Regulatory Considerations During Combination Cancer Immunotherapy Development

ASCPT 2016 Annual Meeting

Friday, March 11, 2016

Atiqur Rahman, Ph.D.

Director, Division of Clinical Pharmacology V

Office of Clinical Pharmacology

OTS, CDER, FDA

The views represent my personal perspectives and do not reflect the official position of the US FDA.

Presentation Outline

- Regulation and Guidance related to combination therapy development

- Case Examples
  - Idelalisib + Rituximab
  - Nivolumab + Ipilimumab

- Regulatory challenges and remedies

Regulation Supports Combination Immunotherapy Development

21 CFR, Subpart B, §300.50 – Fixed-combination prescription drugs for humans

Two or more drugs may be combined in a **single dosage form** 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…

Guidance

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

Guidance for Industry: Co-development of two or more new investigational drugs for use in combination

- Treat a serious disease
- Compelling biological rationale for the combination
- Nonclinical characterizations demonstrate substantial activity of the combination
- Compelling reason why new drugs cannot be developed independently

Combination Immunotherapy Development: Early Human Trials

- Characterize safety and PK of both drugs and the combination-
  - PK characterization
  - Drug interactions
  - Effects of organ function
  - Pharmacogenomics
- Conduct dose response on a relevant biomarker(s) or appropriate clinical endpoint(s)
  - Each individual agent
  - Combination
- Support appropriate dosing for phase 2 testing

Combination Immunotherapy Development: Proof of Concept

Objectives

- Demonstrate contribution of each individual agents
- Provide evidence of effectiveness of the combination
- Optimize dose or doses of the combination for confirmatory trial(s)

Study Design

Scenario	Activity	Design
1	Each component is active	AB vs A vs B vs SOC/Placebo*
2	Each component is sub-therapeutic	AB vs SOC or AB + SOC vs SOC
3	One active and one inactive	AB vs A vs SOC*
		AB + SOC vs A + SOC vs SOC + placebo*

SOC: Standard of Care

* Adaptive design

Combination Immunotherapy Development: Dose Findings

- Conduct dose response and exposure response analyses taking into consideration of dose reductions, interruptions and discontinuations in the model

- Optimize dose or doses of the combination for confirmatory trial(s)

Combination Immunotherapy Development: Confirmatory Studies

- Scenario 1: Contribution of each agent is demonstrated
  - AB versus SOC/Placebo
- Scenario 2: Contribution of each agent is not clear and mono therapy is ethically feasible and effect of SOC is known
  - AB versus A versus B
- Scenario 3: Contribution of each agent is sufficient from phase 2 data
  - AB versus A (where A is more active and can be given alone)
  - Testing more than one dose level of A may be useful

Regulation supports and promotes combination immunotherapy development

Case Examples: Clinical Program

- Idelalisib in combination with Rituximab for the treatment of patients with Chronic lymphocytic leukemia

- Nivolumab in combination with Ipilimumab for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma

