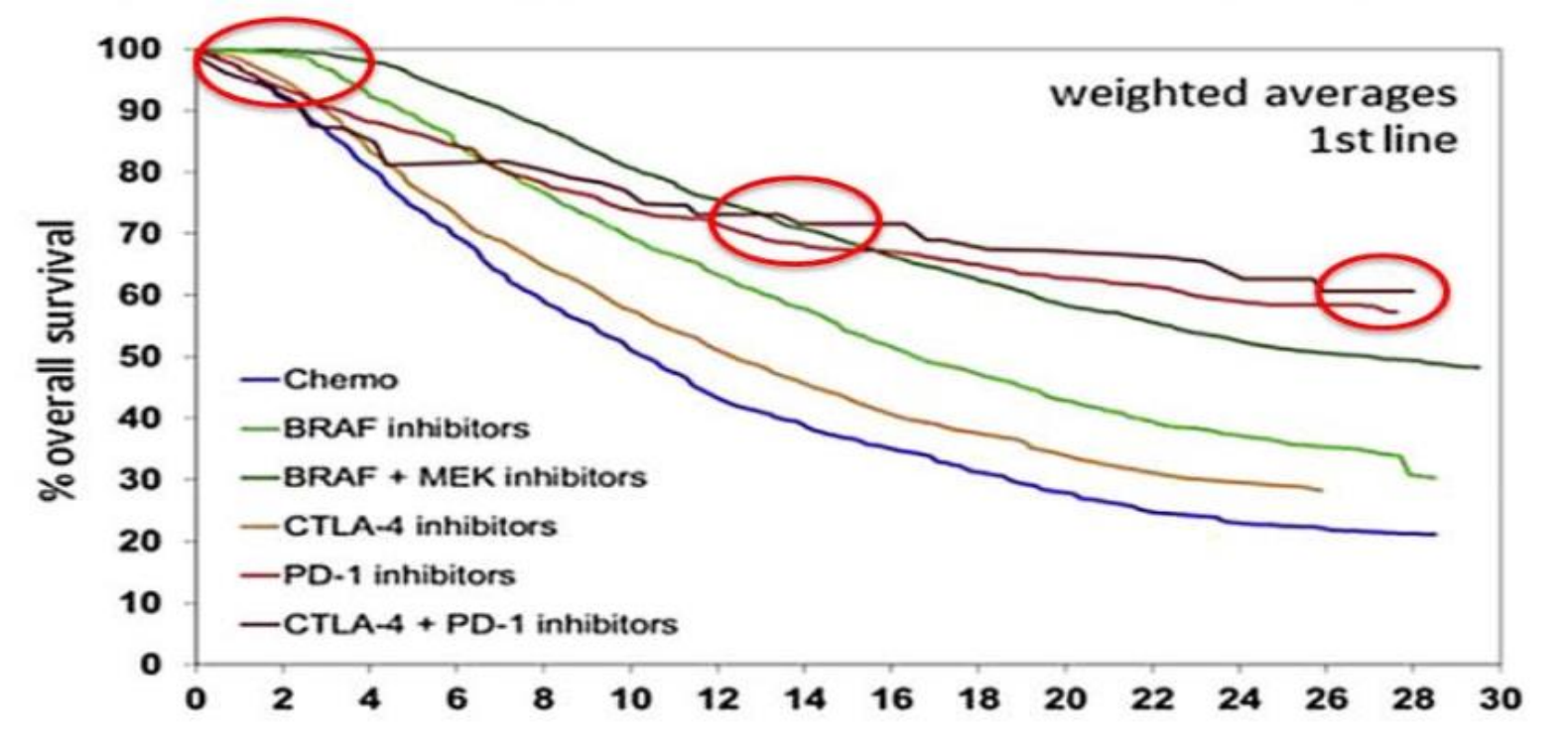
- Consultant: Bristol Myers Squibb, Merck, Incyte, NewLink Genetics, Novartis, Huya, Regeneron, Array Biopharma
- Research Grant: Amgen, Bristol Myers Squibb, Merck, Novartis, Prometheus, Incyte, Roche-Genentech

Stage IV Melanoma: FDA Approvals



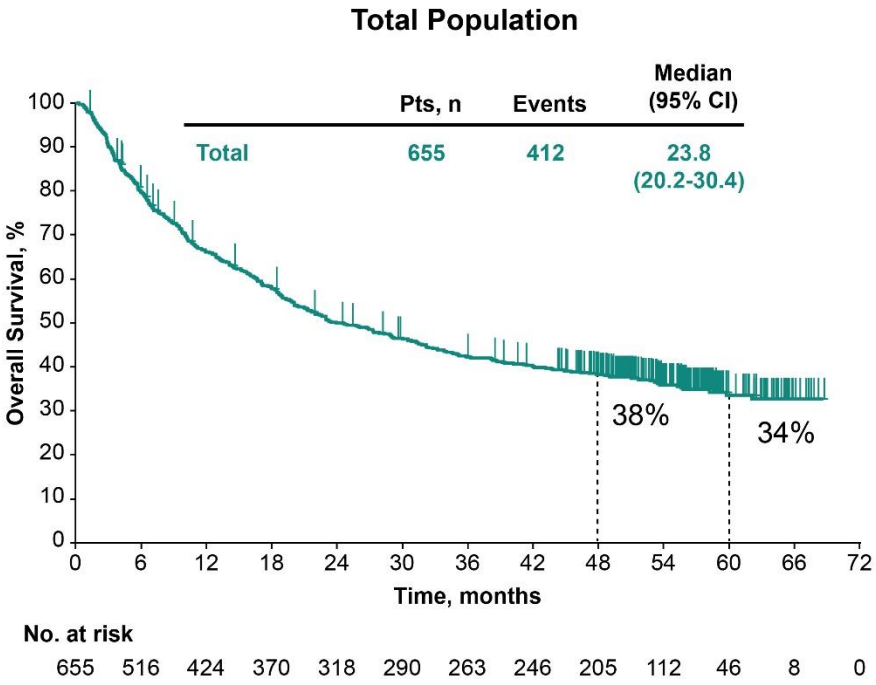
*Korn EL, et al. J Clin Oncol. 2008; **Ugurel S et al. Eur J Cancer. 2017

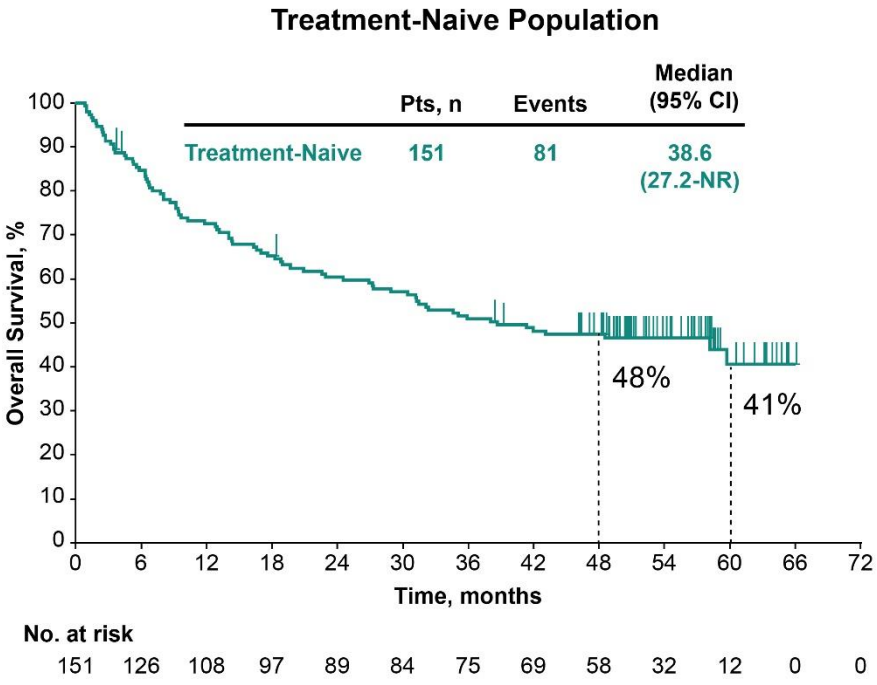
Currently Reported Long-term Survival Outcomes for Stage IV Melanoma



