Accelerating Anticancer Agent Development and Validation Workshop 2018

Combinatorial Strategies in Immuno-oncology: Industry Perspective

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Disclosure Information

Katrin Rupalla PhD, MBA

I have the following financial relationships to disclose:

Stockholder in: Bristol-Myers Squibb

Employee of: Bristol-Myers Squibb

- and -

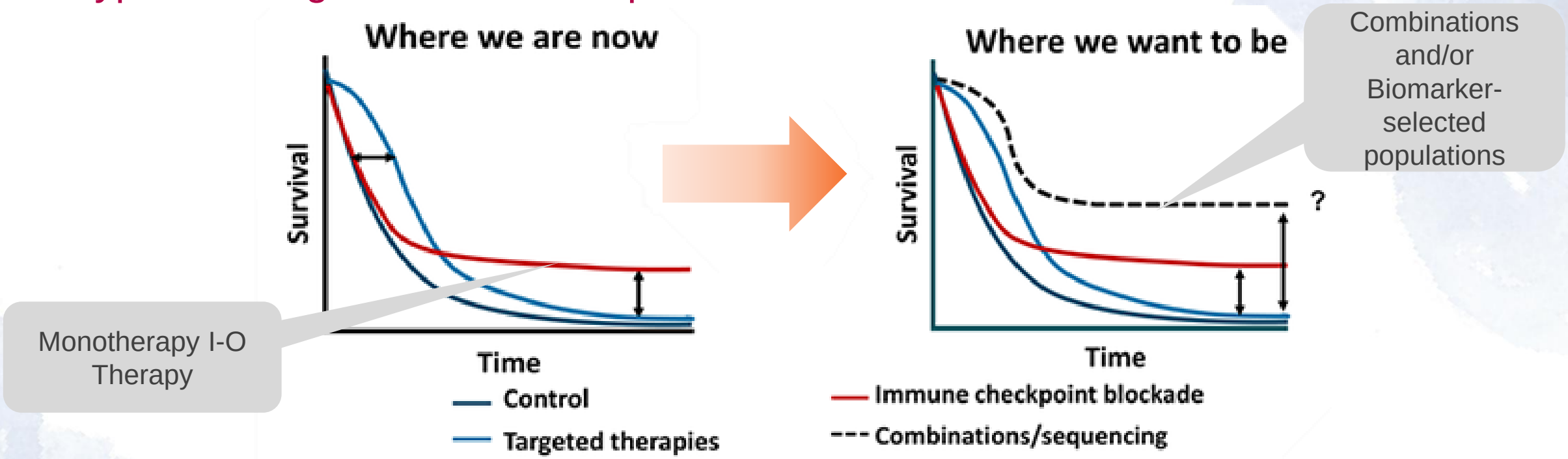
I will discuss the following off label use and/or investigational use in my presentation: None

Regulatory challenges with developing PD-1 combinations

- BMS strategy with combinations
- Opportunities/challenges with
  - Contribution of Components (CoC) based on combination approvals in the US for nivolumab + ipilimumab
- Considerations for drug development from a regulatory perspective

