CANCER IMMUNOTHERAPY

Genentech
A Member of the Roche Group

NCPF

Combination Immunotherapy Development

Immunotherapy Regimens

Daniel S. Chen MD PhD

VP, Global Head for Cancer Immunotherapy Development

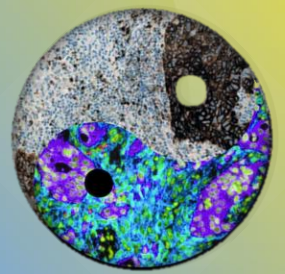
Product Development, Genentech/Roche

Kathie Winson

Global Regulatory Franchise Head, Lung

Product Development Regulatory, Genentech/Roche

July 16th, 2018



Combination Development Differs from Traditional Single-Agent Development

Challenges

Clinical Development

Regulatory

Established guidelines available in US & EU regarding NME combinations; translation to other novel combinations unclear

Clinical Trial designs

Defining optimal dose & schedule is critical for both safety and efficacy

Novel approaches and designs may be explored (e.g. adaptive design)

Biomarker Development

Increased complexity with multiple biomarkers

Operational Execution

Collaboration in reporting

Safety reporting, IB, and many other aspects need to be agreed on with multiple novel molecules

Sponsor Decision-Making

Complexity for combining molecules internally and externally (with partner involved)

Execution

Efficient execution of multiple combination studies in parallel with the right data collection to support decision-making

Key Questions for Development of CIT Combinations

What are the unique regulatory challenges for PD-1/PD-L1 combination therapies?

How can the impact of a second drug be assessed when combined with an existing effective drug; is there a threshold that the combination needs to meet?

How do the information needs and decision-making differ from strategies for developing novel/novel combinations?

Exploring CIT Combinations

What are the unique regulatory challenges for PD-1/PD-L1 combination therapies?

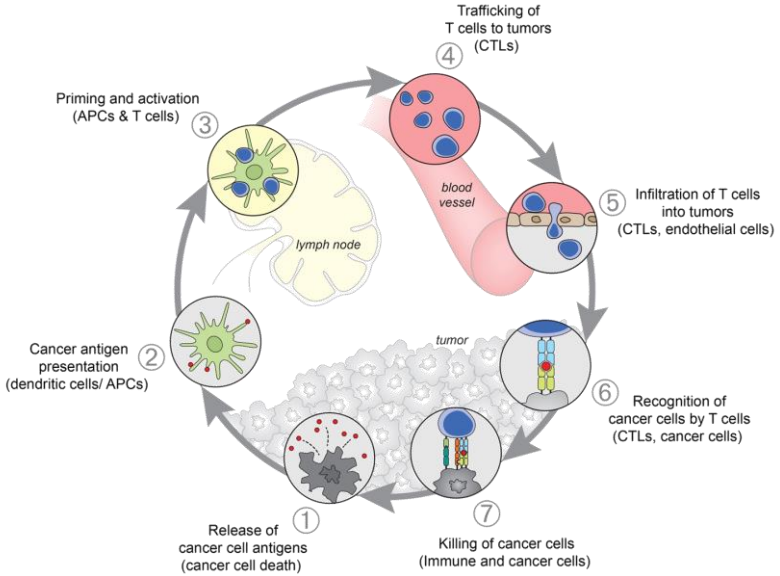
Broadly Active

Complex Biology

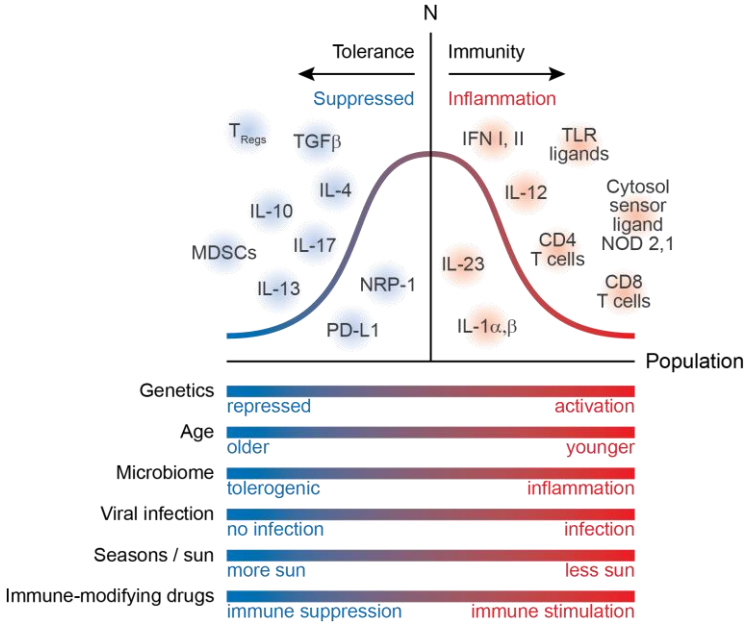
Massive amount of orthogonal in pathway data

A complex set of tumor, host and environmental factors govern strength and timing of anti-cancer immune responses

Immune Set Point: $\int (F_{stim}) - \int (F_{inhib}) \geq 1/\Sigma_{n=1,y} (TCR_{affinity} \times frequency)$