Ugurel S et al. *Eur J Cancer.* 2017;83:247-257

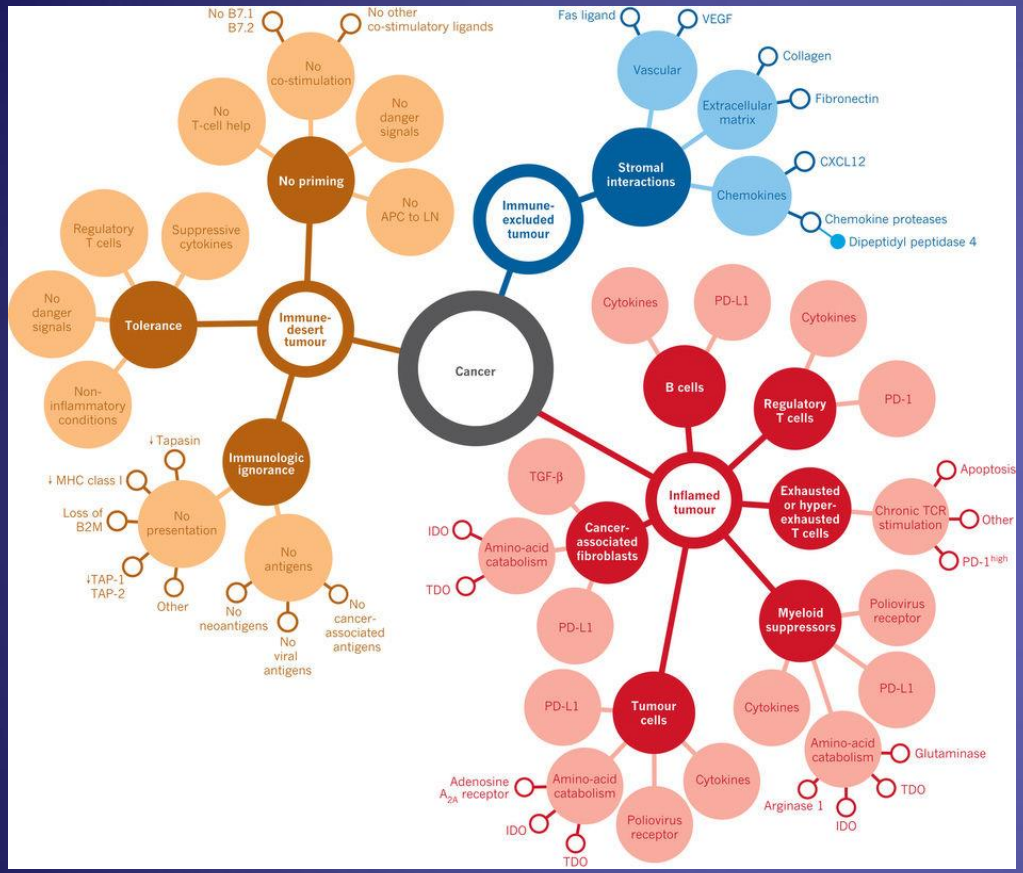
KEYNOTE-001 - Overall Survival



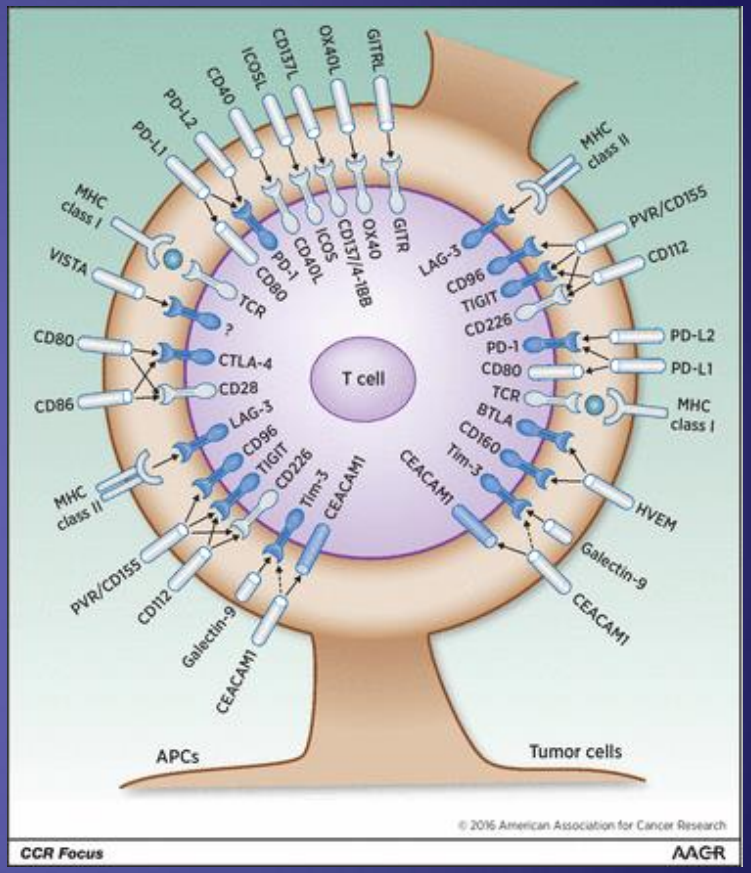


Hamid et al. 2018 ASCO Annual Meeting.

Cancer Immune Phenotypes



Coinhibitory & Costimulatory Receptors



Chen DS, Mellman I Nature 2017; 541, 321–330.
Zaraour H. Clin Cancer Res; 2016; 22(8).

Immunotherapy Combination Strategies

- Immunotherapy + Immunotherapy
- Immunotherapy + Targeted therapy
- Immunotherapy + Chemotherapy
- Immunotherapy + Radiotherapy

Challenges Facing I-O Drug Development

- Series of clinical trials, testing 1 or 2 questions at a time in a single disease
- Time
- Cost
- Competing trials
- Unselected patient populations
- Screen failures
- Rare genetic/other subtypes
- Identifying truly predictive biomarkers

Need to Accelerate Cancer I-O Drug Development

- New more efficient strategies are essential that can test more approaches, more efficiently, in less time
- Master Protocols can be a major methodologic innovation over the traditional approach of a series of clinical trials
  - Overall systematic approach to a disease
  - More efficient screening
  - Increasing the speed of drug development and approvals

Redman MW, Allegra CJ. Semin Oncol. 2015 Oct; 42(5): 724–730

Opportunities for Master Protocols for Immunotherapy

- Improved genomic and immunologic understanding of cancers
  - Incorporation of precision medicine approaches
  - Mechanism-based trials
    - Eligibility based on mechanistic criteria (e.g., MSI-H, biomarker signatures, …)
  - Allowing target and agent prioritization
- Timely assessment of safety and clinical activity of multiple agents in parallel or rapid sequences

Opportunities for Master Protocols

- NCI sponsored cooperative groups could play a major role
  - Robust clinical trial infrastructure
  - Allowing multi-sponsor trials
  - Multi-stakeholder decision-making body

Types of Master Protocols

Umbrella	To study multiple therapies in the context of a single disease (“the umbrella”)
Basket	To study a single therapy in the context of multiple diseases or disease subtypes (“the basket”)
Platform	To study multiple therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

