Innovative oncology trial designs workshop

Combinations

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Disclaimer

- Employee at Bristol Mayers Squibb

Principle underlying combining therapeutic agents

- Maximize efficacy
- Overcome treatment resistance
- Utilizing drugs
  - with known activity
  - different mechanisms of action
  - minimally overlapping toxicities

- Tumors are rarely reliant on one molecular aberrant pathway for survival, which limits the efficacy and durability of response to single agent
- Cytotoxic chemotherapy combinations have had an indispensable impact in oncology and malignant hematology

- Progress impacted by multitude of challenges
  - rational selection of combinations in the disease context (e.g., tumor genomic redundancy and adaptability)
  - considerable intra- and inter-patient heterogeneity

Regulatory considerations for development of combinations

FDA[1,2]

- Certain conventional pharmacology and toxicology studies may be necessary to establish the safety profile of the NME alone (e.g., genotoxicity, mutagenicity, immunotoxicity, and local tolerance) before beginning clinical investigation of the combination product
- When the combination product contains a drug/biologic constituent that is already approved, address the potential for change in the established or understood safety, effectiveness and/or dosing requirements posed by the new combination
- A nonclinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response, or a better toxicity profile than the individual agents

EMA[3]

- Necessary to provide copies of scientific references to each individual active substance
- Necessary to provide pre-clinical data (pharmacokinetic and/or pharmacodynamic) for the combination product to demonstrate its mode of action
- If the pharmacological data have clearly demonstrated no interactions between the active substances, justification for the dose selection can be based on data for each individual active substance

1. Guidance for Industry and FDA Staff Early Development Considerations for Innovative Combination Products
2. Guidance for Industry Codevelopment of Two or More New Investigational Drugs for Use in Combination
3. Guideline on pharmaceutical fixed combination products

FDA Guidance for Industry

- NON-CLINICAL CODEVELOPMENT
  - A. Demonstrating the Biological Rationale for the Combination
  - B. Nonclinical Safety Characterization
- CLINICAL CODEVELOPMENT
  - A. Early Human Studies (Phase 1)
    1. Safety of the Individual New Investigational Drugs
    2. Safety and Dosing of the Combination
  - B. Clinical Pharmacology
  - C. Proof of Concept Studies (Phase 2)
  - D. Confirmatory Studies (Phase 3)

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

Key question for proof of concept: how to establish the contribution of components

Scenario 1: Each drug alone has activity and they can be administered separately

- A phase 2 trial comparing the combination to each drug alone and to placebo or standard of care (SOC) (AB v. A v. B v. SOC or placebo) should be used to demonstrate the contribution of the individual drugs
- An adaptive trial design may demonstrate the contribution of each drug to the activity of the combination without exposing the large number of patients (e.g. endpoints response rate)

Scenario 2: The individual drugs cannot be administered separately

- A proof-of-concept evidence for the combination ordinarily should come from a study directly comparing the combination (AB) to SOC