Chen and Mellman. *Immunity* 2013



Chen and Mellman. *Nature 2017*

Combination Therapy Approaches

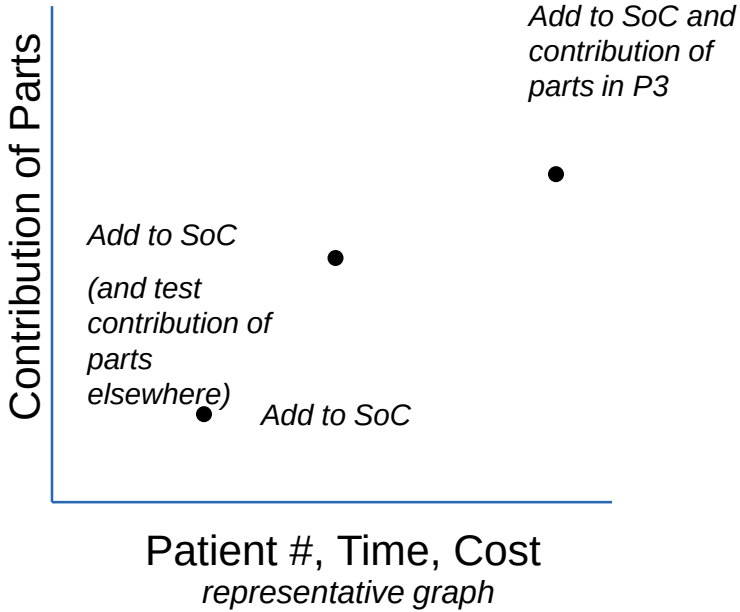
- Combination with **SoC**
  - Chemotherapy in 1L NSCLC
  - Chemotherapy + bevacizumab in 1L NSCLC
- Combination with an **established in-class therapeutic**
  - bevacizumab in 1L RCC
  - bevacizumab in 1L HCC
- Combination with **established agent but in an indication where it is not established (investigational)**
  - bevacizumab in melanoma
- Combination with **new molecular entity** (new indication)
  - aCEA-CD3 bispecific in CRC

Considerations for combinations with PDL1/PD1

- PDL1/PD1 inhibitors are broadly active
- Efficacy can be measured as
  - ORR only
  - ORR, PFS, OS
  - ORR, OS only
  - PFS, OS only
  - PFS only
  - OS only
- Indication (1L vs 2L vs adjuvant)
- Subsets (eg PDL1+, TMB high, MSI high)
- Strength of SoC (eg R-CHOP in 1L DLBCL)
- Complex regimen (3 or more biologic regimen)

Clinical Study Design Options for Combination Therapies

- Add to SoC
  - Chemotherapy+bevacizumab±atezolizumab in 1L NSCLC
- Add to SoC and test contribution of parts
  - Chemotherapy±bevacizumab±atezolizumab in 1L NSCLC
  - Sunitinib vs atezolizumab±bevacizumab in 1L RCC
- Replace SoC with regimen
  - Sunitinib vs Nivolumab+ipilimumab



representative graph

Case Study: IMPower150

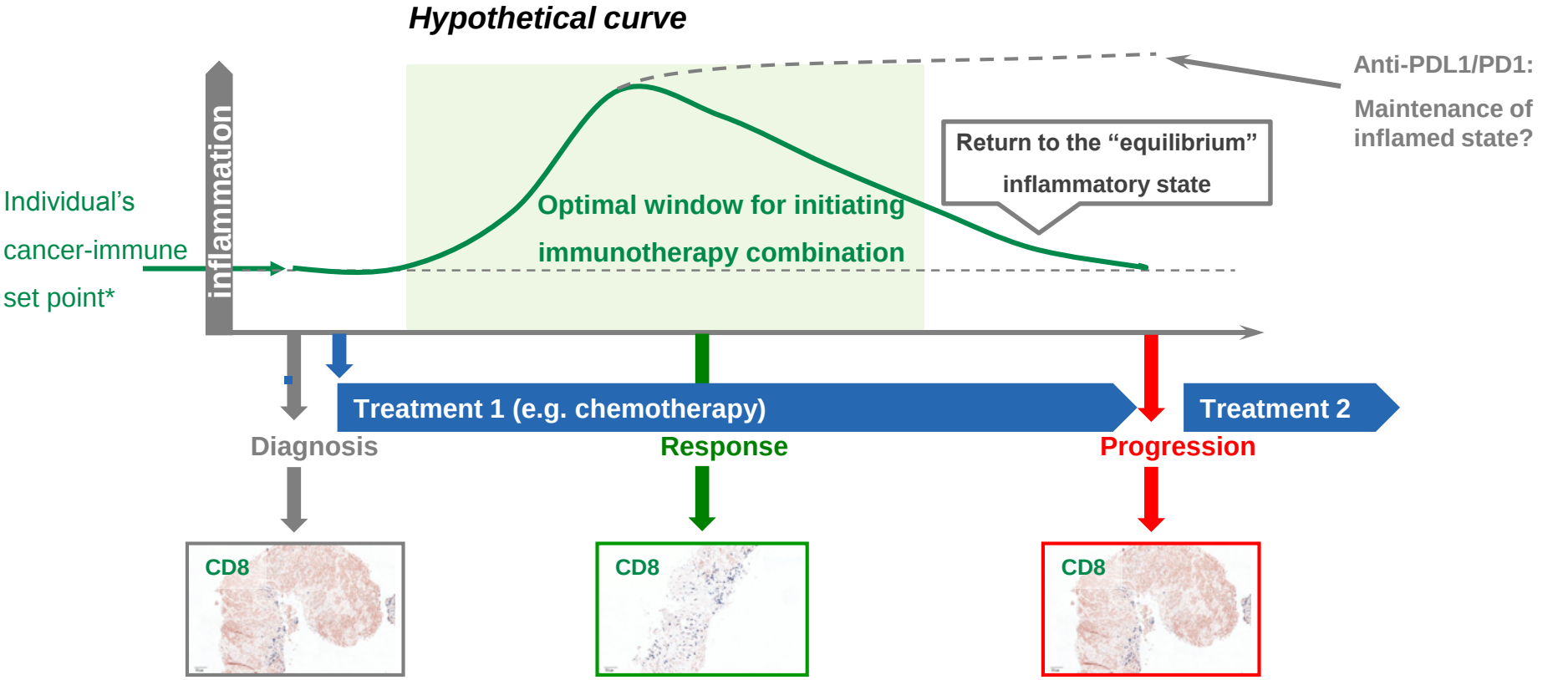
Atezolizumab + bevacizumab + carboplatin + paclitaxel