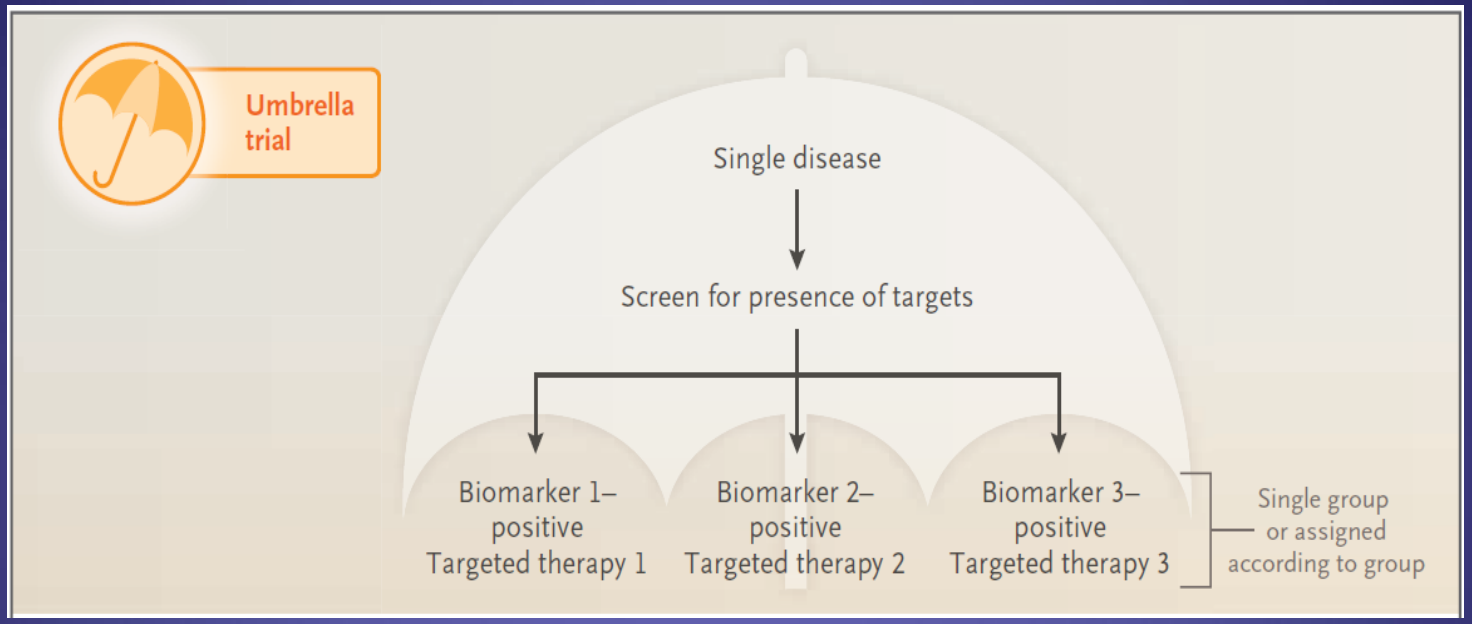
Woodcock J, LaVange LM. N Engl J Med 2017;377:62-70
Renfro LA, Sargent DJ. Ann Oncol. 2017 Jan 1;28(1):34-43
Redman MW, Allegra CJ. Semin Oncol. 2015 Oct; 42(5): 724–730

Types of Master Protocols

Umbrella	To study multiple therapies in the context of a single disease (“the umbrella”)
Basket	To study a single therapy in the context of multiple diseases or disease subtypes (“the basket”)
Platform	To study multiple therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock J, LaVange LM. N Engl J Med 2017;377:62-70
Renfro LA, Sargent DJ. Ann Oncol. 2017 Jan 1;28(1):34-43
Redman MW, Allegra CJ. Semin Oncol. 2015 Oct; 42(5): 724–730

Umbrella Trial



- Evaluates various subgroups within a conventionally defined disease
  - Subgroups often biomarker-defined
- Patients screened for the presence of a biomarker/other characteristic and assigned a stratum
- Multiple drugs are studied in the various strata
- Design may be randomized or may use external controls

Woodcock J, LaVange LM. N Engl J Med 2017;377:62-70.

NCI-Match

- Umbrella trial to determine whether treating cancers according to molecular abnormalities is effective
- Advanced solid tumor, lymphoma, myeloma (each, a separate “umbrella” within a “basket”)
- DNA sequencing for actionable mutations
- Multiple treatments that target gene abnormalities
- Exploratory, multicenter, non-comparative
- Endpoints: Tumor response (primary) and PFS
- Size: 35 patients per sub-study

We might envision an anti-PD1/PD-L1 backbone trial in a certain disease (“umbrella”) where patients are screened based on the presence of biomarker(s) (e.g., PD-L1, CD8, MSI-H, mutational burden, other specific markers, …) and allocated to certain strata (combinations)

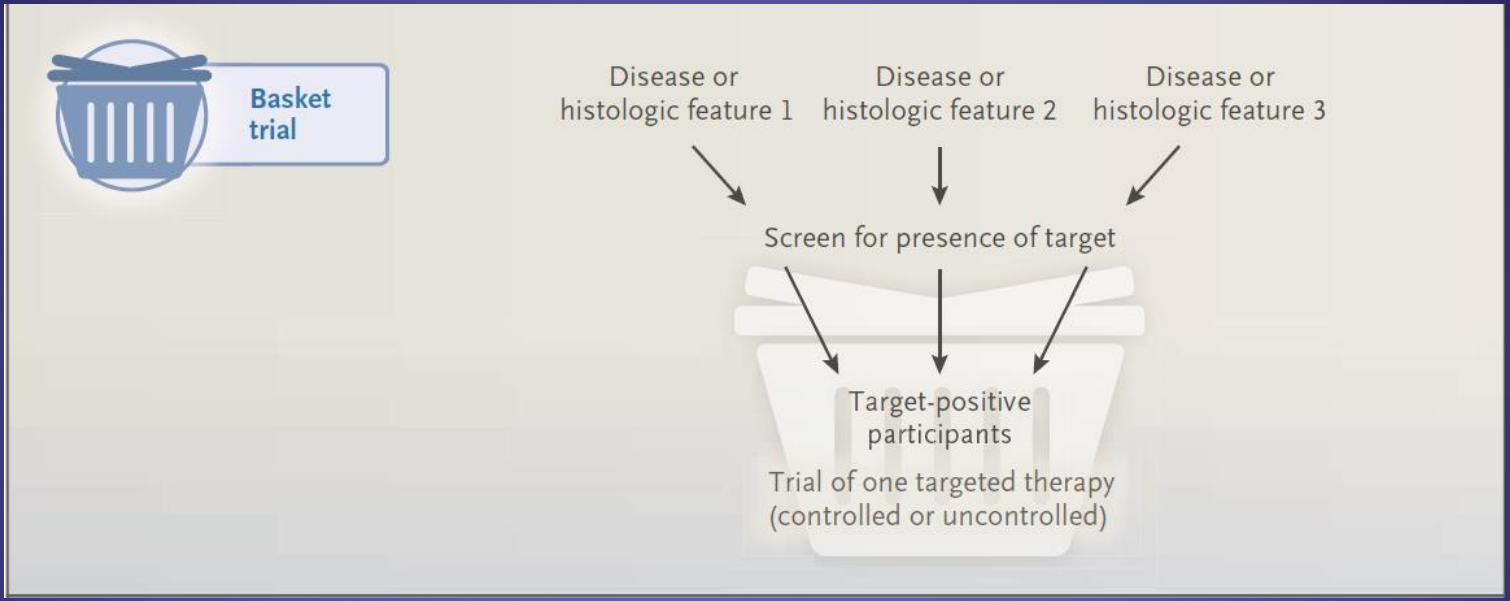
National Cancer Institute (http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match).

Types of Master Protocols

Umbrella	To study multiple therapies in the context of a single disease (“the umbrella”)
Basket	To study a single therapy in the context of multiple diseases or disease subtypes (“the basket”)
Platform	To study multiple therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock J, LaVange LM. N Engl J Med 2017;377:62-70
Renfro LA, Sargent DJ. Ann Oncol. 2017 Jan 1;28(1):34-43
Redman MW, Allegra CJ. Semin Oncol. 2015 Oct; 42(5): 724–730

Basket Trial



- Involves multiple diseases or histologic features
- Participants screened for the presence of a target & entered
- Could contain multiple strata that test various biomarker–drug pairs

Woodcock J, LaVange LM. N Engl J Med 2017;377:62-70.