Immunotherapy as a potential revolutionary treatment platform

Hypothetical goals of I-O therapies

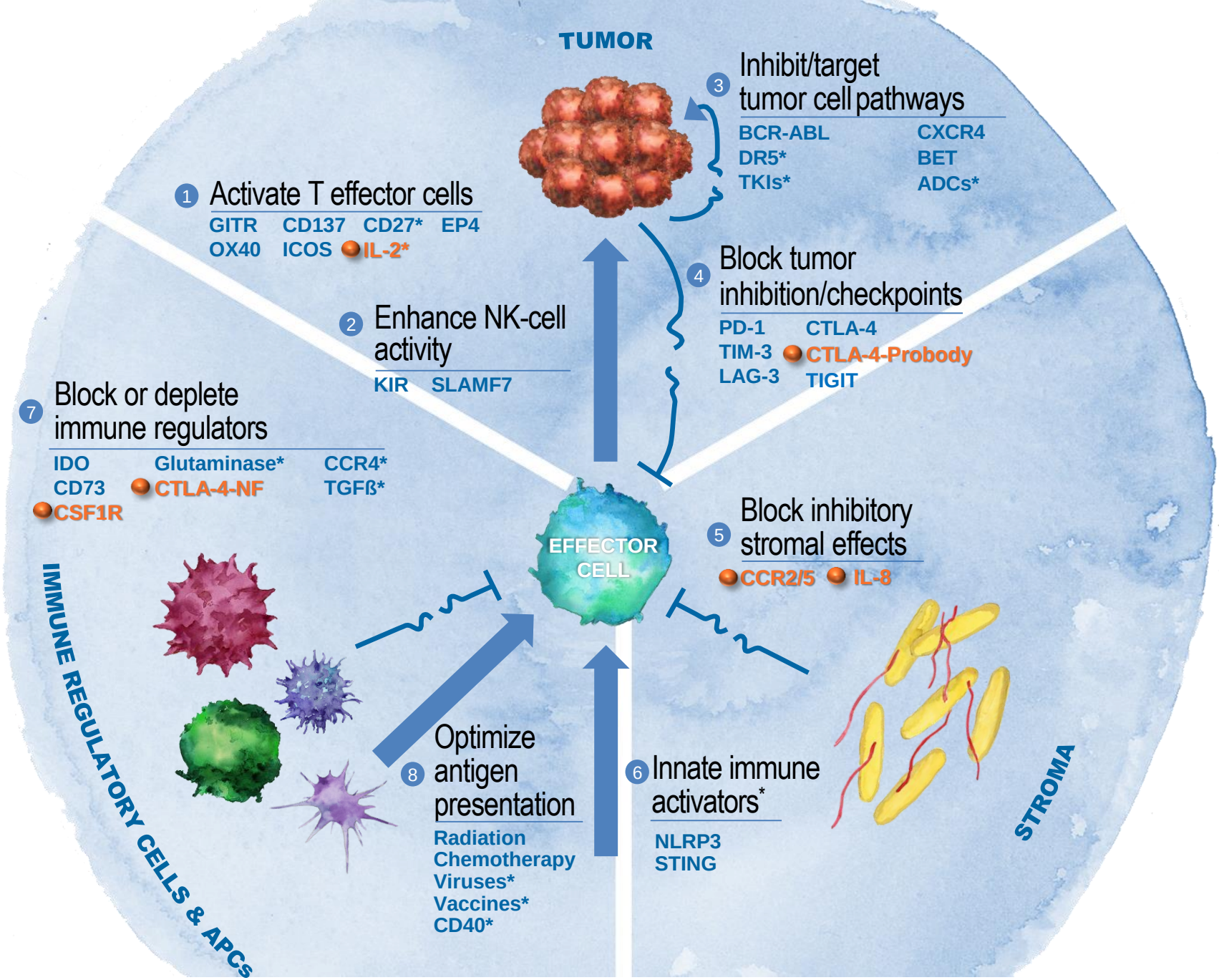


Hypothetical slide illustrating a scientific concept that is beyond data available so far. These charts are not intended to predict what may actually be observed in clinical studies.

I-O, immuno-oncology.

Figure is adapted from Ribas A, et al. Clin Cancer Res 2012;18:336–41.