Addition of atezo to a SoC

Chemo+2 biologics

First 1L NSCLC combo cancer immunotherapy P3 readout

Combination of immunotherapy with chemotherapy

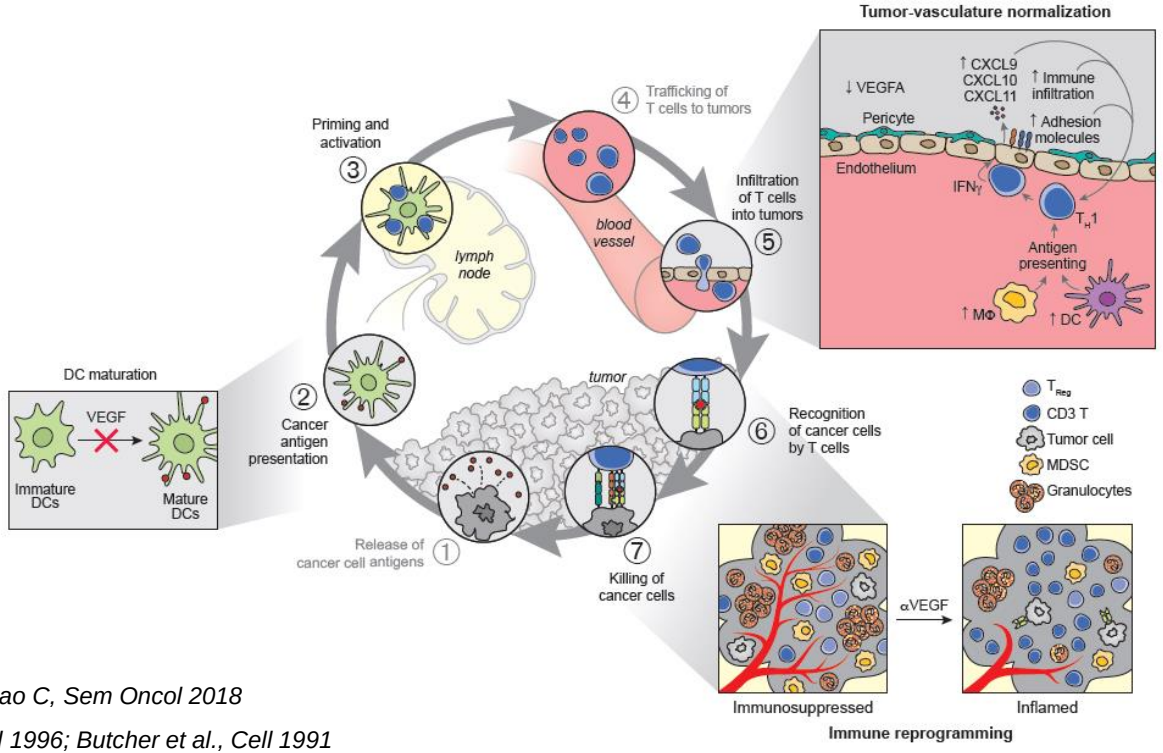


CD8 staining images are illustrative

**Chen and Mellman Nature 2017*

CANCER IMMUNOTHERAPY

VEGF inhibition As Immunotherapy



Hegde PS, Wallin J, Mancao C, Sem Oncol 2018

Gabrilovich et al., Nat Med 1996; Butcher et al., Cell 1991

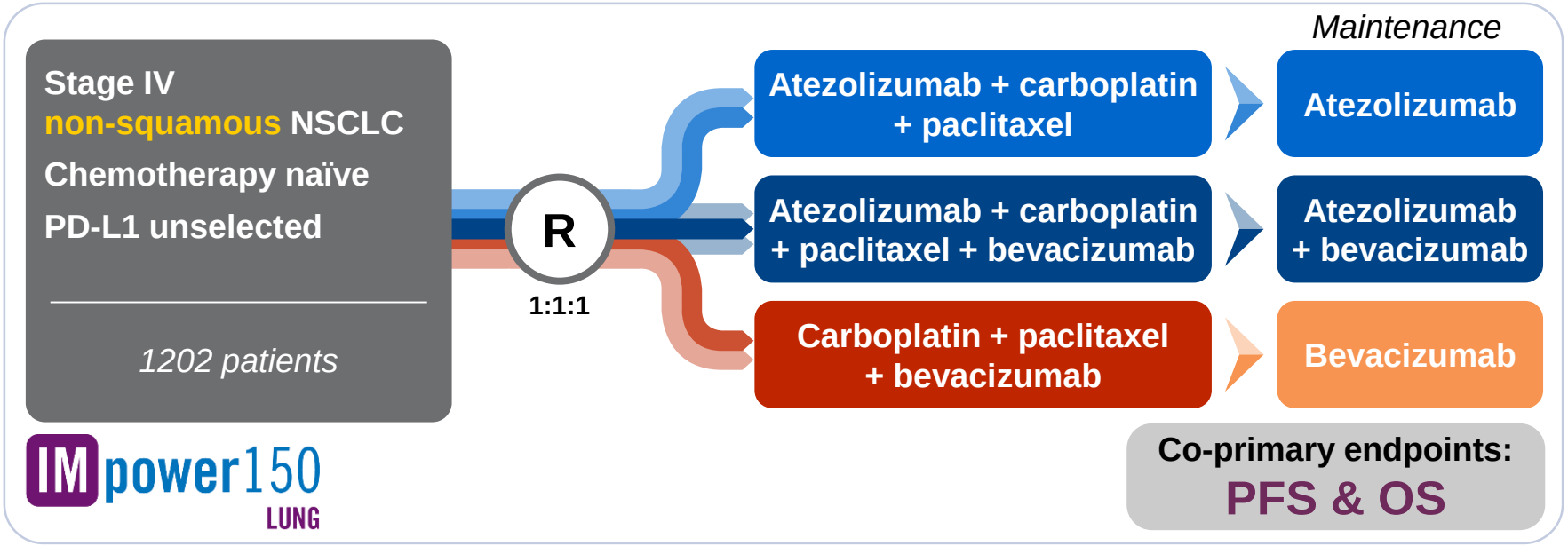
Springer et al., Cell 1994; Motz et al., Nat Med 2014

