Selected Regulatory Considerations for Cancer Immunotherapeutic Combinations: Contribution of Individual Components to Effect of Combination

Addressing Resistance in the Development of Cancer Immune Modulator Therapeutics

Session 5: Criteria to Assess Cancer Immunotherapy Combinations in Early-Phase Clinical Trials

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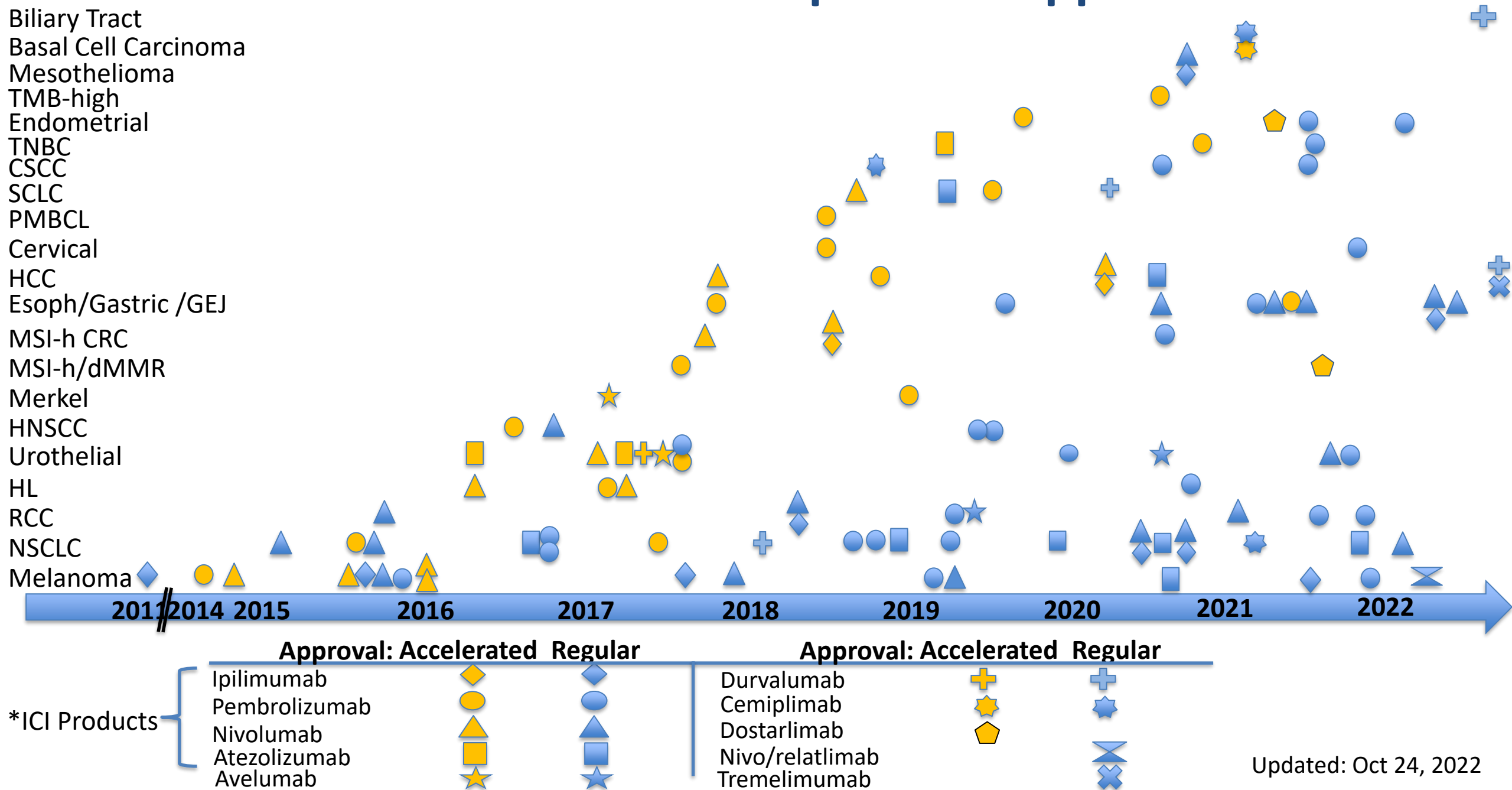
Disclosures

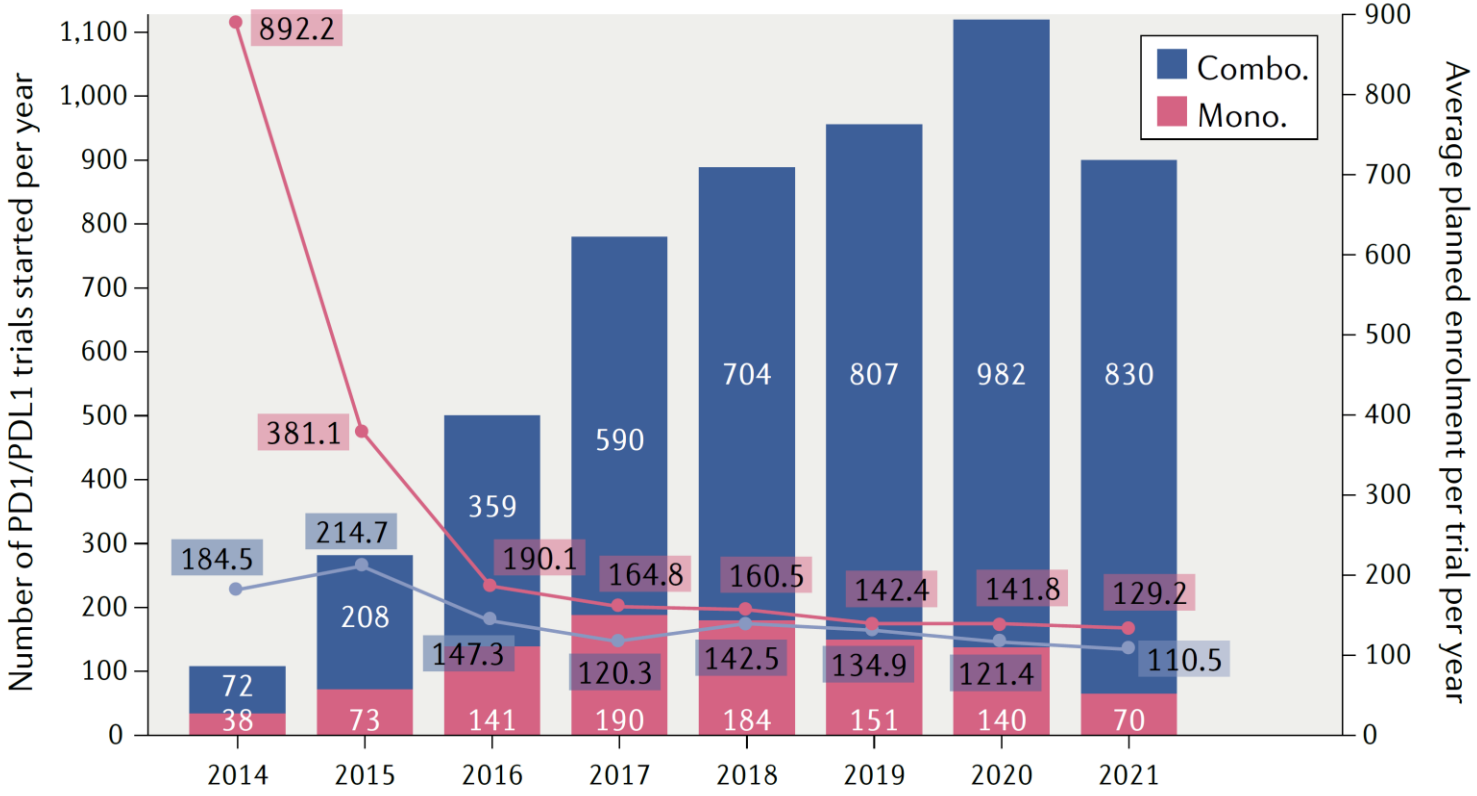
- I have no financial conflicts of interest
- I will not discuss off-label use
- Views expressed here are those of the presenter and not necessarily those of the U.S. FDA.