BRAF V600

- Basket trial to evaluate the efficacy of vemurafenib
- Multiple non-melanoma caners with BRAF V600 mutations
- Phase 2, non-comparative, adaptive trial using Simon 2-stage
- Response rate

Hyman DM, et al. N Engl J Med 2015;373:726-36.

ECHO-202 / KEYNOTE-037

- Phase 2 Study
- Exploring efficacy of pembrolizumab and epacadostat
- ORR by modified RECIST v1.1
- Selected solid tumors and DLBCL
- Sample size 25 - 42 subjects

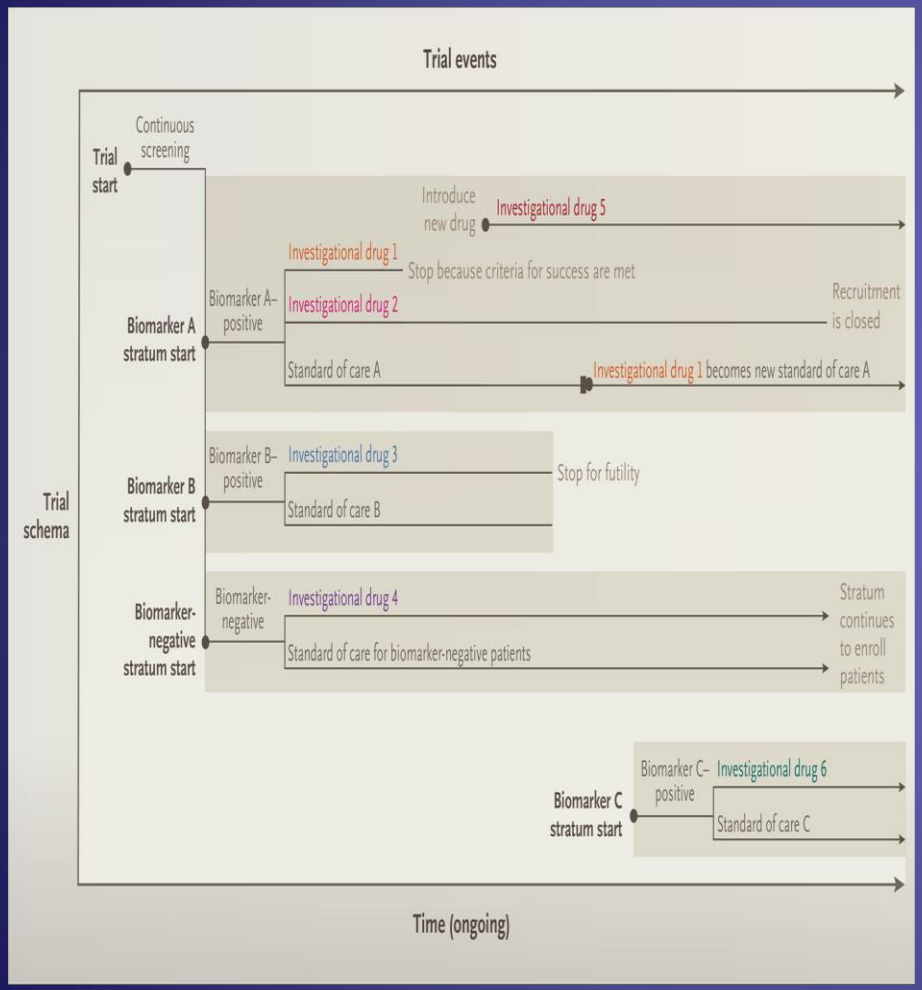
ClinicalTrials.gov: NCT02178722

Types of Master Protocols

Umbrella	To study multiple therapies in the context of a single disease (“the umbrella”)
Basket	To study a single therapy in the context of multiple diseases or disease subtypes (“the basket”)
Platform	To study multiple therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock J, LaVange LM. N Engl J Med 2017;377:62-70
Renfro LA, Sargent DJ. Ann Oncol. 2017 Jan 1;28(1):34-43
Redman MW, Allegra CJ. Semin Oncol. 2015 Oct; 42(5): 724–730

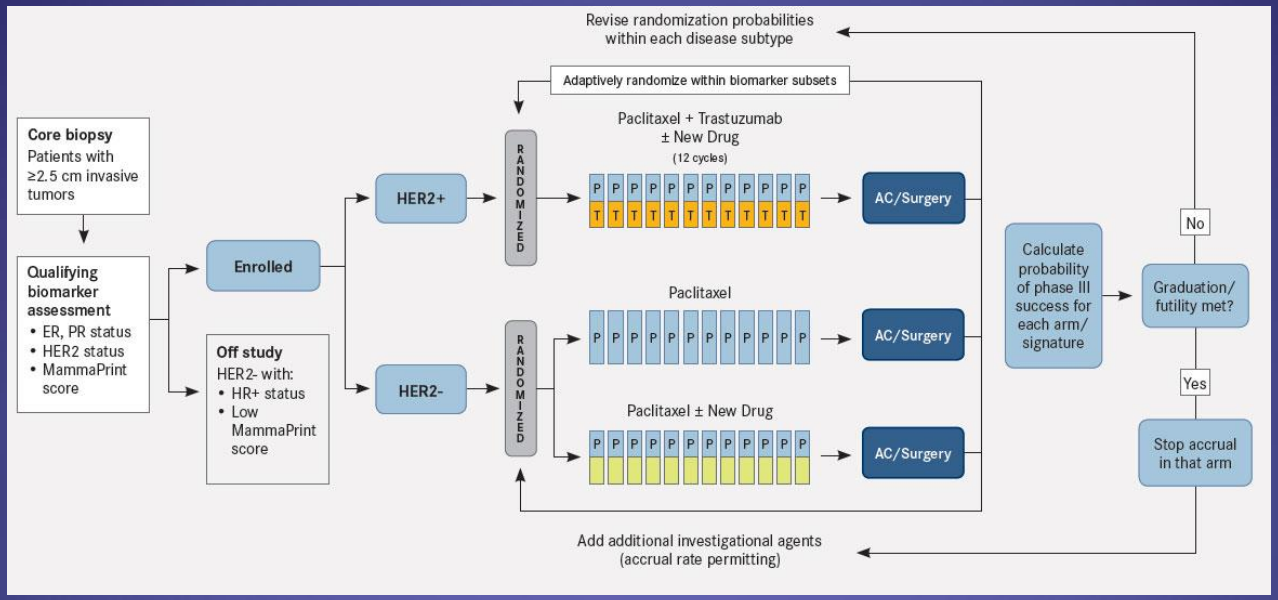
Potential Design of a Platform Trial Involving a Single Disease.