Case Examples
Idelalisib + Rituximab

Rationale for the Combination

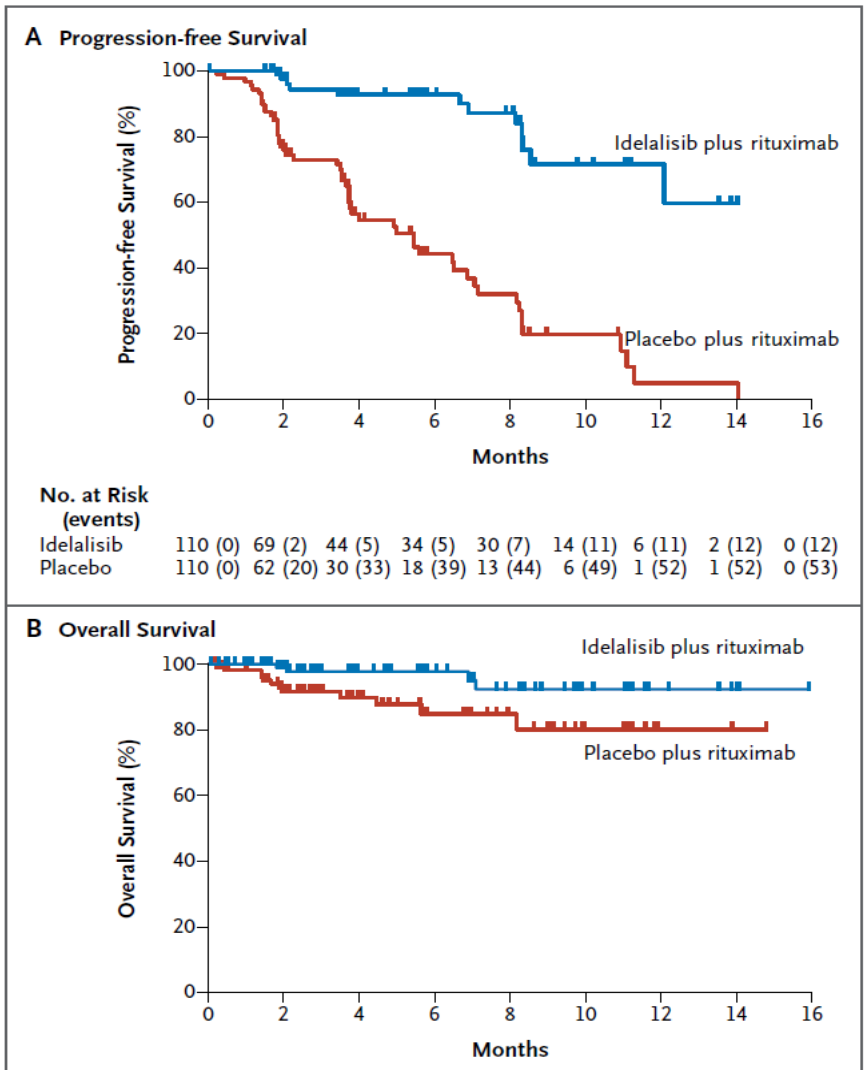
- Treating serious disease: Chronic Lymphocytic Leukemia
- Both demonstrated activity as monotherapy
- Compelling biological rationale for the combination
  - Idelalisib is a kinase inhibitor with selectivity toward PI3Kδ. Inhibits ATP binding to the catalytic domain of PI3Kδ resulting in inhibition of phosphorylation of PIP and Akt and downstream effects on malignant B-cell survival and proliferation
  - Rituximab is a monoclonal antibody that mediates B-cell lysis through CDC and ADCC

Overall Development Plan

- Early Phase Trial
  - Phase 1 trial with two doses of Idelalisib (100 mg or 150 mg bid) plus 325 mg/m^2 doses of Rituximab for 8 weeks
  - Efficacy, Safety of the combination and PK of idelalisib
  - High overall response rate and longer duration of response observed
- Registration Trial
  - Phase 3, 1:1 randomized , double-blind, placebo-controlled trial in 220 CLL patients
  - Dose: Idelalisib, 150 mg bid, Rituximab, 325 mg/m^2 followed by 500 mg/m^2 for 8 doses
  - Endpoint: PFS

Clinical trial information:NCT01088048

Eye-Popping Efficacy with Reasonable Toxicity



	Idelalisib + R	Placebo + R
Overall Response	81%	13%
OS at 12 month	92%	80%
SAE	40%	35%

SAE: Serious Adverse Effects

	Idelalisib + R	Placebo + R
Median (months)	NR (10.7, NR)	5.5 (3.8, 7.1)
Hazard Ratio (95% CI)	**0.18 (0.10, 0.32)**	
P-value	<0.0001*	

* Stratified log-rank test

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206545lbl.pdf

Furman et al., N Eng J Med, 2014, 370(11)

Case Examples
Nivolumab + Ipilimumab

- Rationale for the Combination
  - Treating serious disease: metastatic melanoma
  - Both demonstrated activity as monotherapy
  - Both enhance T-cell mediated immune response through complimentary mechanisms
    - Ipilimumab a monoclonal blocks binding of B7.1 and B7.2 to the CTLA-4 receptor, prevents inhibitory signal, and promotes T-cell activation and proliferation
    - Nivolumab is a monoclonal antibody that binds to PD1 receptors on T-cells and blocks its interaction with PD-L1 and PD-L2 expressed by cancer cells thereby restoring the immune surveillance by T-cells and invoking immune response