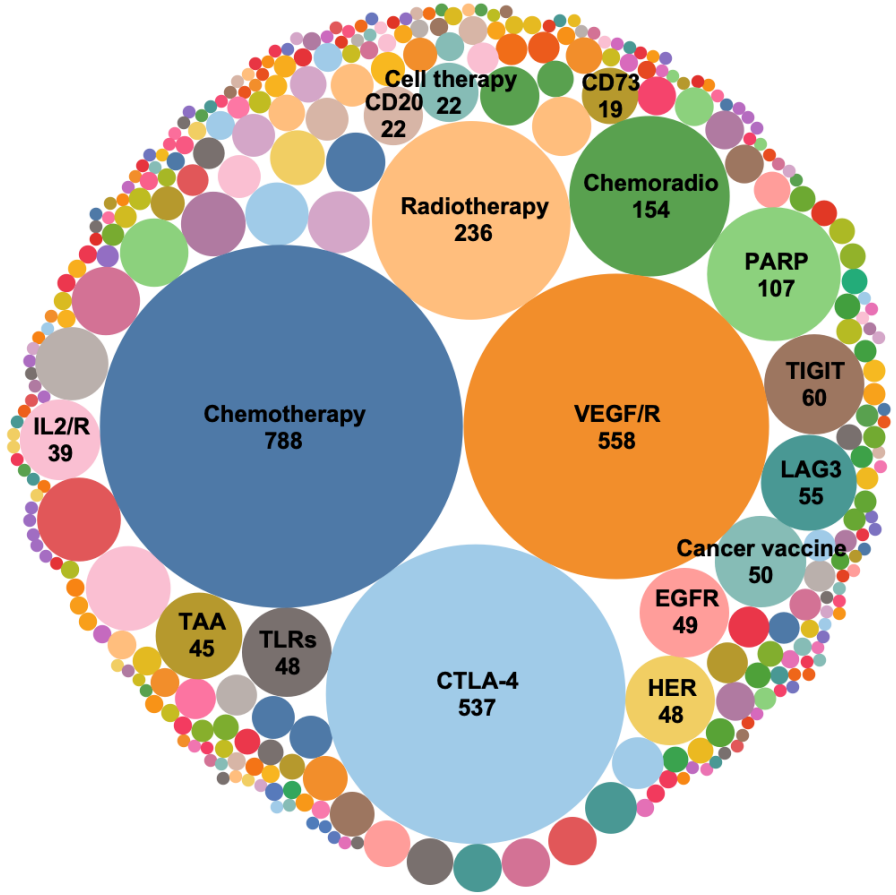
Treatment Landscape: ICI* Approvals



Updated: Oct 24, 2022

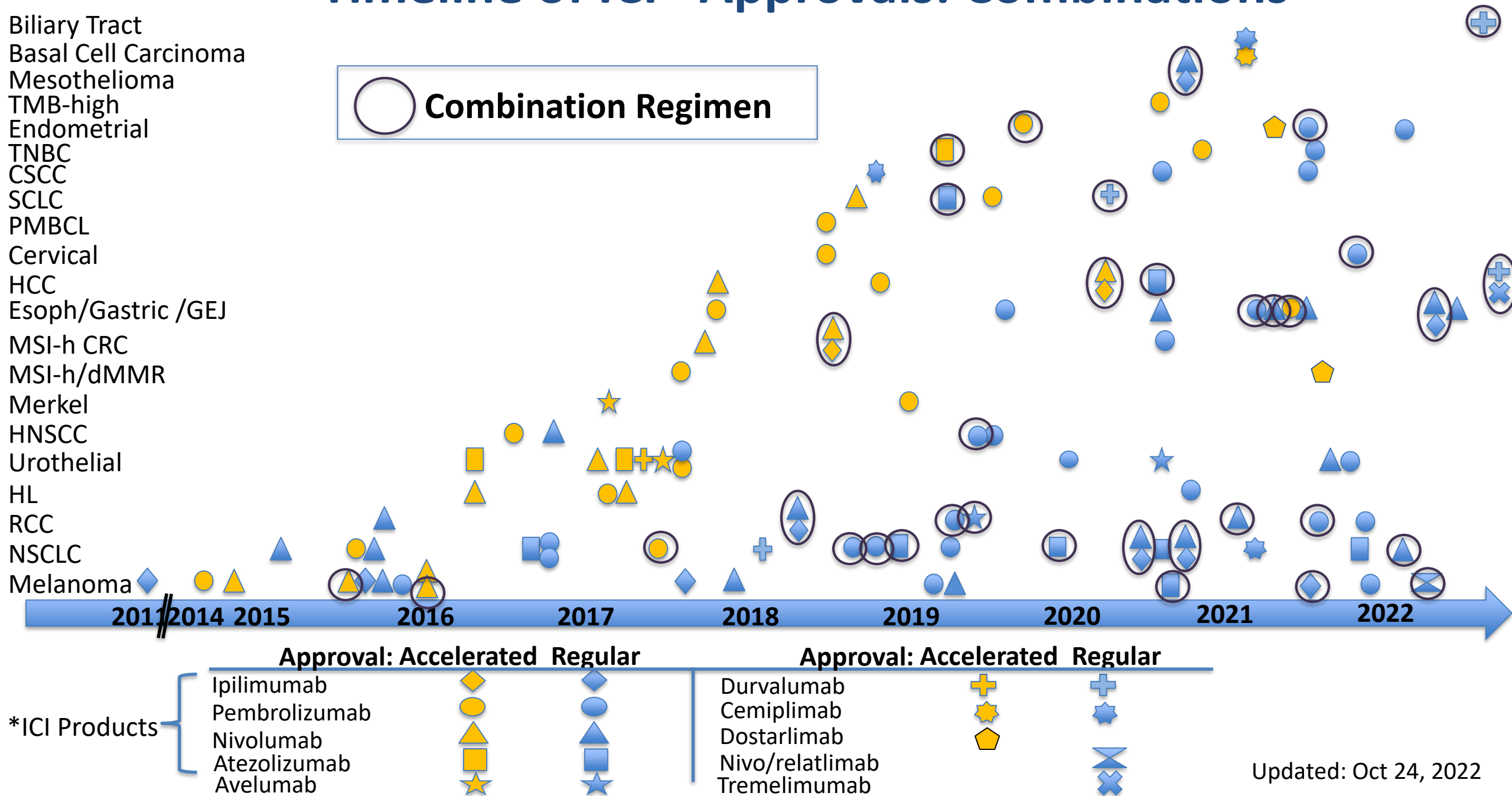
Landscape: PD-(L)1 Inhibitor Combination Regimens





Upadhaya et al., Nat Rev Drug Discov, 2022