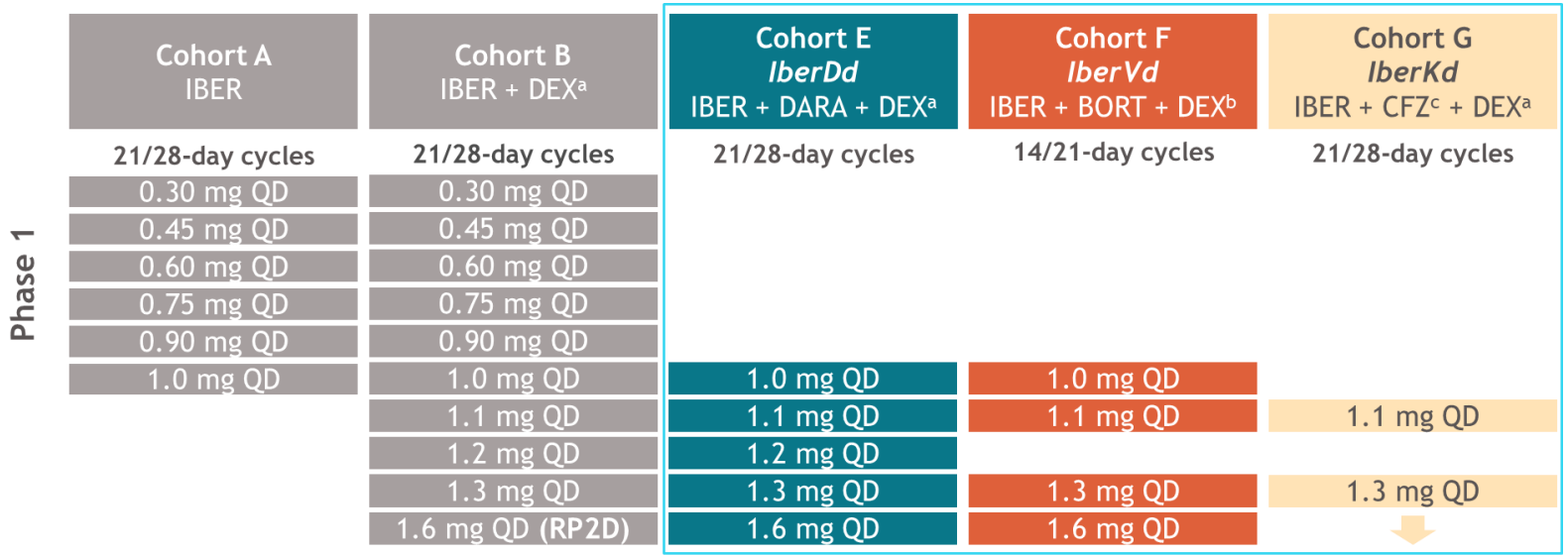
Scenario 3: When administered separately, one drug is active and one is inactive

- A proof of concept and the contribution of each new investigational drug could be demonstrated using a three-arm comparison of the active drug alone, the combination, and SOC (A v. AB v. SOC)

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