Hodi et al., Canc. Immunol Res 2014; Kim and Chen, Annals of Onc, 2016

CANCER IMMUNOTHERAPY

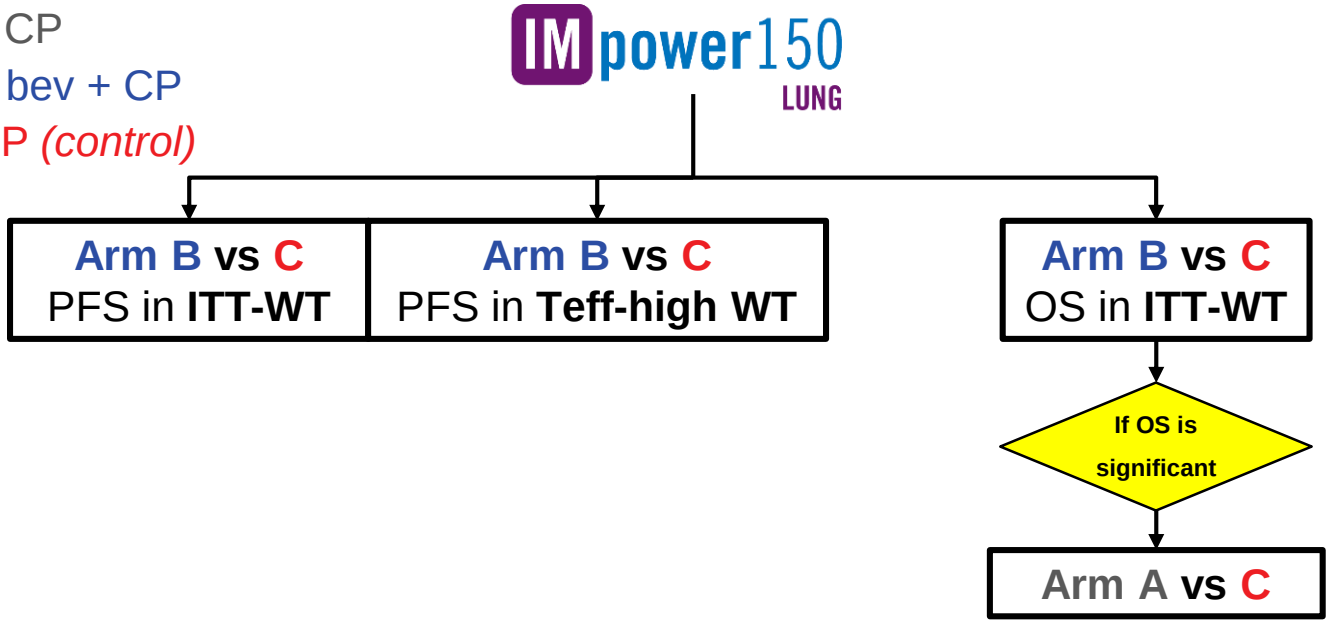
IMpower150 is an ongoing phase III study of atezolizumab plus chemotherapy and bevacizumab

Adding chemotherapy with or without anti-VEGF therapy to PD-L1 inhibition may further enhance the immune response



Statistical Testing Plan for the Co-primary Endpoints in IMpower150

Arm A: atezo + CP
Arm B: atezo + bev + CP
Arm C: bev + CP *(control)*



Socinski et. al. ASCO 2018

Socinski et. al. NEJM 2018

This presentation focuses on the interim OS data for IMpower150 in all study arms in the primary study population and in key patient subgroups

Atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.

IMpower150 1L NSCLC NSQ

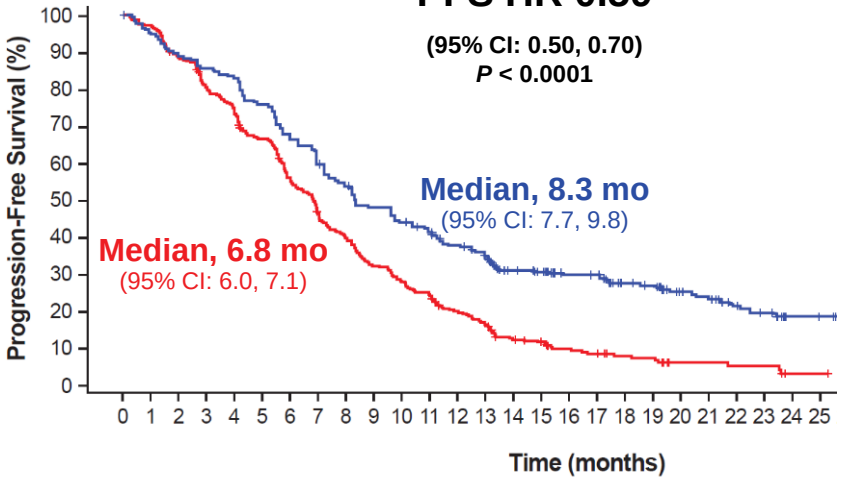
Updated PFS ITT-WT

Median follow-up: ~20 mo

Atezo+Bev+CP
Bev+CP

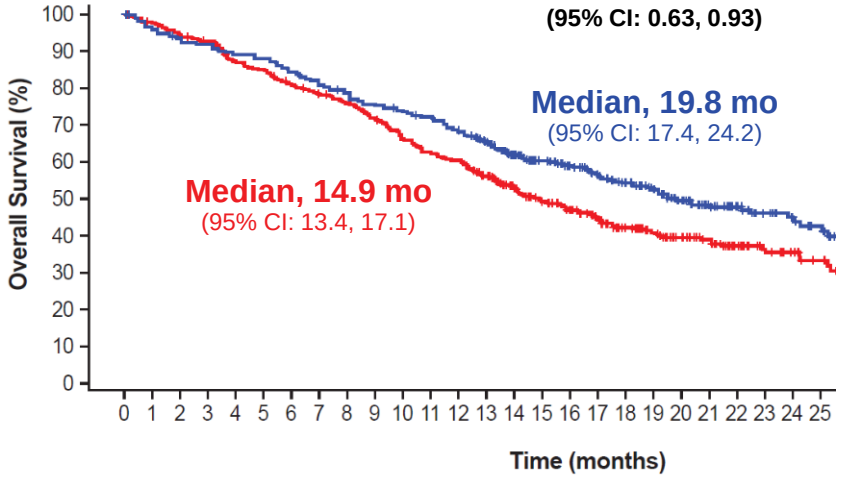
PFS HR 0.59

(95% CI: 0.50, 0.70)
***P* < 0.0001**



Updated OS ITT

OS HR 0.76
(95% CI: 0.63, 0.93)