Timeline of ICI* Approvals: Combinations



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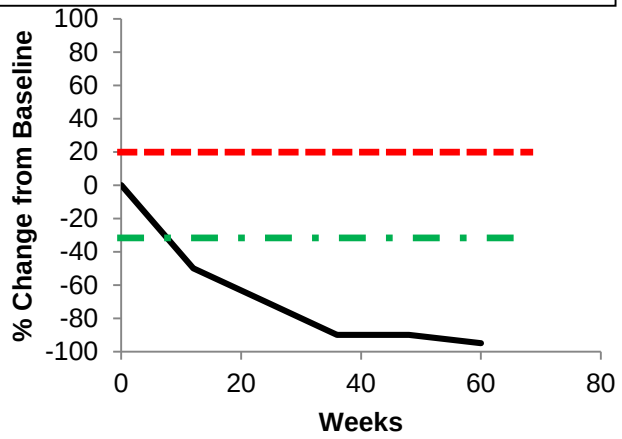
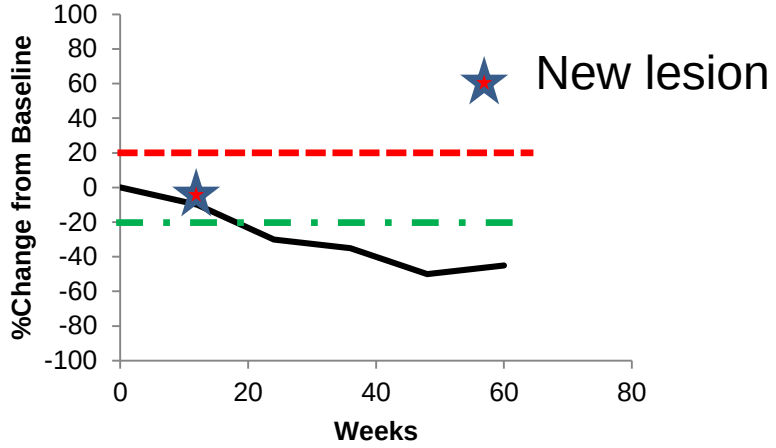
Immunotherapy: Patterns of Response