New agent in combination with established SOC
Dose escalation

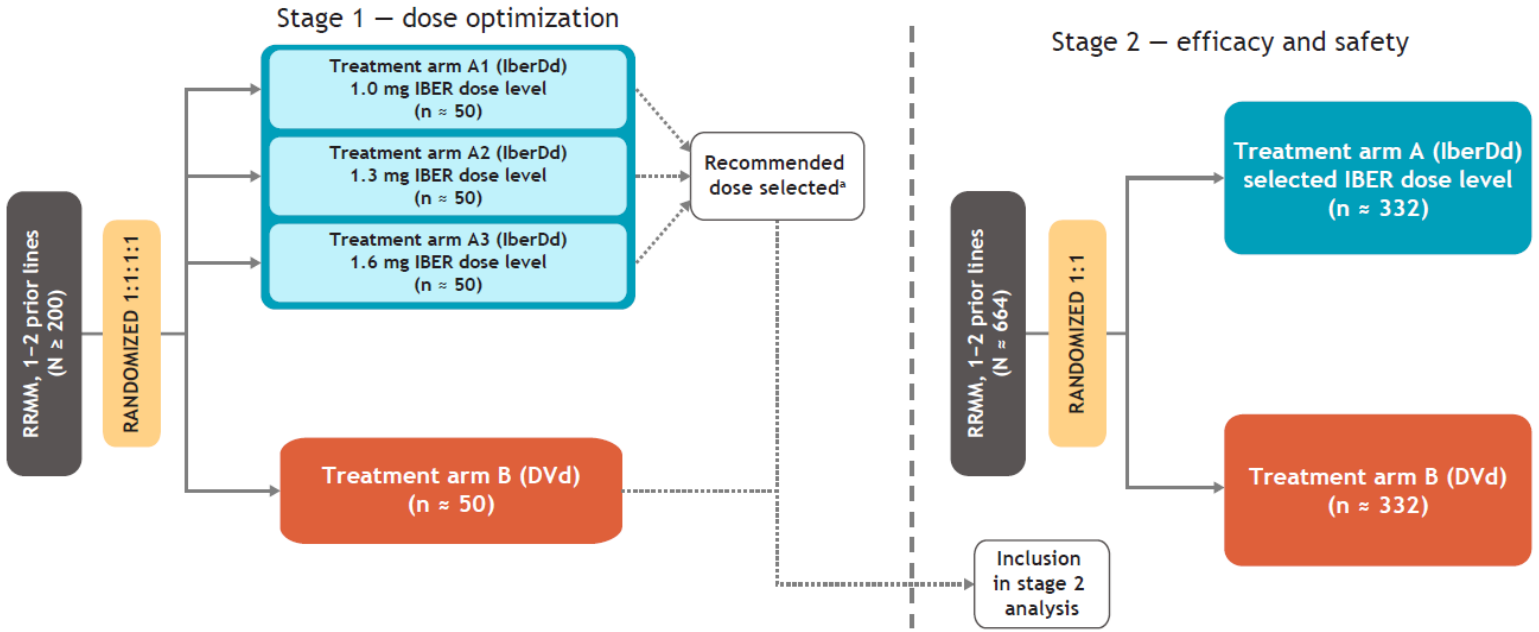
- FDA scenario 1 – a new active drug for which should be determined recommended dose as single agent and in combination
- Example of a new CelMod (iberdomide) development in Multiple Myeloma
- Phase 1 study to determine the recommended dose