BMS purpose-built deep portfolio of clinical stage combination therapies



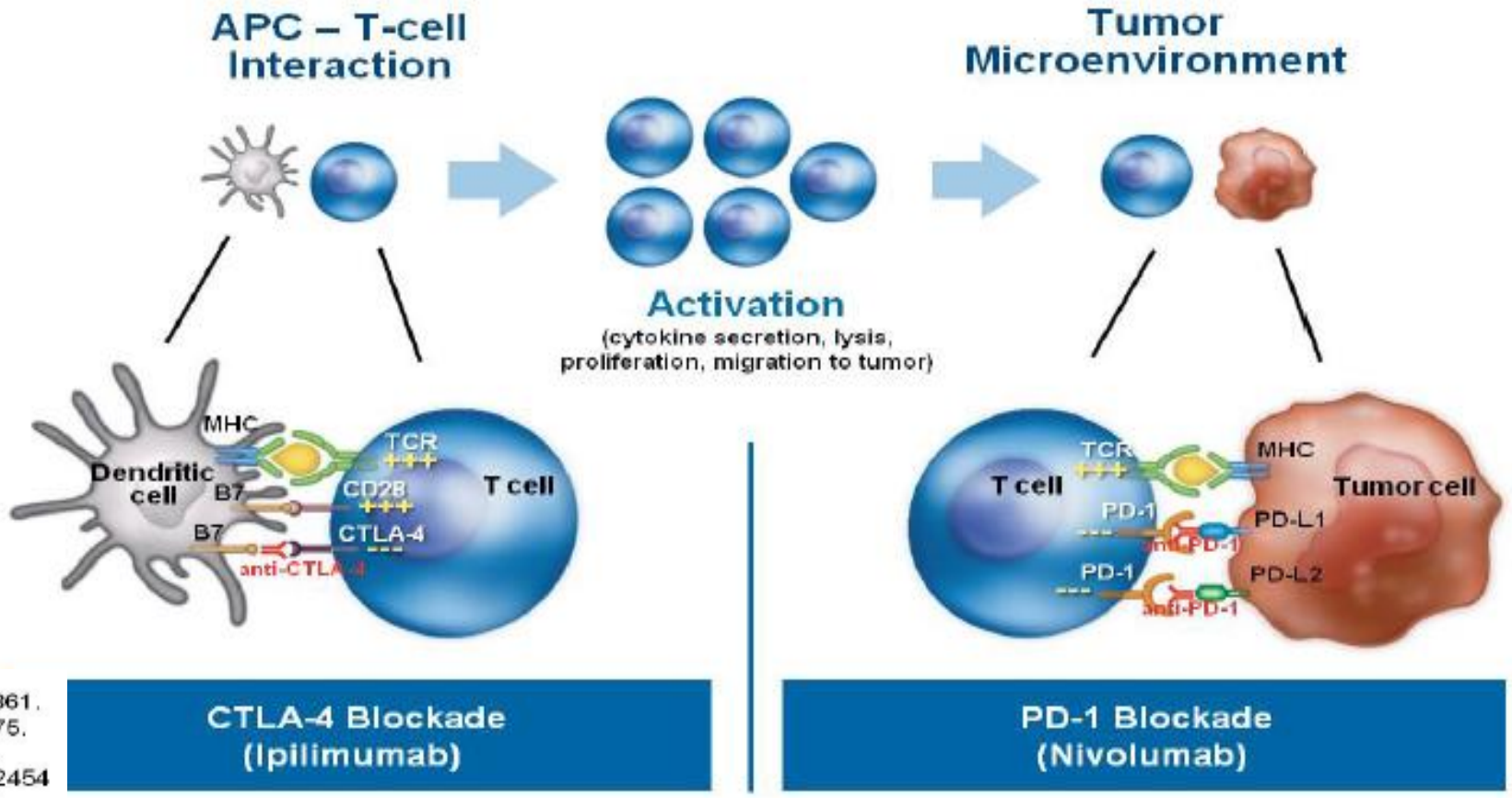
* Includes clinical collaborations.

BMS experience with late stage combination development & regulatory approvals

- Challenge of combination mostly if new MOA or less established compounds combined
  - Not with chemo combos or combos with RT for example
- Case by case development with tailored study designs depending on data/scientific rationale
- Three combination approvals in the US of nivolumab + ipilimumab
  - 1L unresectable or metastatic melanoma (FDA AA Oct'15 & Jan'16)
  - 1L advanced renal cell carcinoma (FDA approval April'18)
  - 3L metastatic CRC-MSI H (FDA AA approval July '18)

Strong scientific rationale for combining PD-1 and CTLA checkpoint blockade*

- Nivolumab & ipilimumab enhance T-cell antitumor activity through distinct but complimentary mechanisms



1. Hamid O, et al. *Exp Opin Biol Ther.* 2013;13:847–861.
2. Brahmer JR, et al. *J Clin Oncol.* 2010;28:3167–3175.
3. Wang C, et al. *Cancer Immunol Res.* 2014;2:1–11.
4. Topalian SL, et al. *N Engl J Med.* 2012;366:2443–2454
5. Pardoll D, et al. *Nat Rev Cancer.* 2012;12:252-264.