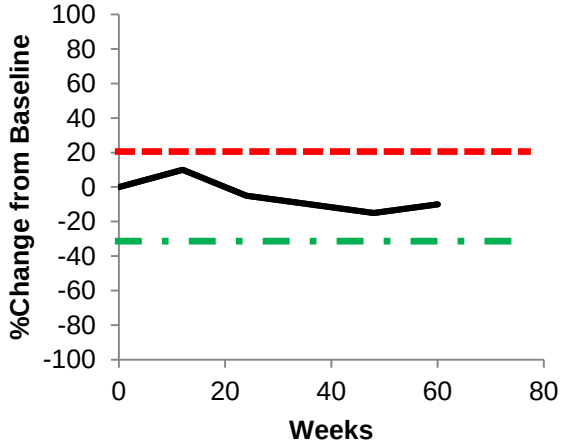
Continued Reduction in Lesions



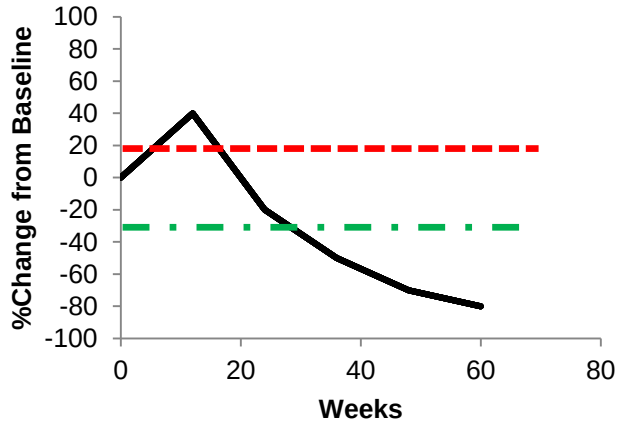
Reduction in Lesions with New Lesions



Stable Lesions



Initial Increase then Decrease in Lesions



Adapted from Wolchok, 2009, Clin Cancer Res

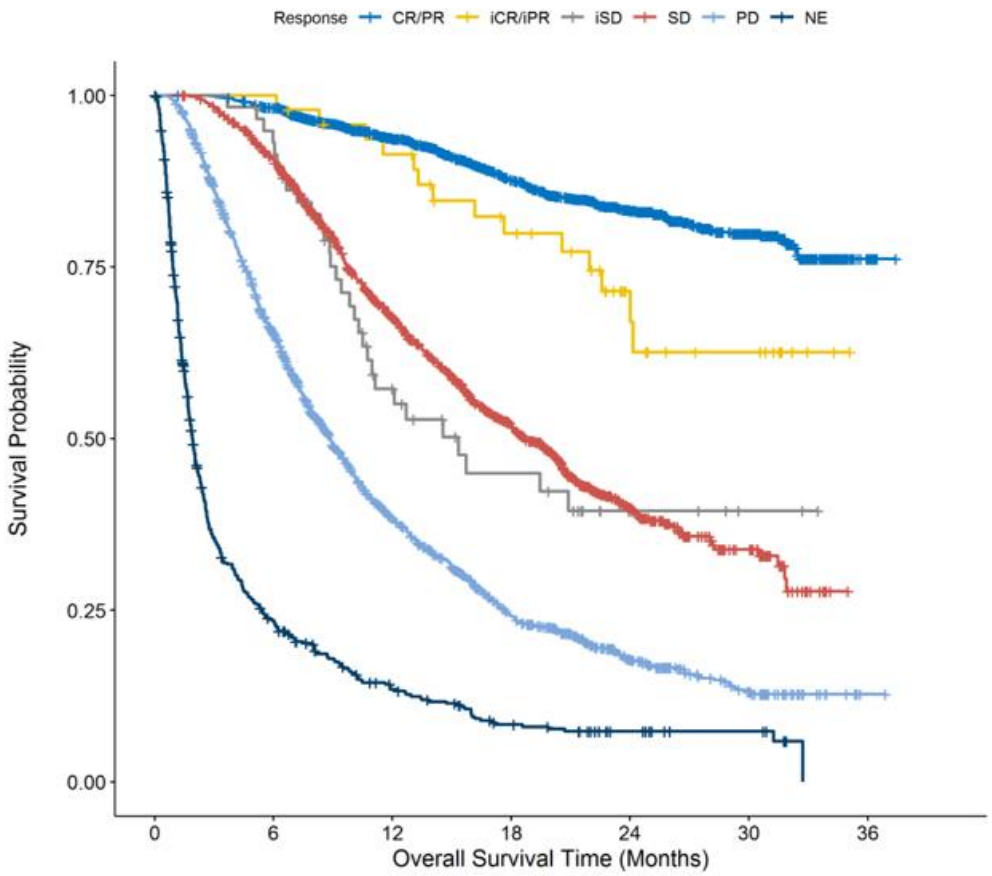
Analyses of Treatment Beyond Progression (TBP) with Anti-PD-1 mAbs

	Disease	N	PD, n	TBP, n (%)	Reference Tumor Burden	TBP Responders[d]	
						% of All Pts	% of TBP Pts
George 2016	RCC	168	154	62 (37%)[a]	Baseline	7	19
Escudier 2017	RCC	406	316	153 (42%)[b]	PD	5	13
Kazandijan 2017	NSCLC	535	420	121 (23%)[c]	Baseline	2	8
Long 2017	Mel	526	306	85 (16%)[b]	Baseline	5	28
Beaver 2018	Mel	2624	1361	692 (26%)[c]	PD	4	14

[a] TBP at least 4 weeks
[b] TBP at least 6 weeks
[c] Any TBP
[d] ≥30% Decrease in Target Lesion Tumor Burden

Modified from Blumenthal, Theoret, Pazdur, 2017, JAMA Oncol

Anti-PD-(L)1 mAbs – Overall Survival by Best Overall Response per RECIST 1.1 and iRECIST



Number at risk
(number censored)

CR/PR	1449 (0)	1403 (20)	1105 (260)	853 (447)	535 (727)	292 (954)	12 (1226)
iCR/iPR	48 (0)	48 (0)	42 (2)	33 (6)	16 (20)	10 (24)	0 (34)
iSD	59 (0)	54 (1)	26 (10)	17 (14)	6 (23)	2 (27)	0 (29)
SD	1110 (0)	974 (34)	619 (159)	363 (286)	133 (450)	42 (526)	0 (564)
PD	1597 (0)	989 (68)	505 (167)	265 (233)	112 (331)	43 (380)	1 (421)
NE	539 (0)	112 (38)	54 (52)	28 (59)	13 (71)	7 (77)	0 (82)

Mulkey, Theoret, et al., 2020, J Immunother Cancer

Major Principles Discussed -- anti-PD-(L)1 mAb Refractory / Resistant Population

- Adequate Exposure to anti-PD-(L)1 mAb by Specifying Dose and Length of anti-PD-(L)1 Therapy Prior to Disease Progression
- Best Response to anti-PD-(L)1 mAb Prior to Disease Progression
- Confirmation of Disease Progression (including the timing of confirmation)
- *Minimize Likelihood of Late Response to an anti-PD-(L)1 mAb or with Re-exposure of anti-PD-(L)1 mAb*

Kluger et al., 2019, J Immunother Cancer
FOCR, 2019 Annual Meeting, Session 2 White Paper
, https://www.focr.org/sites/default/files/pdf/Panel-2_Combo_IO_Tx_2019AM.pdf.