- Platform trial ongoing over time, with no fixed stopping date, and governed by a master protocol that envisions adding and dropping strata
- Other types of adaptive designs are possible, including adaptive randomization, as are the use of other criteria for early stopping

Woodcock J, LaVange LM. N Engl J Med 2017;377:62-70

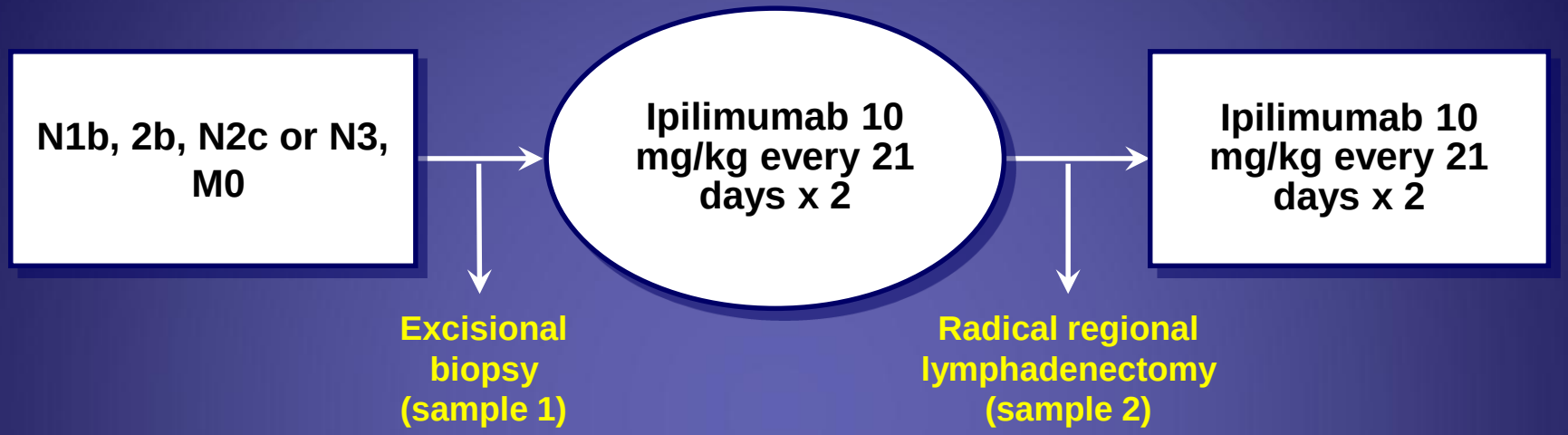
I-SPY 2



- Adaptive platform Phase 2 rtandomized trial
- Locally advanced breast cancer in the context of neoadjuvant therapy on the basis of biomarker signatures
- Biomarkers: hormone-receptor status, HER2 status, and MammaPrint risk score - define eight genetic sub-groups
- Primary endpoint: Pathological complete response

Barker AD, etal. Clin Pharmacol Ther 2009;86:97-100.
Berry SM, et al. JAMA 2015;313:1619-20.

Neoadjuvant Ipilimumab in N1b, 2b, N2c, N3 Melanoma



Advantages of Neoadjuvant Therapy

Clinically,

- Improved clinical outcome

Experimentally,

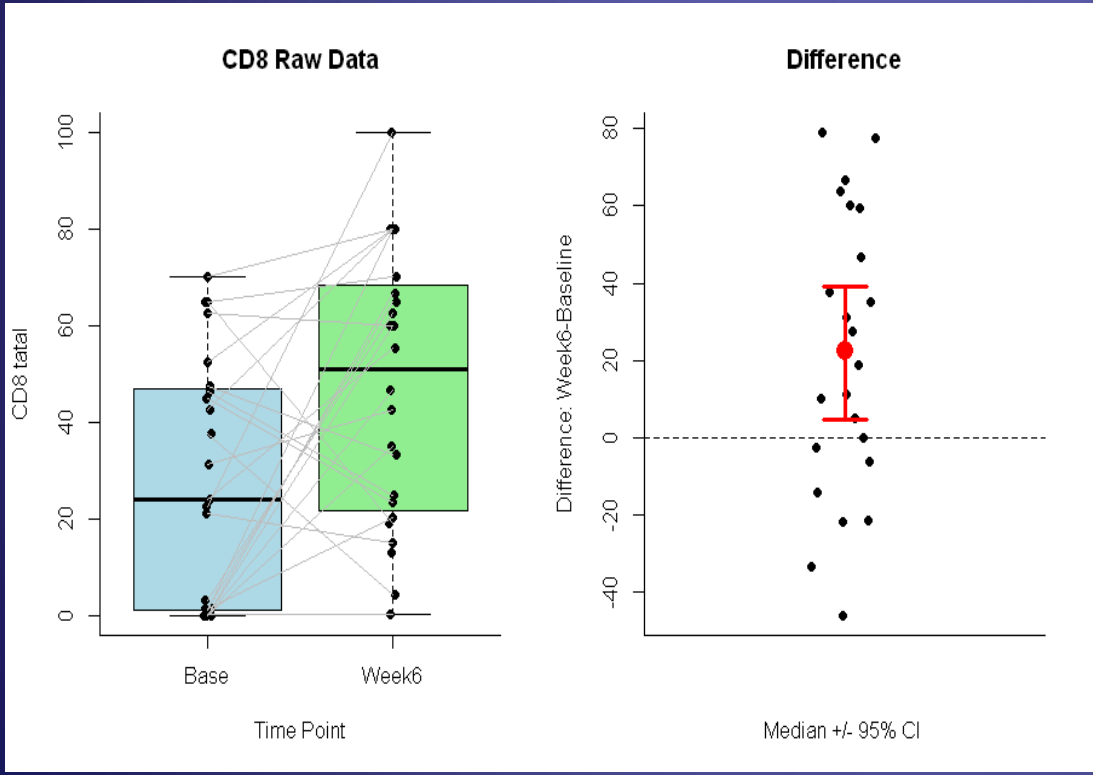
- Evaluate clinical/radiologic as well as pathologic responses
- Access to tumor & blood before & after
  - Investigation of antitumor mechanisms of action
  - Biomarker studies

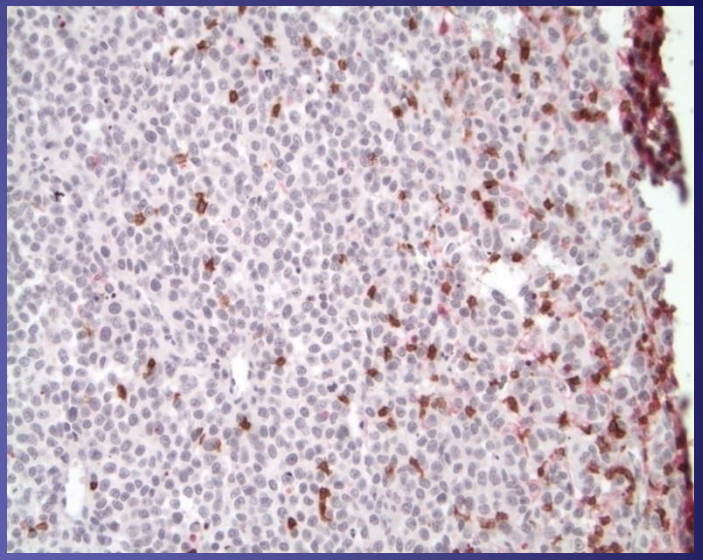
Tarhini, et al. PLOS One 2014
Tarhini. Am Soc Clin Oncol Educ Book. 2015

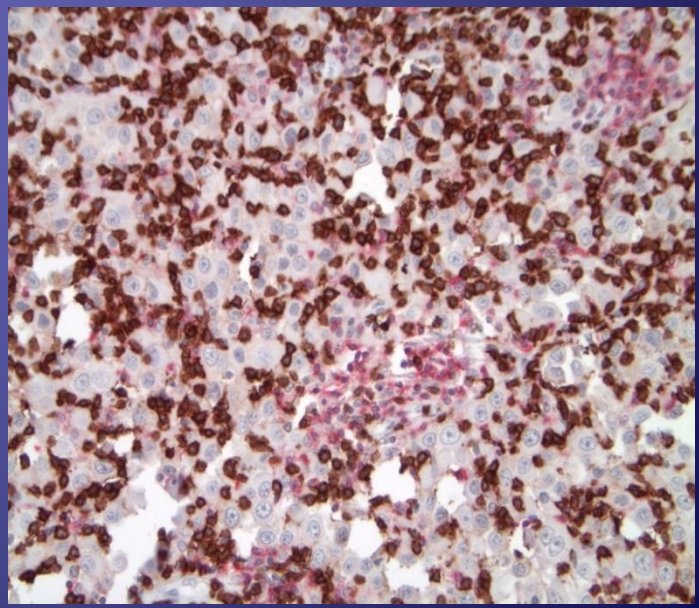
Tumor TIL by IHC (N=24): CD8+ T Cells

TIL	Median Δ (Wk6 – Baseline) with 95%CI	P-value
CD8+ T Cells	19 (4.79,39.25)	0.019