Early Phase Trial

- Phase 1 dose escalation trial with more than 1 dose level of nivolumab and ipilimumab was tested in 53 advanced melanoma patients
- Efficacy and Safety of the combinations were assessed

Dose (mg/kg)	N	ORR % (95% CI)	Clinical Activity %(95% CI)	>80% Tumor reduction (%)
Nivo 0.3 + Ipi 3	14	21 (5-51)	50 (23-77)	29
Nivo 1 + Ipi 3*	17	53 (28-77)	65(38-86)	41
Nivo 3 + Ipi 1	15	40 (16-68)	73(45-92)	33
Nivo 3 + Ipi 3**	6	50 (12-88)	83(36-100)	0

Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg was tested in the confirmatory trial

Registration Trial

– Phase 2, 2:1 randomized, double-blind, placebo-controlled, 2-arm trial of Nivolumab with Ipilimumab versus Ipilimumab in BRAF wild-type metastatic melanoma patients

Endpoint	Nivolumab plus Ipilimumab (n = 72)	Ipilimumab plus placebo (n = 37)
Objective Response Rate (95% CI)	60% (48,71)	11%(3,25)
Difference in ORR (95% CI)	**49 (31,61)**	
CR (%)	17%	0
PR (%)	43%	11%
Progression-free Survival		
Median (months) (95% CI)	8.9 (7.0, NA)	4.7 (2.8, 5.3)
Hazard Ratio (95% CI)	**0.40 (0.22 – 0.71)**	

Safety of Combination Immunotherapy

Safety Events	Nivolumab + Ipilimumab (n = 94)	Ipilimumab + Placebo (n = 46)
SAE	62%	39%
Adverse Reactions leading to:		
Discontinuation	43%	11%
Dose delay	47%	22%
Adverse Reactions (Grade 3 and 4)	69%	43%
AE Leading to Discontinuation		
Colitis	16%	2%
Diarrhea	4%	4%
Increased ALT	4%	0%
Increased AST	3%	0%
Pneumonitis	3%	0%

Immune mediated reactions include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and encephalitis.

Regulatory Challenges

- Expansion cohorts
- Establishment of the contribution of each component
- Trial Design
- Assessment of efficacy
  - Traditional endpoints
  - Alternate endpoints
- Potential safety concerns
  - Immune mediated toxicities
- Balancing benefit risks of the combination

Remedies

Early & Frequent Communication with FDA

- Consult FDA on the appropriateness of codevelopment before initiation of clinical development of a combo.
  - PreIND
- Consult FDA as needed throughout the development process.
  - EOP1, EOP2, etc.
- Discuss submission content in the Pre-NDA or Pre-BLA meeting.
- Consult FDA to discuss approaches to post-marketing safety monitoring.

Communication will help facilitate development of the combination therapy and assure safe and effective combination therapy for the patients.

ACKNOWLEDGEMENT

- Hong Zhao
- Sarah Schrieber
- Eric Masson
- John Kurland
- Shruti Agrawal
- Paul Statkevich
- Shiew Mei Huang