Contribution of Individual Products to Treatment Effect of Combination Use

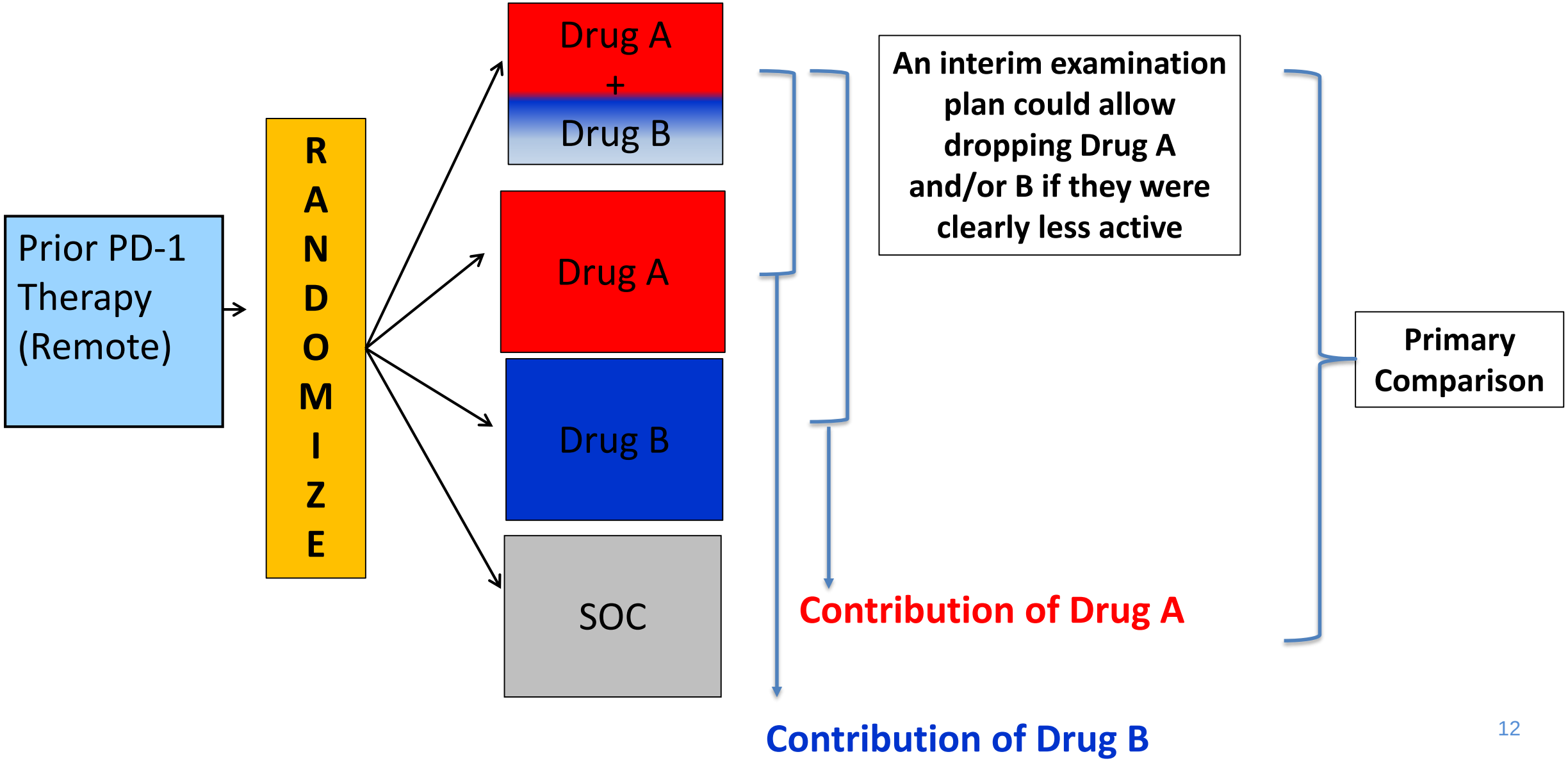
- **C/W Requirement for Demonstrating Contributions of Components of Fixed-Drug Combinations** (21 CFR 300.50 *Fixed-combination prescription drugs for humans*)
  - Two or more drugs may be combined "…when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy"
- **"The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."** (21 CFR 314.126 *Adequate and well-controlled studies*)
- **FDA "is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards" for safety and effectiveness** (21 CFR 314.105(c))
- **FDA "has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness"** (21 CFR 312, subpart E, *Drugs intended to Treat Life-threatening and Severely-debilitating Illnesses)*

Demonstrating Contribution of Individual Drugs to Effect (COE) of Novel Combination

- Randomized, Controlled Factorial Design for COE When Feasible
- External Data[1] to Demonstrate COE May Be Supported By
  - Strong Biological Rationale
  - Natural history of the disease is highly predictable
  - Safety and Efficacy Demonstrated in Other Indications
  - Monotherapy Known to be Minimally Active
  - Novel Combination Has Large Magnitude of Treatment Effect
- Key Considerations
  - Source of Data
  - Suitability of Data
  - Endpoints

[1]Data Source is External to the Registration Trial Demonstrating Safety and Effectiveness of Combination Regimen

Hypothetical Examples of Contribution of Effect (COE): Multi-arm with Each Monotherapy