Significant increase in cytotoxic CD8+ TIL after Ipi

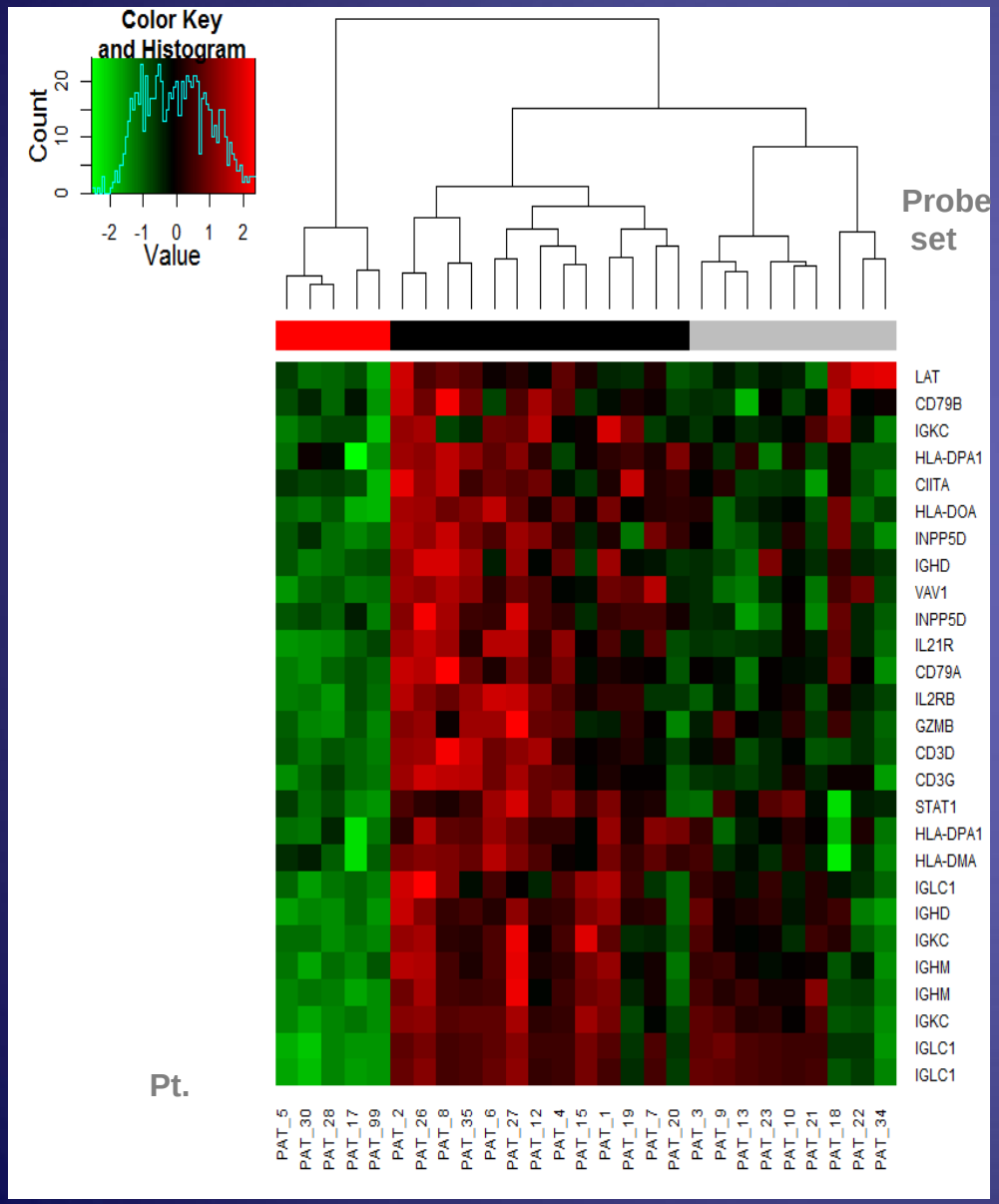


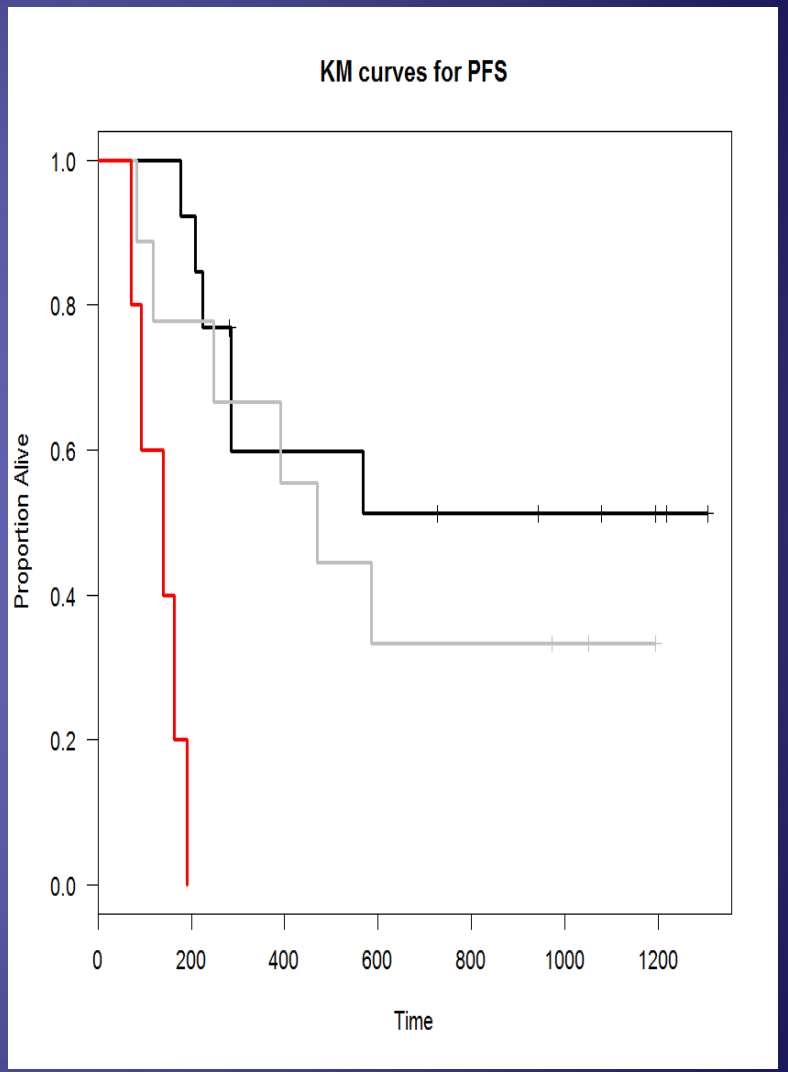




Tarhini et al. PLOS One 2014

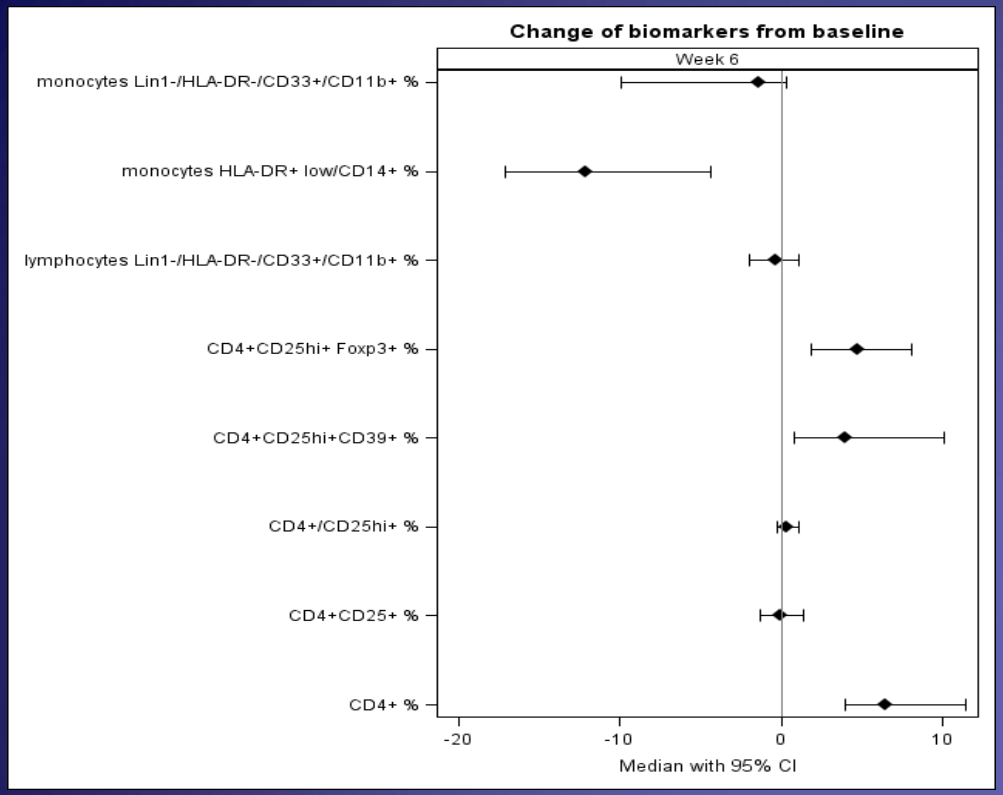
RFS by Baseline Expression Level





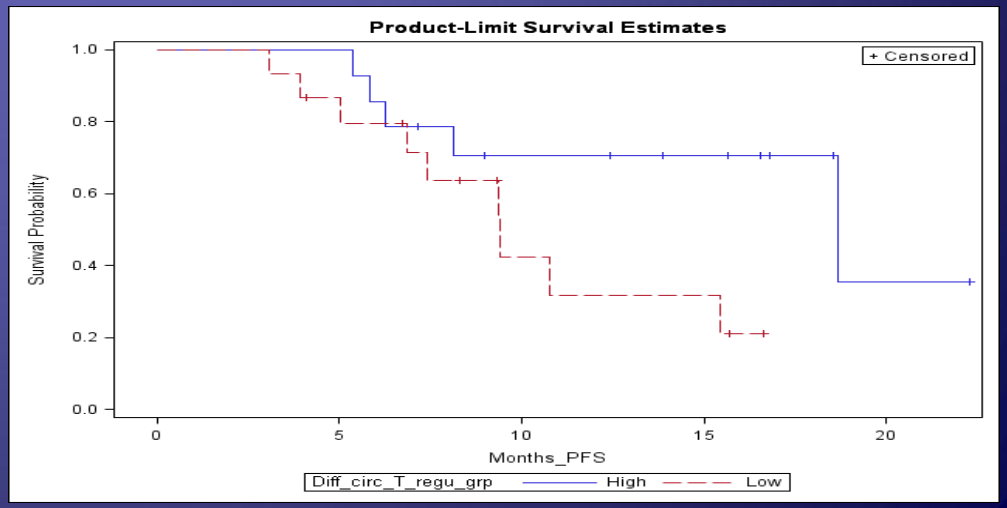
Tarhini et al. Oncoimmunology 2017

Neoadjuvant Ipi: Circulating MDSC and T-reg by Flow (N=27)



Summary of most significant changes (%) at week 6			
	Δ at Wk 6	Sd Dev of Δ at Wk6	P-value
T-Regs			
CD4+ %	+6.79	9.09	<0.0001
CD4+CD25hi+CD39+ %	+5.39	8.63	0.001