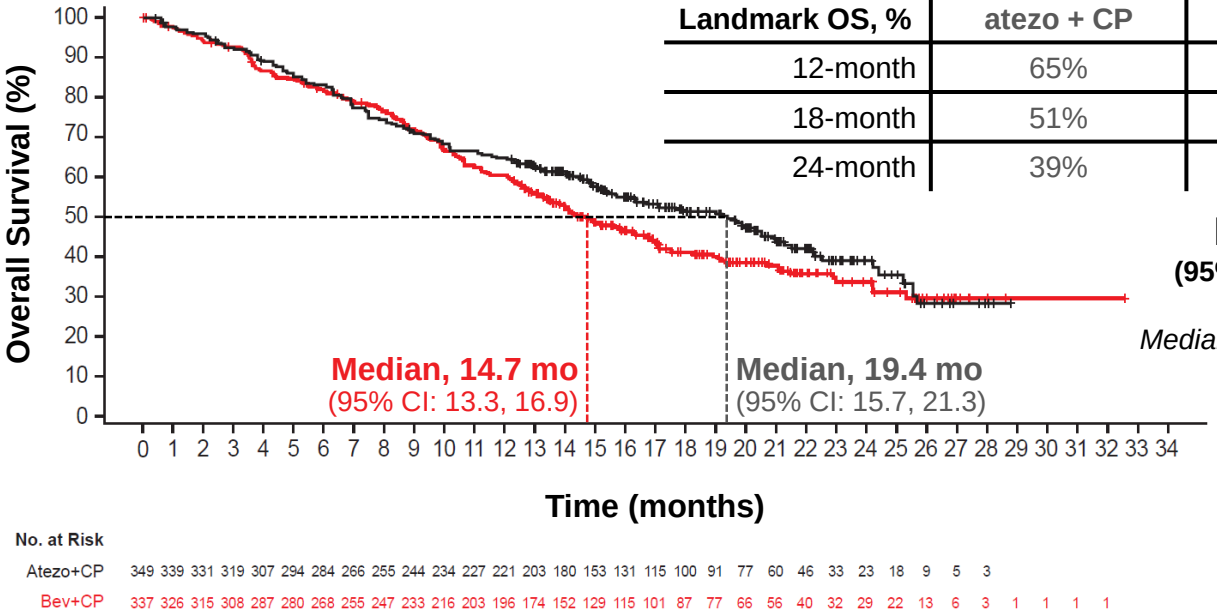


Socinski et. al. ASCO 2018

Socinski et. al. NEJM 2018

CANCER IMMUNOTHERAPY

OS in the ITT-WT (Arm A vs Arm C)



Landmark OS, %	Arm A: atezo + CP	Arm C: bev + CP
12-month	65%	61%
18-month	51%	41%
24-month	39%	34%

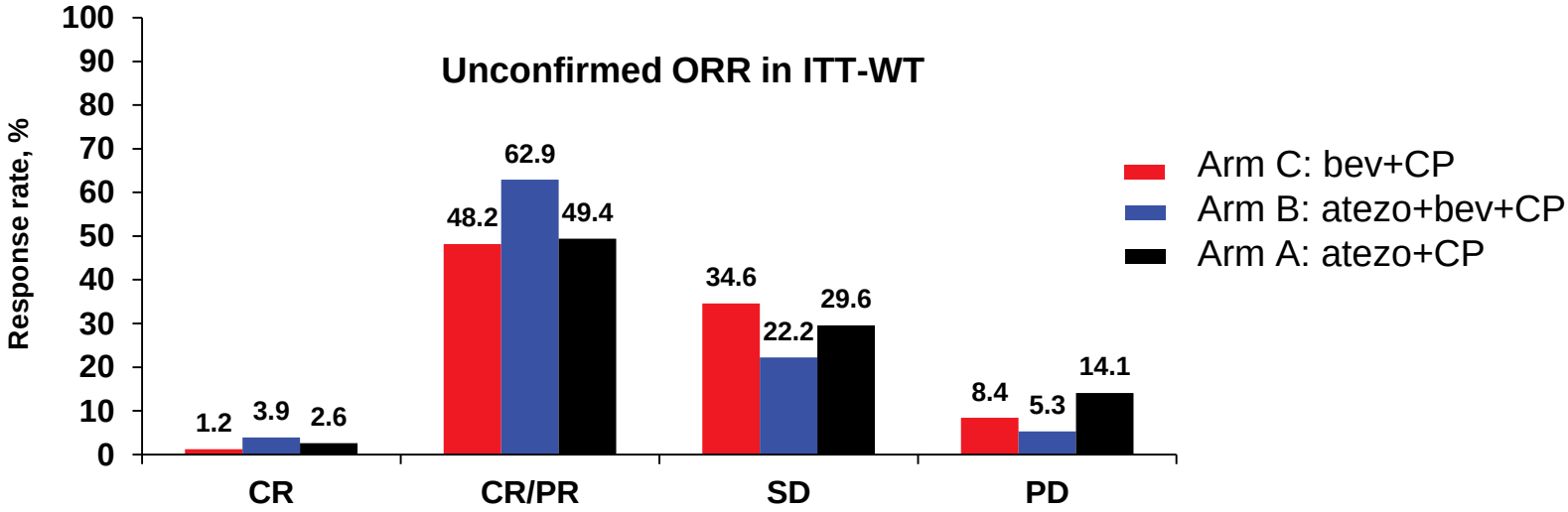
HR[a], 0.88
(95% CI: 0.72, 1.08)
***P* = 0.2041**
Median follow-up: ~20 mo

- A trend toward OS benefit was observed with atezolizumab + chemotherapy vs bevacizumab + chemotherapy, but the efficacy boundary has not yet been crossed and will be tested again at the time of the final analysis

[a] Stratified HR.