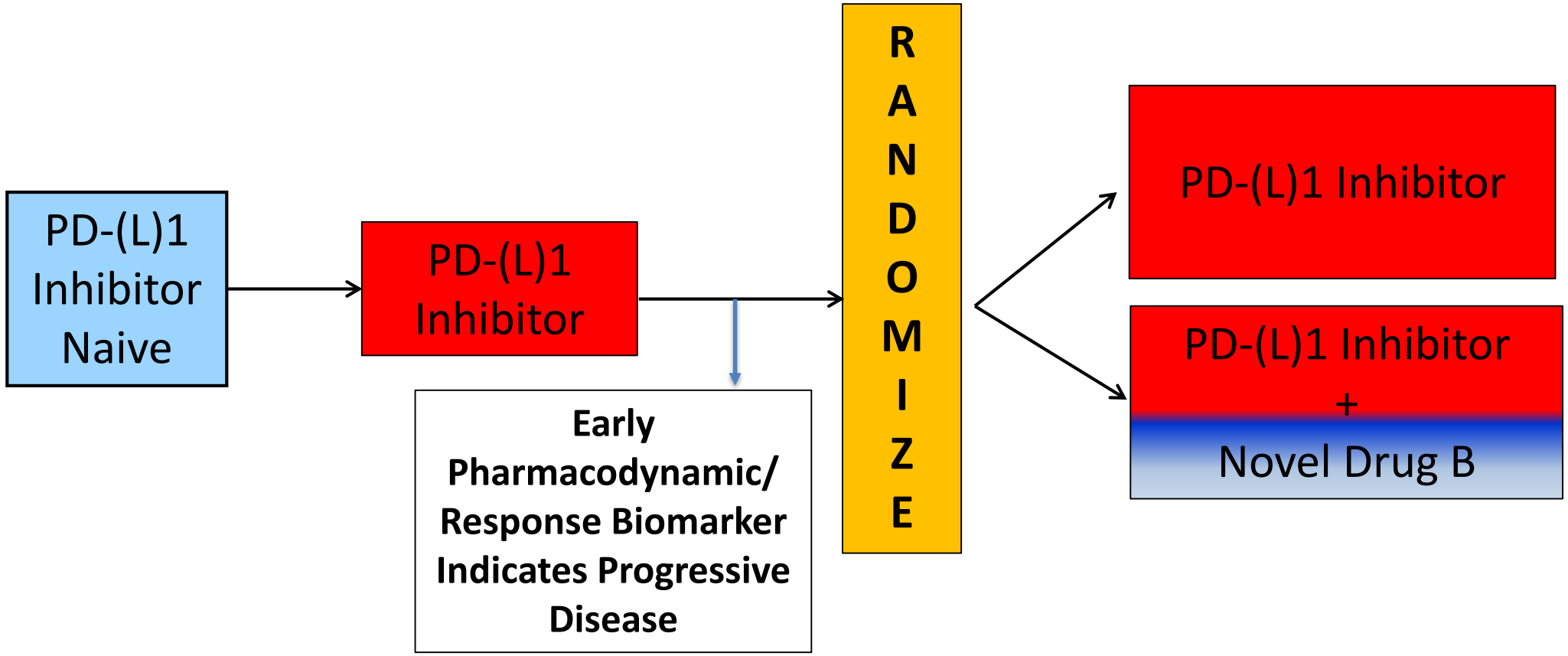


New Investigational Drug with Drug Approved in Different Indication

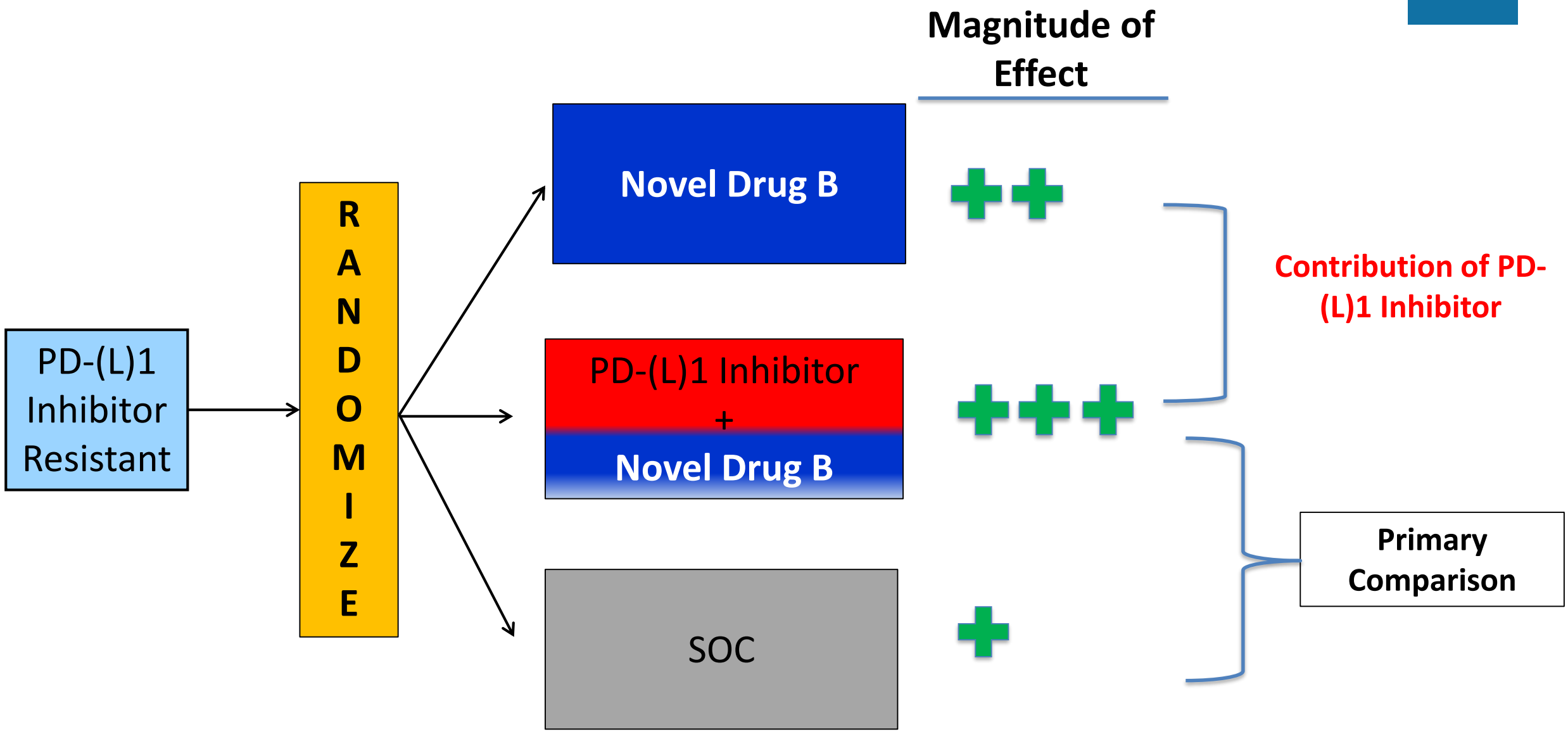
- Randomized Trial to Demonstrate Contribution of Components
- Greater Uncertainty With External Data Source May Preclude Use For
  - New investigational drug
  - Settings where treatment effect less reliable based on natural history
  - Novel combinations where magnitude of treatment effect is modest
- Strong Biologic Rationale And Nonclinical And/Or Early Clinical Evidence Supporting Necessity Of Each Drug May Reduce Uncertainty
  - External data from clinical trials investigating the previously approved[1] drug(s) as monotherapy in the same indication as for the novel combination regimen

[1]Previously approved for a different indication than that under investigation for the novel combination regimen