Phase I/II data of combination nivolumab & ipilimumab

- Data indicate potential for αPD-1/αCTLA-4 to have greater activity with deeper response* than αPD-1 alone – example melanomas, RCC and CRC MSI-H

Tumor	αPD-1/αCTLA-4 (%)	αPD-1 (%)
	ORR	
Melanoma[1]	~60	~40
RCC[2,3]	~40	~20
MSI-H CRC[7]	~55	~30[7]

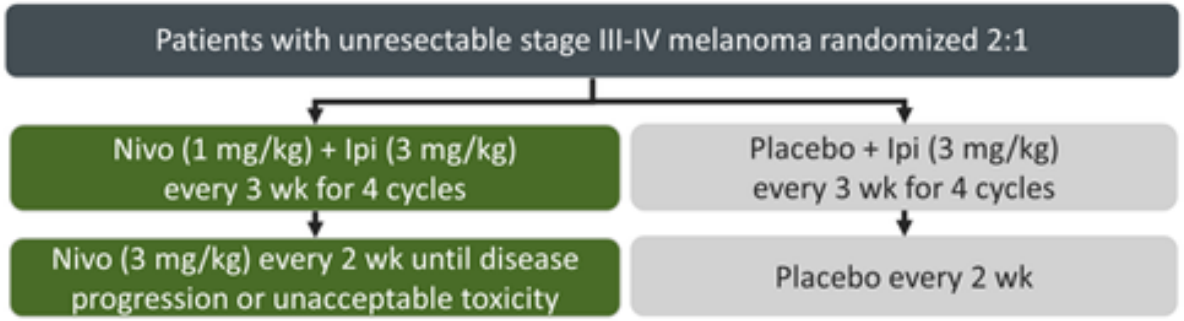
1. Larkin et al. NEJM 2015;373:23–34. 2. Hammers et al. JCO 2017;35:3851–8. 3. Motzer et al. NEJM 2015;373:1803–13. . 7 Opdivo PI 2018

Key regulatory challenges of nivolumab & ipilimumab combination development

- Risk/benefit ratio – higher toxicity than monotherapy, additional benefit sufficient?
  - Patient population becoming increasingly fragmented – who benefits most?
    - PD-L1+/-, TMB, inflammation/immune signature, etc
- Contribution of component?
  - What is single agent contribution of nivolumab and ipilimumab?
  - What evidence is needed?

Design of study in 1L line melanoma : Two-arm phase 2 study

CheckMate 069



Key Data From CheckMate 069

Outcome	Nivo/Ipi (n = 95)	Ipi (n = 47)	*P* value
ORR, %	59	11	<.0001
CR, %	22	0	
mPFS, mo	NR	3	<.0001
mOS, mo	NR	NR	
Grade 3/4 AEs, %	54	20	

- No change in ORR, PFS or OS as a function of PD-L1 or *BRAF* status

Hodi FS, et al. *Lancet Oncol.* 2016;17:1558-1568.