Data cutoff: January 22, 2018

IMpower150: INV-assessed ORR in ITT-WT



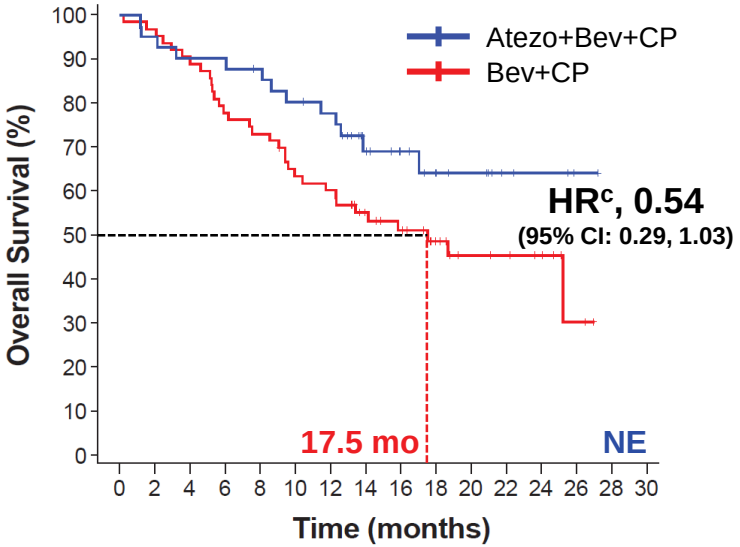
Confirmed responses	Bev+CP (C)	Atezo+Bev+CP (B)	Atezo+CP (A)
ITT-WT	n=134	n=197	n=146
ORR (%)	40.4	55.3	41.9
CR rate (%)	0.6	2.5	2.0
SD rate (%)	40.1	28.9	36.2
Median DOR (95% CI), mo	6.4 (5.7, 7)	11.5 (8.9, 16.2)	9.2 (7.4, 13.9)
No. of ongoing responses, n (%)	18 (13.4%)	77 (39.1%)	53 (36.3%)

CCOD: 22 January 2018

Tecentriq Lung Team

Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of *EGFR/ALK*+ Patients

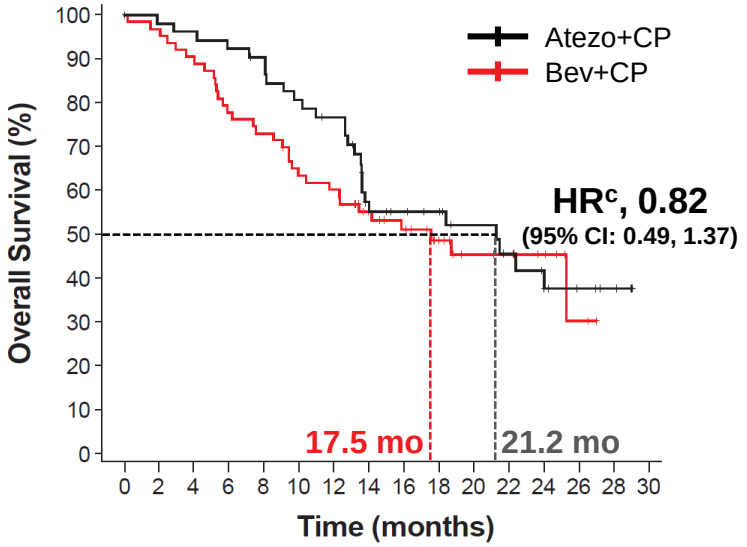
Arm B vs *Arm C*



No. at Risk

Atezo+Bev+CP	41	39	37	37	35	32	30	20	15	11	9	5	4	2
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

Arm A vs *Arm C*



No. at Risk

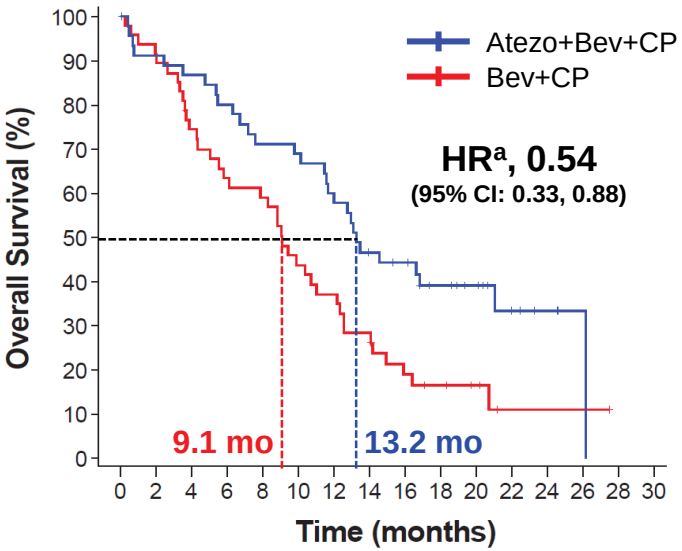
Atezo+CP	53	51	50	48	46	41	37	24	22	20	16	13	8	6	4
Bev+CP	63	61	57	49	46	39	37	28	24	17	12	11	7	2

Socinski et. al. ASCO 2018
Socinski et. al. NEJM 2018

CANCER IMMUNOTHERAPY

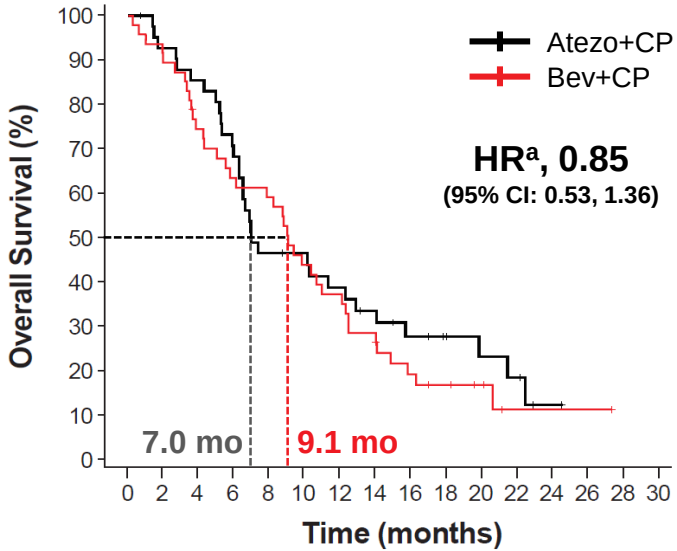
Addition of Bevacizumab to Atezolizumab and Chemotherapy Prolongs Survival of Patients With Liver Metastases in the ITT-WT