COE Examples (cont'd): Add-on Design

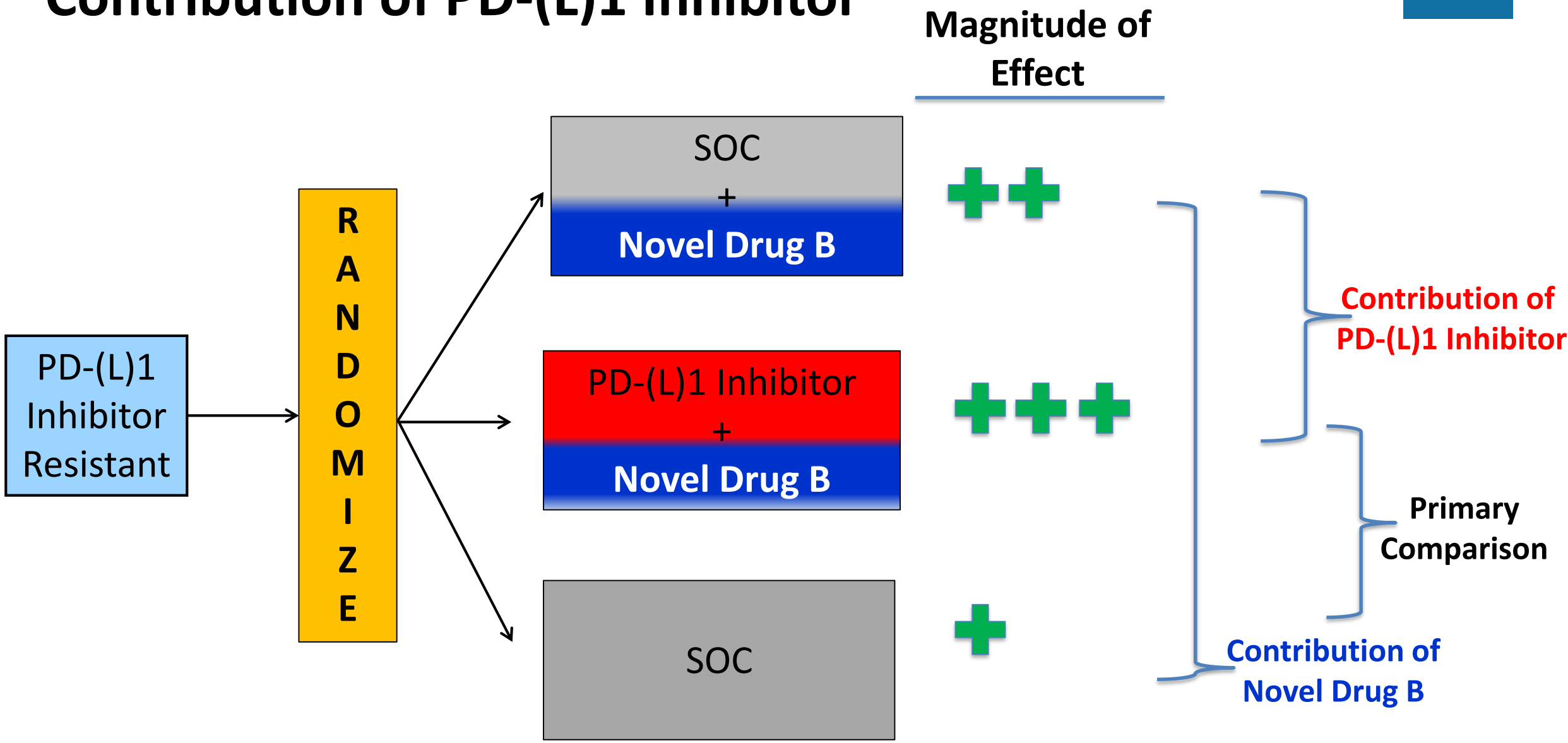


COE Examples (cont'd): Monotherapy Novel Drug B



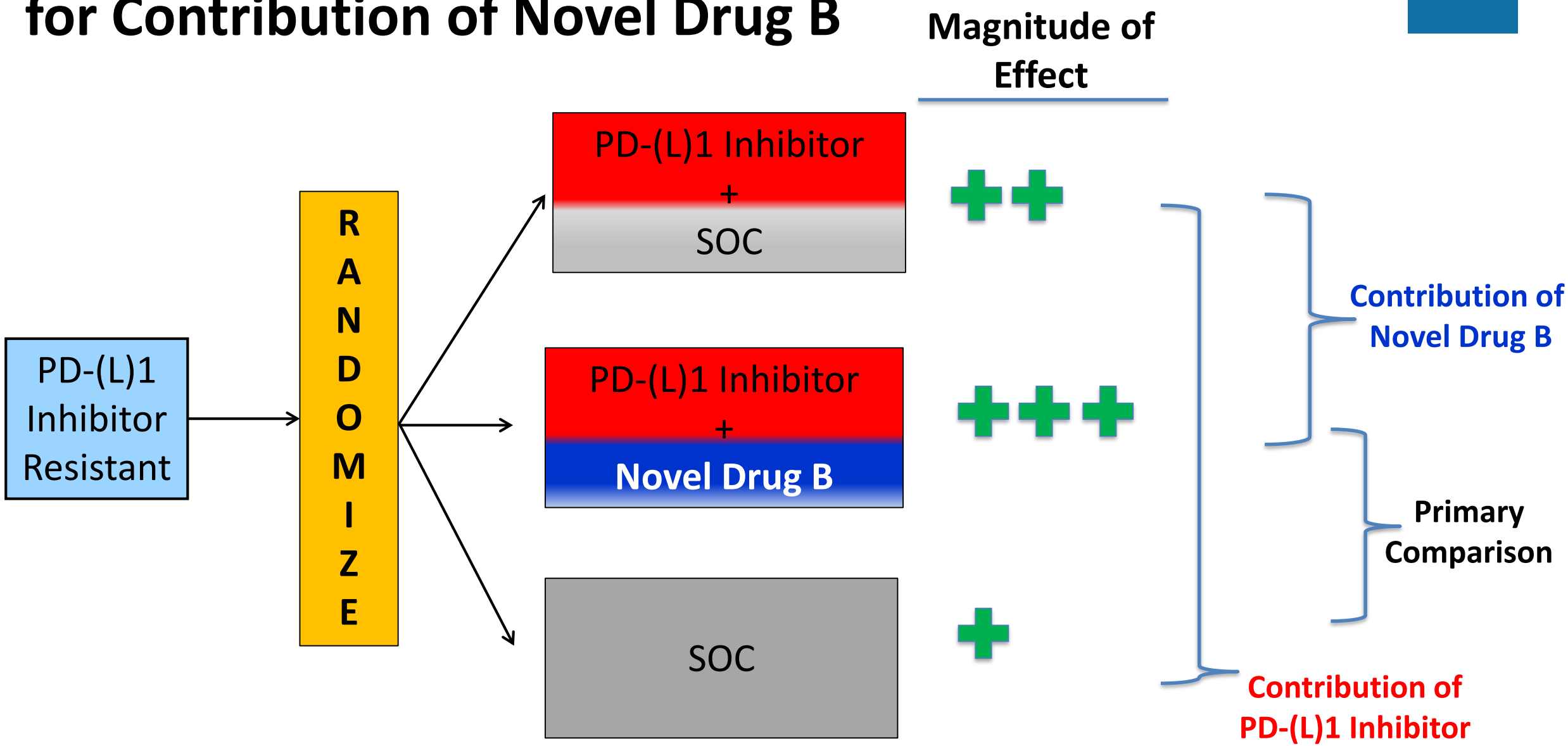
Note: External Data to Support PD-(L)1 Inhibitor Monotherapy is Minimally Active