Design: AB vs B

Rationale:
B = SOC
AB = High ORR in phase 1

Supported accelerated approval in BRAF wild type patients

Design of follow up study in 1L line melanoma: Three arm phase 3 study

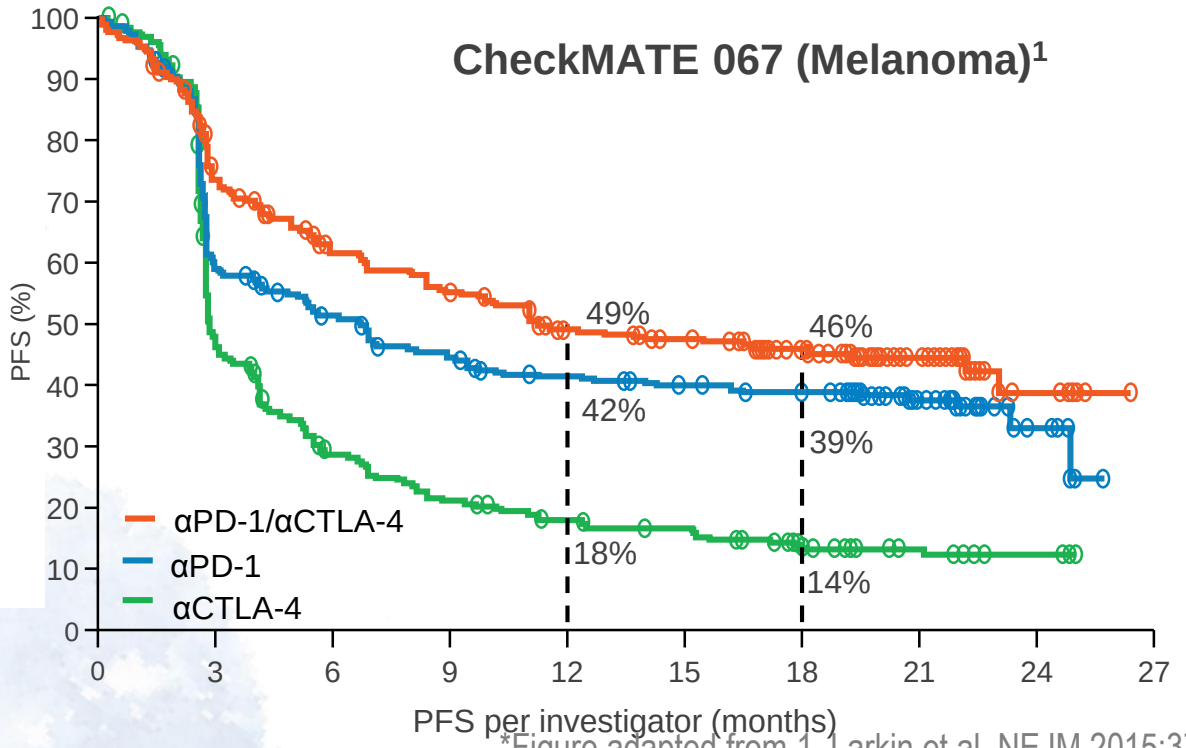


*Figure adapted from 1. Larkin et al. NEJM 2015;373:23–34.

Design: AB vs A vs B

Rationale:

B = SOC

A = significant activity

AB = high ORR in phase 2

Supported accelerated approval in all comers population

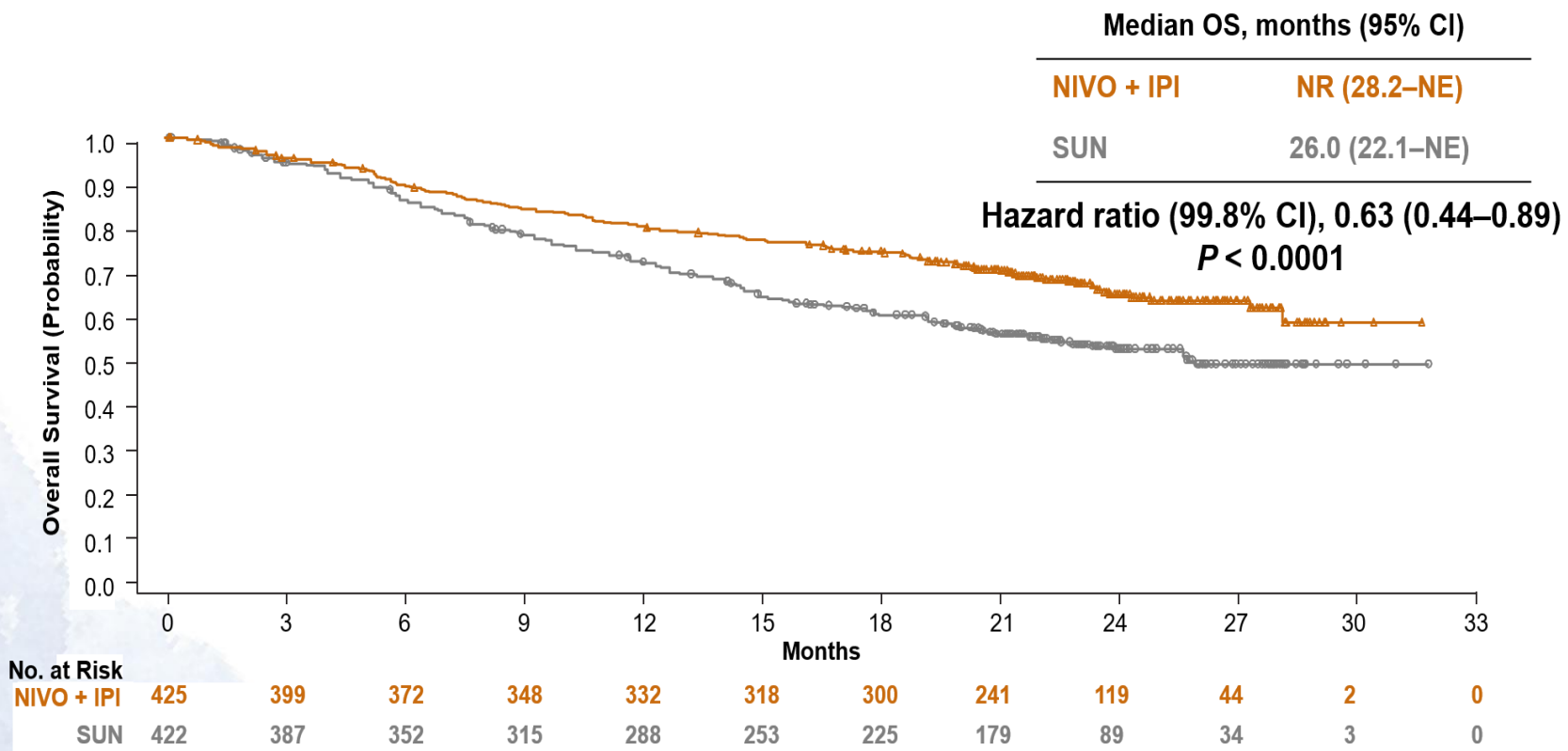
Safety of combination vs monotherapy agents