Arm B vs *Arm C*



No. at Risk													
Atezo+Bev+CP	47	41	39	36	32	31	26	20	18	13	10	5	3	1
Bev+CP	47	42	34	29	27	20	17	13	8	6	4	1	1	1

Arm A vs *Arm C*



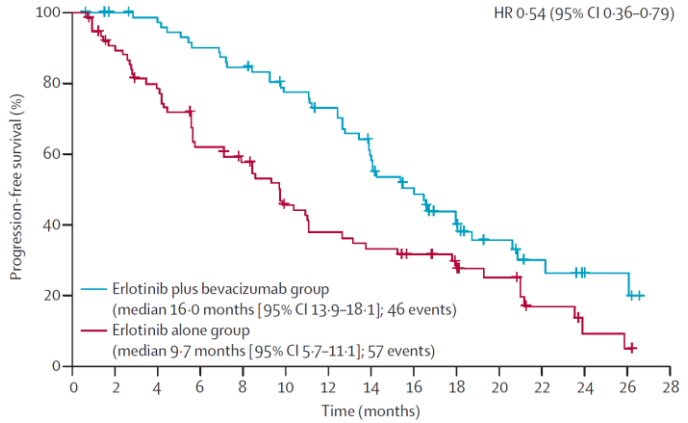
No. at Risk													
Atezo+CP	42	38	35	28	19	18	15	12	9	7	5	4	1
Bev+CP	47	42	34	29	27	20	17	13	8	6	4	1	1	1

Socinski et. al. ASCO 2018
Socinski et. al. NEJM 2018

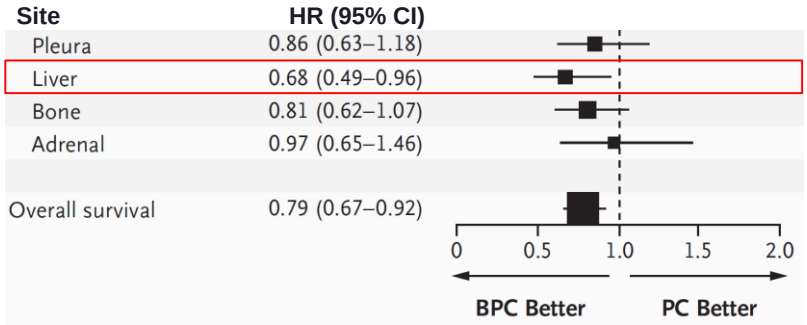
CANCER IMMUNOTHERAPY

Historical data for the benefit of bevacizumab in key clinical subgroups

JO25567: PFS benefit with bevacizumab + erlotinib vs erlotinib alone in patients with *EGFR* Mut+ NSCLC[1]

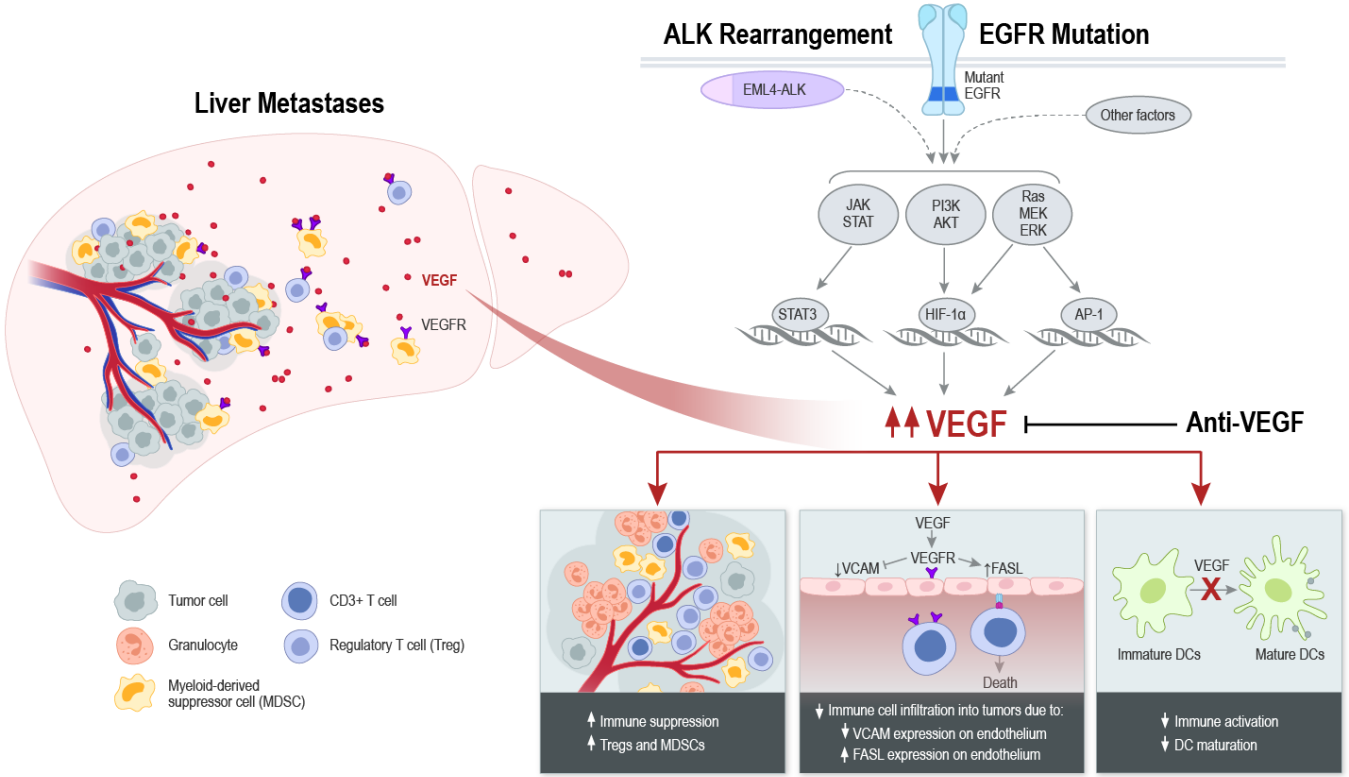


E4599: OS benefit with bevacizumab + carbo + pac vs carbo + pac in patients with liver metastases[2]