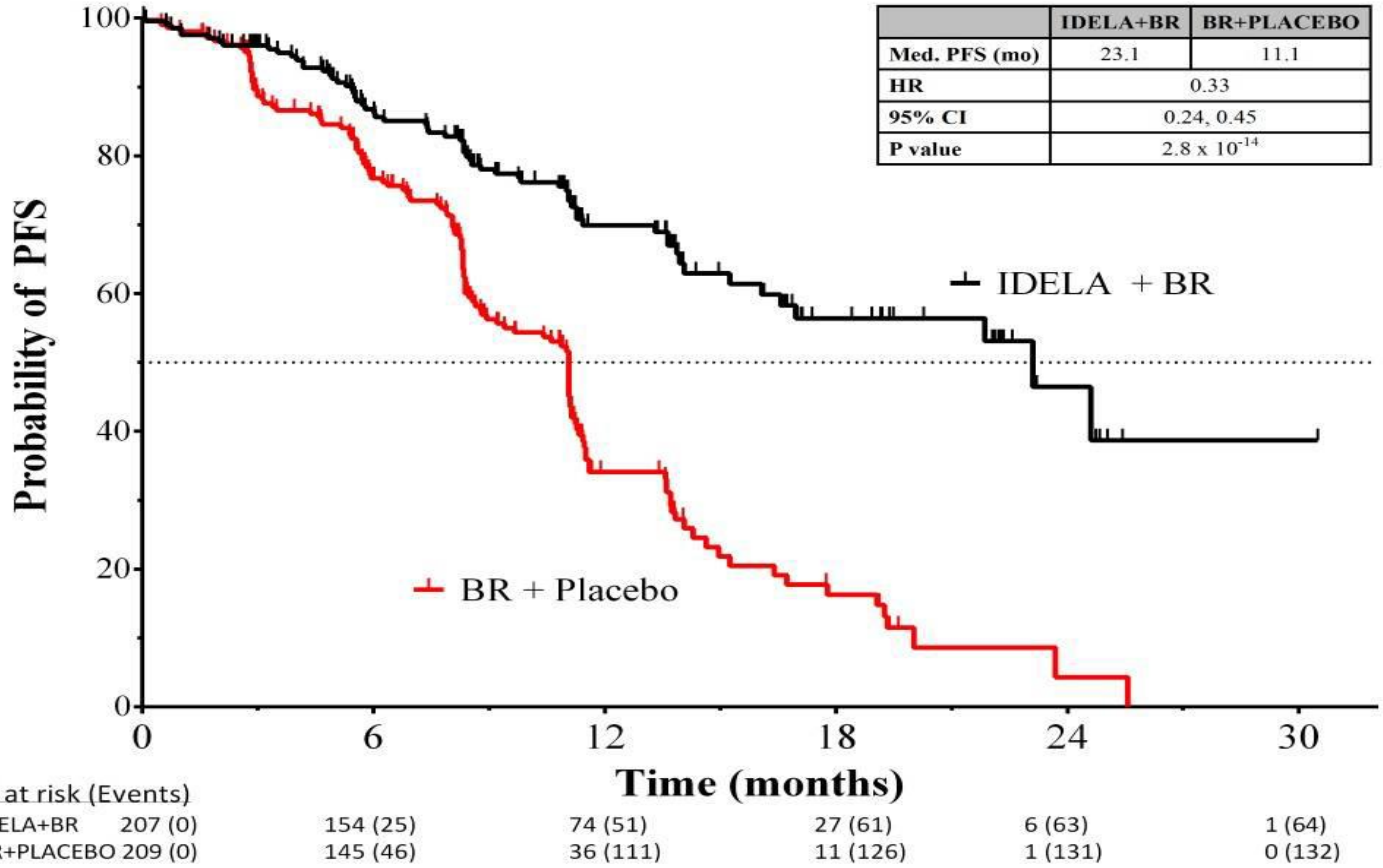
BACK UP Slides

What is Combination Development from Regulatory Perspectives?

- Fixed combination in a single dosage form
- Fixed combination of approved drugs
- Fixed combination of a new investigational drug in combination with a previously approved drug
- Two or more new investigational drugs in combination

Drugs include both small and large molecules

Idelalisib Plus Bendamustine and Rituximab in CLL



Phase 3 Randomized, Double blind, Placeo-controlled Trial in 416 patients

mOS not reached (HR = 0.55; p-value 0.008, 95% CI 0.36 – 0.86)

Guidance

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

Guidance for Industry: Co-development of two or more new investigational drugs for use in combination

- Treat a serious disease
- Compelling biological rationale for the combination
- Nonclinical characterizations demonstrate substantial activity of the combination
- Short-term clinical studies provide significant therapeutic advance
- Compelling reason why new drugs cannot be developed independently

Safety of Combination Immunotherapy

Immune mediated reactions include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and encephalitis.

Safety Events	Nivolumab + Ipilimumab (n = 94)	Ipilimumab + Placebo (n = 46)
SAE	62%	39%
Adverse Reactions leading to:		
Discontinuation	43%	11%
Dose delay	47%	22%
Adverse Reactions (Grade 3 and 4)	69%	43%
AE Leading to Discontinuation		
Colitis	16%	2%
Diarrhea	4%	4%
Increased ALT	4%	0%
Increased AST	3%	0%
Pneumonitis	3%	0%