COE (cont'd): Comparison of Combinations for Contribution of PD-(L)1 Inhibitor



Note: External Data to Support PD-L(1) Inhibitor Monotherapy Minimally Active

COE Examples (cont'd): Comparison of Combinations for Contribution of Novel Drug B



Note: External Data to Support Novel Drug B Monotherapy is Minimally Active

Two or More Previously Approved[1] Drugs

- Randomized Trial to Demonstrate Contribution of Components
- Prior Determinations of Safety and Effectiveness May Provide Opportunity to Rely on Additional Sources of External Data, with Consideration of
  - Similarity of biologic underpinnings across diseases or clinical context of that disease
  - Strength of rationale for use of combination in a specific disease
  - Strength of external data sources demonstrating contribution of effect in other indications
  - Quality and quantity of clinical data demonstrating contribution of individual component in other indications
  - Clinical importance of the benefit with the novel combination

[1]Previously approved for a different indication than that under investigation for the novel combination regimen

Selected Take Home Points – PD-1 Inhibitor Refractory / Resistance And Novel Combination Regimens

- No Formal Regulatory Definition
- Consider Impact of Definition on the Intended Patient Population
- Combination Regimen – Demonstration of Contribution of Effect
- Select Endpoints That Capture the Treatment Effect
- Randomized Trials Early in Development Program
- Magnitude of Treatment Effect of the Single Agent? Combination?
- Encourage Discussing Plans to Demonstrate Contribution of Effect in Advance with With Review Division

Thank you

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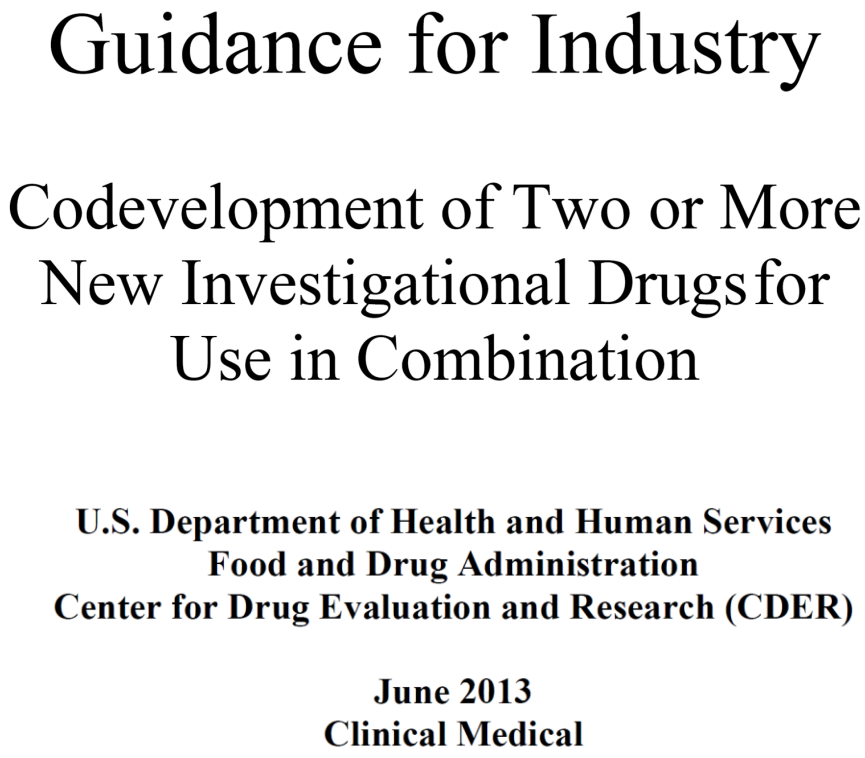
Novel Combination Regimens


Guidance for Industry

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

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

June 2013
Clinical Medical

Key Concepts

- Nonclinical & Early Clinical Development Considerations
- Appropriate Development Context -Risks of Codevelopment
- Contribution of Components
- Trial Designs

https://www.fda.gov/media/80100/download (Accessed 11/2022)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Development Program Examples – Prior Ipilimumab

Two anti-PD-1 mAbs approved in 2014 for

- treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

Development Program Examples – Prior Ipilimumab

Considerations Related to Ipilimumab

- Ipilimumab - OS Benefit / Modest Effects on ORR and PFS
- Unmet needs
- "Late effects" of ipilimumab In prior ipilimumab-exposed patients

Eligibility Criteria for Prior Ipilimumab in the Registration Trials:

	PN001 (Pembrolizumab)	CA209037 (Nivolumab)
# of Prior Doses	Previously treated with ≥ 2 doses	Not specified
Prior Dosage	≥3 mg/kg administered q3W	Not specified
Confirmation of Disease Progression	Confirmed progression per immune-related response criteria within 24 weeks of last dose	Progression after anti-CTLA-4 treatment – Confirmed progression not required

FDA Clinical and Statistical Reviews of Nivolumab Original BLA and Pembrolizumab Original BLA, Drugs@FDA

Development Program Examples – Prior Ipilimumab

	Pembrolizumab	Nivolumab
Intended Approval Pathway	Accelerated	Regular or Accelerated
Trial Design/Arms	Randomized, Dose-Comparison Pembro 2 mg/kg vs. 10 mg/kg	Randomized Controlled Trial Nivolumab vs. Chemo
Primary Endpoint(s)	ORR	ORR / OS
Statistical Considerations	Exclude ORR <10% Comparison of ORR of 2 doses	Exclude ORR < 15% Comparison of OS

FDA Clinical and Statistical Reviews of Nivolumab Original BLA and Pembrolizumab Original BLA, Drugs@FDA