Lonial, et al. EHA 2021. Abstract S187
Lonial, et al. ASCO 2023. Abstract P257

New agent in combination with established SOC
Dose optimization & evaluation of Benefit/Risk

- A 2-stage, multicenter, randomized, open-label, phase 3 trial
- Phase 2 study portion to determine dose optimization, following FDA project Optimus
- Phase 3 study portion to determine efficacy and safety



Lonial, et al. EHA 2021. Abstract S187
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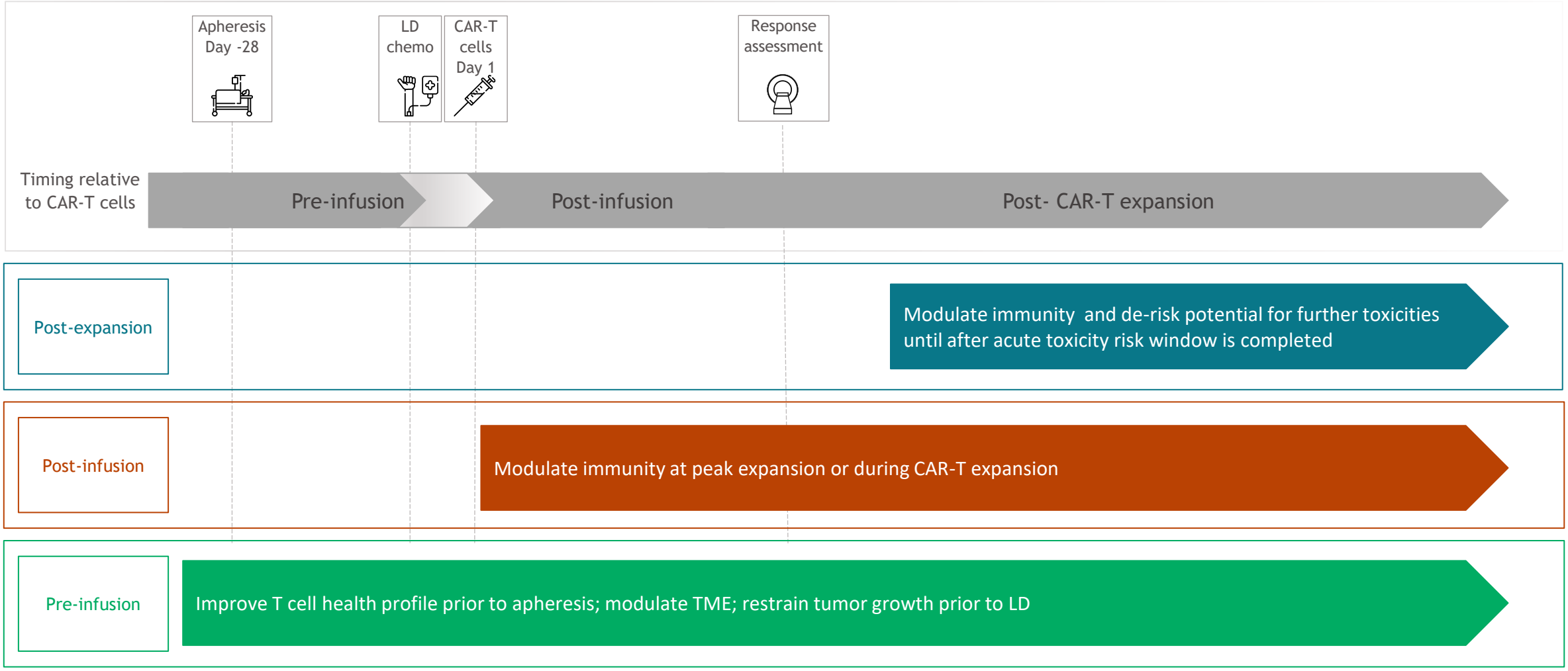
Combinations in Cellular Therapy – CAR-T cells example