CD4+CD25hi+ Foxp3+ %	+4.05	8.13	0.02
Conclusion: ↑ in CD4+ T-Cells is mostly accounted for by the ↑ in Tregs			
MDSC			
% lymphocytes Lin1-/HLA-DR-/CD33+/CD11b+	-0.72	3.19	0.34
% monocytes HLA-DR+ low/CD14+	-12.84	12.06	<0.0001
% monocytes Lin1-/HLA-DR-/CD33+/CD11b+	-2.99	16.18	0.19

Greater ↑ in circulating T-reg associate with improved RFS (p=0.034; HR=0.57)

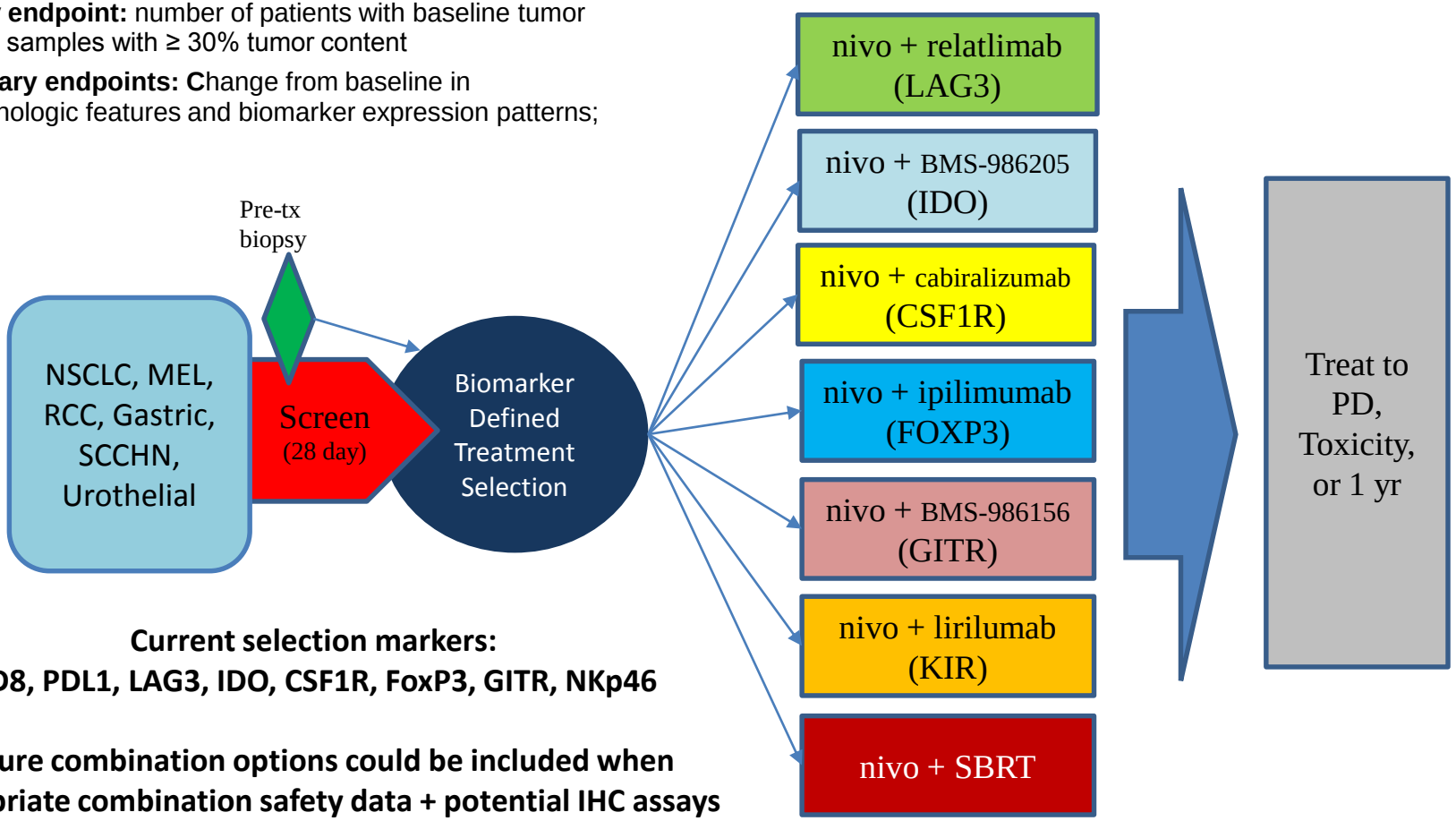


Tarhini et al. PLOS One 2014

BMS CA028-001: ADaptiVe Biomarker Trial that InformS Evolution of therapy after nivolumab (ADVISE)