Opdivo® USPI Nivolumab 1mg/kg + ipilimumab 3mg/kg

Table 6: Adverse Reactions Occurring in ≥10% of Patients on the OPDIVO plus Ipilimumab Arm or the OPDIVO Arm and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (CHECKMATE-067)

Adverse Reaction	Percentage (%) of Patients					
	OPDIVO plus Ipilimumab (n=313)		OPDIVO (n=313)		Ipilimumab (n=311)	
	All Grades	Grades 3-4	All Grades	Grades 3-4	All Grades	Grades 3-4
General Disorders and Administration Site Conditions						
Fatigue[a]	59	6	53	1.9	50	3.9
Pyrexia	37	1.6	14	0	17	0.6
Skin and Subcutaneous Tissue Disorders						
Rash[b]	53	5	40	1.6	42	3.9
Gastrointestinal Disorders						
Diarrhea	52	11	31	3.8	46	8
Nausea	40	3.5	28	0.6	29	1.9
Vomiting	28	3.5	17	1.0	16	1.6
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	20	2.2	12	1.3	13	0.6

Design of registration study in 1L line RCC: Two-arm phase 3 study



Presented By Dr. Escudier 2017 ESMO: CheckMate 214: Efficacy and Safety of Nivolumab Plus Ipilimumab vs Sunitinib for Treatment-Naïve Advanced or Metastatic Renal Cell Carcinoma, Including IMDC Risk and PD-L1 Expression Subgroups

Design: AB vs SOC

Rationale:

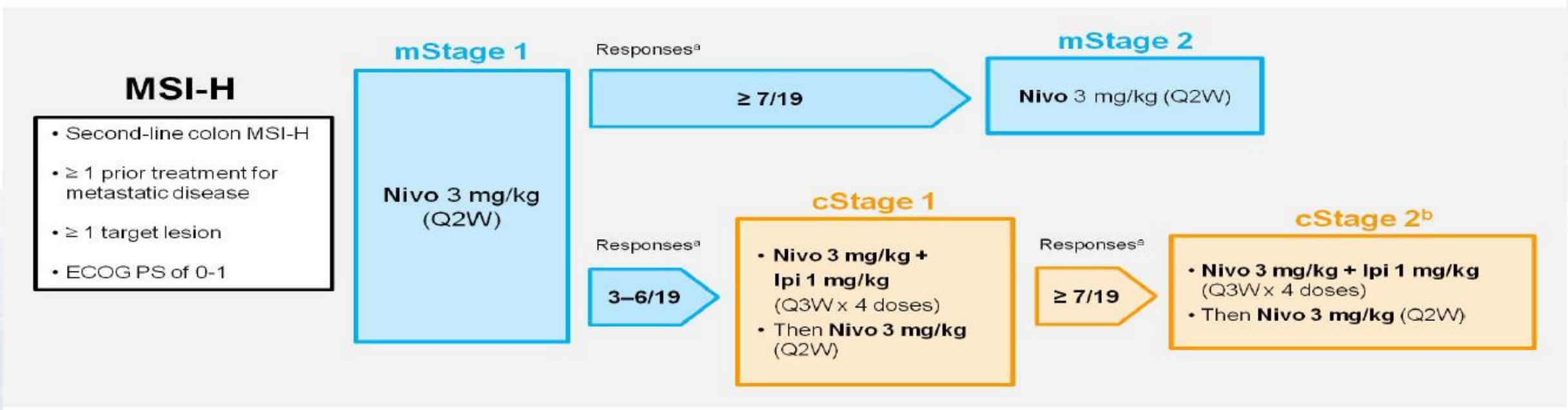
B: minimal activity

AB: Double ORR compared to A mono

SOC: TKI

Design of registration study in 3L line CRC MSI-H: Multi cohort, non randomized phase 2