- CAR-T therapies have demonstrated encouraging activity in adult and pediatric subjects
- While high response rates have been reported after CAR T cell infusion, responses in some are transient and subjects have been shown to relapse in the presence of persistent CAR T cells
- Possible explanations for this are:
  - Immunological exhaustion of circulating T cells and/or changes in T lymphocyte populations
  - Down regulation of the tumor target on the tumor cell surface
  - An effect of the tumor microenvironment, eg, CAR T cells are suppressed by the tumor microenvironment and lose their antitumor activity before they are able to eliminate all tumor cells
- In hematological diseases combination agents with immunomodulatory effect are also active drugs in the specific tumor types

Timing & objective of adding a combo agent during autologous CAR-T treatment journey



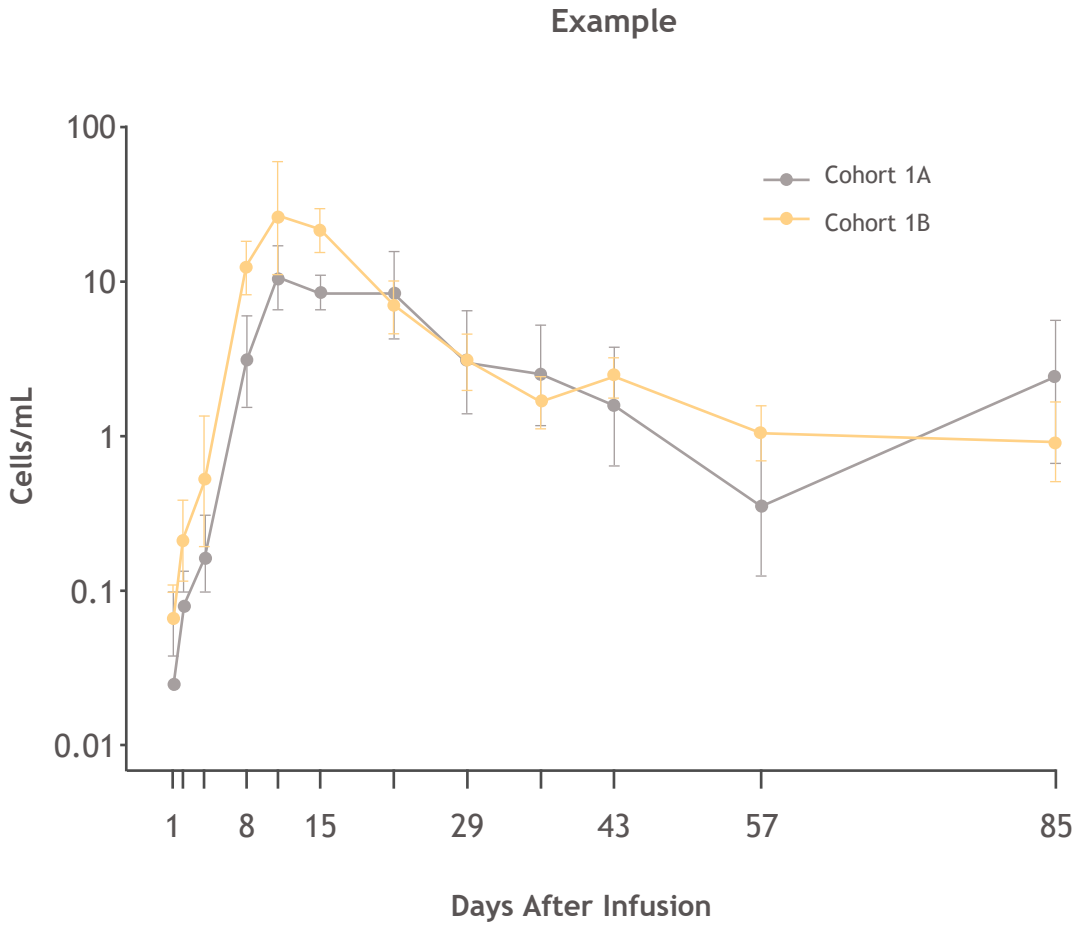
Example of dose escalation for CAR-T in combination

Cohort	Sub-cohort	CAR-T Dose	Combination Agent Dose	Combination Agent Schedule
Cohort 1 Post-infusion	A	X x 10^6 CAR+T cells	Dose L1 mg	Days 15-21 and 29-85 post-CAR-T infusion
	B			Days 8-21 and 29-85 post-CAR-T infusion
	C			Days 1-21 and 29-85 post-CAR-T infusion
	A+1	X x 10^6 CAR+T cells	Dose L2 mg	Days 15-21 and 29-85 post-CAR-T infusion
	B+1			Days 8-21 and 29-85 post-CAR-T infusion
	C+1			Days 1-21 and 29-85 post-CAR-T infusion
	A-1	X x 10^6 CAR+T cells	Dose L2 mg	Days 15-21 and 29-85 post-CAR-T infusion
	B-1			Days 8-21 and 29-85 post-CAR-T infusion
	C-1			Days 1-21 and 29-85 post-CAR-T infusion

- Open questions
  - If the combination agent is an active drug, how much length of exposure need to be tested for contribution of component?
  - If you have a defined CAR-T dose, do you need to restart dose escalation for CAR-T, if the combination agent impacts CAR-T expansion?

Does the increase in peak expansion requires dose escalation of CAR-T?

- An increase in the CAR-T expansion could change efficacy and safety profile
- Usually higher peak expansion is associated with higher toxicity
- Anyhow, there's lot of interpatient variability in the pharmacokinetic profile
- Are pre-clinical models informative on PK profile? Probably not enough…



Conclusions

- Development of combinations is strictly regulated by FDA and EMA and pre-clinical and clinical data are required
- Demonstration of contribution of components is a key factor
- Dose optimization increase the complexity of study designs, but is a great opportunity to improve the safety and efficacy profile of combination treatments
- In oncology it is rare to have one component that is not an active drug
- Cellular therapies open up new challenges:
  - How to measure the contribution of components?
  - How to determine the need for dose escalation for both components?