Primary endpoint: number of patients with baseline tumor biopsies samples with ≥ 30% tumor content

Secondary endpoints: **C**hange from baseline in histopathologic features and biomarker expression patterns; safety



Current selection markers:
CD8, PDL1, LAG3, IDO, CSF1R, FoxP3, GITR, NKp46

Future combination options could be included when appropriate combination safety data + potential IHC assays

Courtesy of Jason Luke, MD

ClinicalTrials.gov Identifier: NCT03335540

Considerations for Master Protocols Clinical Trial Design

- Histology specific (certain tumor type) or histology agnostic (various tumor types)
- Study Endpoints
  - RR (PR, CR), PFS
  - pCR (Neoadjuvant)
- Randomized versus historical controls

Considerations for Master Protocols Clinical Trial Design

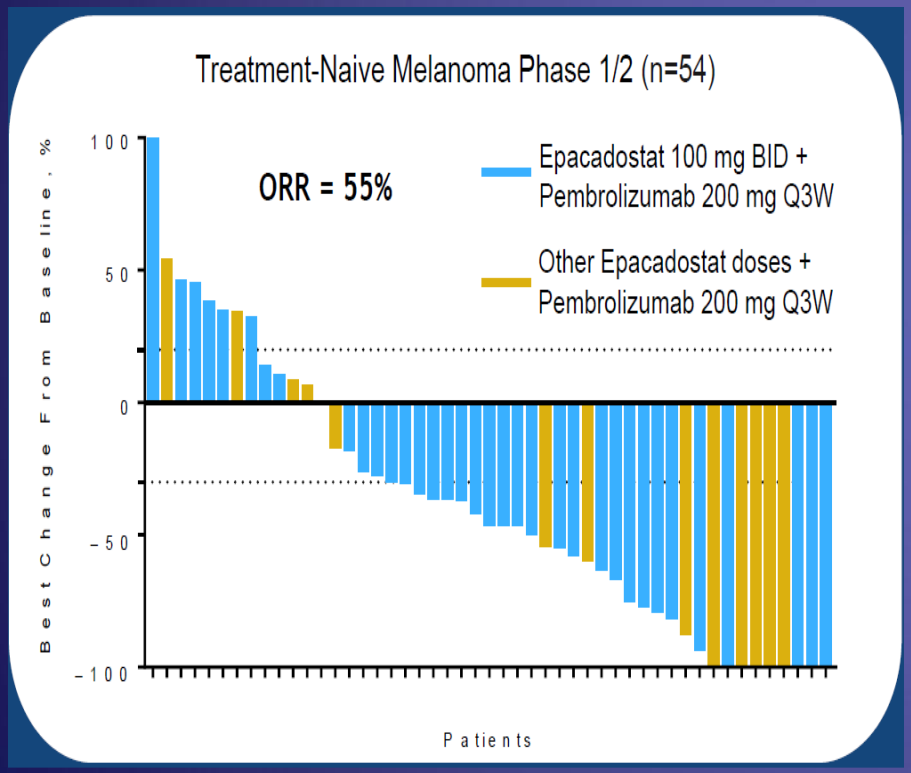
- Eligibility Criteria
- Interim Analyses and Stopping Rules
- Biomarker and Enrichment Strategies
  - PD-L1 status
  - Microsatellite instability high (MSI-H)
  - Tumor mutation burden (TMB)
  - Immune related mRNA signatures
- Statistical Analysis Plans
- Registrational Intent

Challenges for Master Protocols in I-O and Potential Disadvantages

- Meaningful short-term study endpoints that may allow adaptive designs
- The right biomarkers that may allow adaptive designs
- Collaborations across competing pharmaceutical companies
- Logistical and Operational Considerations
- Funding & Cost

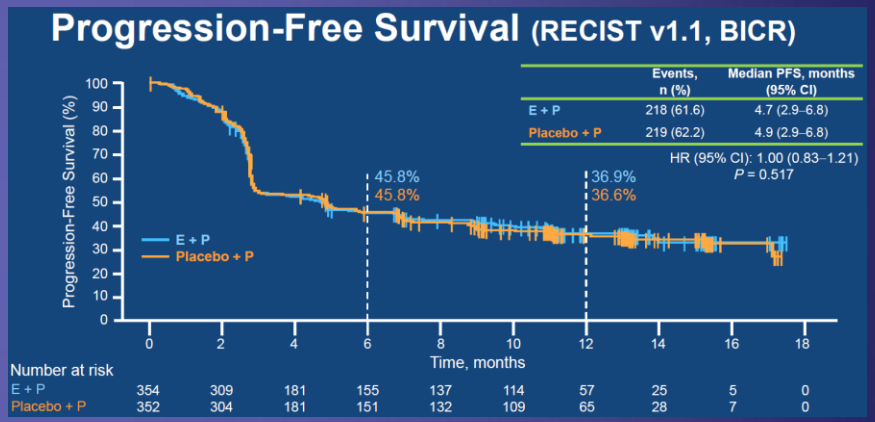
Epacadostat + Pembrolizumab in Melanoma

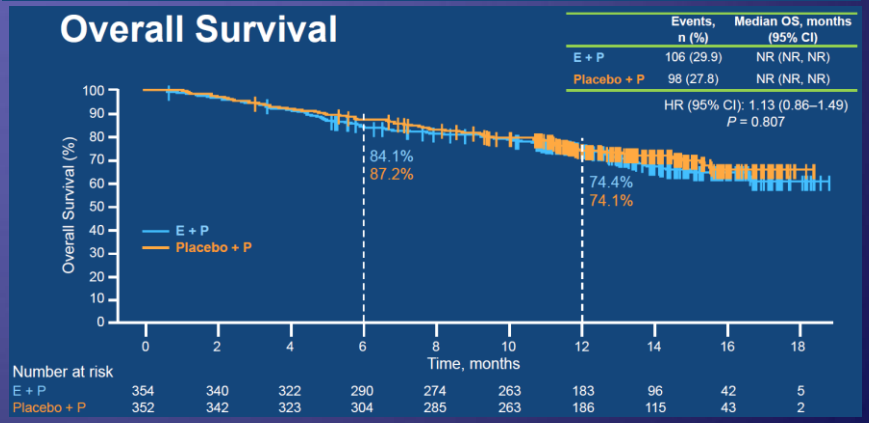
ECHO-202 / KEYNOTE-037



Phase 3 ECHO-301/KEYNOTE-252

Response, n (%)	Epacadostat + Pembrolizumab (n=354)	Placebo + Pembrolizumab (n=352)
ORR	121 (34.2)	111 (31.5)





Long J, et al. J Clin Oncol 36, 2018 (suppl; abstr 108)

What went wrong?

- RR as the primary endpoint
  - ? Central review …
- Single arm/historical control prior to Phase III
  - ? Randomization
- Eligibility / representative population
  - ? Mandating evaluation of low & high risk
- Right dose
  - ? Careful PK/PD
- Biomarker, pCR, …
  - ? Neoadjuvant evaluation

Recommendations

- Unique designs for unique questions
- Study arms that may provide options for “Screen Failures”
- The importance of obtaining tumor tissues in I-O clinical trials to investigate biomarkers & resistance pathways
- Standardized biospecimen acquisition and storage
- Consider neoadjuvant evaluation
- Collaboration & coordination between the pharmaceutical industry, NCI, FDA, academia, community oncology programs
- Taking advantage of NCI sponsored cooperative group infrastructure
- Guidance to community sites to allow broader participation
- Patient & health care provider education
- Reward participation and team work