Checkmate-142



Checkmate-142 results in CRC MSI-H

Opdivo® USPI

Table 33: Efficacy Results – CHECKMATE-142

	OPDIVO MSI-H/dMMR Cohort		OPDIVO + Ipilimumab MSI-H/dMMR Cohort	
	All Patients (n=74)	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=53)**	**All Patients (n=119)**	**Prior Treatment (Fluoropyrimidine, Oxaliplatin, and Irinotecan) (n=82)**
IRRC Overall Response Rate; n (%)	24 (32%)	15 (28%)	58 (49%)	38 (46%)
(95% CI)[a]	(22, 44)	(17, 42)	(39, 58)	(35, 58)
Complete Response (%)	2 (2.7%)	1 (1.9%)	5 (4.2%)	3 (3.7%)
Partial Response (%)	22 (30%)	14 (26%)	53 (45%)	35 (43%)
Duration of Response				
Proportion with ≥6 months response duration	63%	67%	83%	89%
Proportion with ≥12[b] months response duration	38%	40%	19%	21%

In the monotherapy cohort, 55% of the 20 patients with ongoing responses were followed for less than 12 months from the date of onset of response. In the combination cohort, 78% of the 51 patients with ongoing responses were followed for less than 12 months from the date of onset of response.

Safety of combination vs monotherapy agents

Opdivo® USPI Nivolumab 3mg/kg + ipilimumab 1mg/kg

Table 20: Adverse Reactions Occurring in ≥10% of Patients (CHECKMATE-142)

	OPDIVO MSI-H/dMMR Cohort (n=74)		OPDIVO plus Ipilimumab MSI-H/dMMR Cohort (n=119)	
	Percentage (%) of Patients			
Adverse Reaction	**All Grades**	**Grades 3-4**	**All Grades**	**Grades 3-4**
General Disorders and Administration Site Conditions				
Fatigue[a]	54	5	49	6
Pyrexia	24	0	36	0
Edema[b]	12	0	7	0
Gastrointestinal Disorders				
Diarrhea	43	2.7	45	3.4
Abdominal pain[c]	34	2.7	30	5
Nausea	34	1.4	26	0.8
Vomiting	28	4.1	20	1.7
Constipation	20	0	15	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain[d]	28	1.4	36	3.4
Arthralgia	19	0	14	0.8
Skin and Subcutaneous Tissue Disorders				
Pruritus	19	0	28	1.7
Rash[e]	23	1.4	25	4.2
Dry Skin	7	0	11	0
Infections and Infestations				
Upper respiratory tract infection[f]	20	0	9	0
Metabolism and Nutrition Disorders				
Decreased appetite	14	1.4	20	1.7
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	26	0	19	0.8
Dyspnea	8	1	13	1.7
Nervous System Disorders				
Headache	16	0	17	1.7
Dizziness	14	0	11	0
Endocrine Disorders				
Hyperglycemia	19	2.7	6	1
Hypothyroidism	5	0	14	0.8
Hyperthyroidism	4	0	12	0
Investigations				
Weight decreased	8	0	10	0
Psychiatric Disorders				
Insomnia	9	0	13	0.8

General considerations based on BMS experience (1)

- When were data generated and how reliable?
  - Early data may look significantly better or worse for both mono and combination
- Ethical considerations of mono vs combo data generation in mid/later stage trials
- Different population based on newly introduced biomarker – difficult to rely on historical data for monotherapy of components since often data missing

General considerations based on BMS experience (2)

- Global health authorities may not yet be prepared for master protocols
  - Administrative hurdles for clinical trial approval, e.g. in EU
- Multi-cohort non randomized studies not globally accepted by regulators
- What evidence is needed by which authority?
  - E.g. amount of monotherapy data required for which component?
- What endpoints can be used ORR/DOR sufficient to demonstrate contribution of each component?
- Important to understand existing clinical data/evidence of anti-PD-1
  - Demonstration of contribution of component must be part of clinical development strategy


THANK
YOU