1. Seto, et al. Lancet Oncol 2014; 2. Sandler, et al. N Engl J Med 2006

VEGF suppresses anti-cancer immunity



Chen and Hurwitz, 2018 publication pending

Safety

Incidence, n (%)	Arm A: atezo + CP (n = 400)		Arm B: atezo + bev + CP (n = 393)		Arm C (*control*): bev + CP (n = 394)	
Median doses received (range), n						
Atezolizumab	10 (1-43)		12 (1-44)		NA	
Bevacizumab	NA		10 (1-44)		8 (1-38)	
Treatment-related AE[a]	377 (94%)		370 (94%)		377 (96%)	
Grade 3-4	172 (43%)		223 (57%)		191 (49%)	
Grade 5[b]	4 (1%)		11 (3%)		9 (2%)	
Serious AE	157 (39%)		174 (44%)		135 (34%)	
AE leading to withdrawal from any treatment	53 (13%)		133 (34%)		98 (25%)	
Immune-related AEs[c] in > 5 patients in any arm	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**
Rash	119 (30%)	14 (4%)	117 (30%)	9 (2%)	53 (14%)	2 (1%)
Hepatitis[d]	42 (11%)	12 (3%)	54 (14%)	20 (5%)	29 (7%)	3 (1%)
Laboratory abnormalities	36 (9%)	10 (3%)	48 (12%)	18 (5%)	29 (7%)	3 (1%)
Hypothyroidism	34 (9%)	1 (<1%)	56 (14%)	1 (<1%)	18 (5%)	0
Pneumonitis[d]	23 (6%)	8 (2%)	13 (3%)	6 (2%)	5 (1%)	2 (1%)
Hyperthyroidism	11 (3%)	0	16 (4%)	1 (<1%)	5 (1%)	0
Colitis	3 (1%)	2 (1%)	11 (3%)	7 (2%)	2 (1%)	2 (1%)

The safety profiles of ABCP and ACP were similar to A, B and C+P individually; no new safety signals were identified with the combinations

[a] Related to any study treatment. [b] Including fatal hemorrhagic AEs: Arm A: 2; Arm B: 6; Arm C: 3. [c] Immune-related AEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality. [d] In Arm A, 1 patient had grade 5 acute hepatitis and 1 patient had grade 5 interstitial lung disease. Data cutoff: January 22, 2018

Challenges with CIT Combination Development in the Future

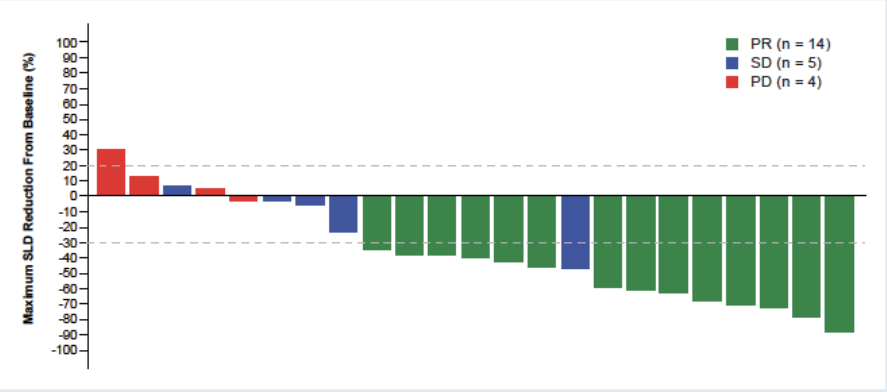
How do the information needs and decision-making differ from strategies for developing novel/novel combinations?

combination of novel regimen in an indication

combination including a completely novel agent

1L HCC Phase Ib of Tecentriq + Avastin:
known regimen, known pathways in disease, unapproved in indication

Figure 2. Investigator-Assessed Response to Atezolizumab + Bevacizumab Therapy

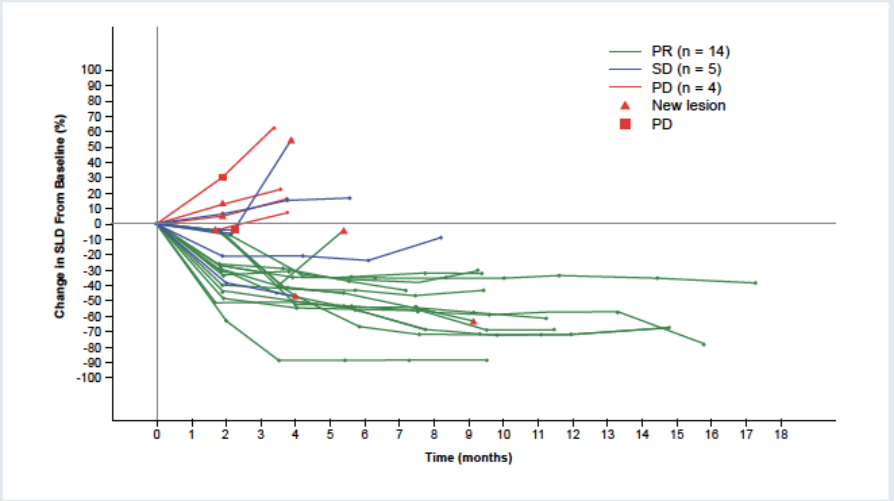


PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

Table 4. Best Overall Response (BOR)

BOR	INV-Assessed per RECIST v1.1 (n = 23)	IRF-Assessed per RECIST v1.1 (n = 23)
ORR, n (%)	**14 (61%)**	**15 (65%)**
CR	0	1 (4%)
PR	14 (61%)	14 (61%)
SD	5 (22%)	7 (30%)
PD	4 (17%)	1 (4%)

Figure 3. Investigator-Assessed Change in Tumor Burden Over Time and Response Duration per RECIST v1.1



PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

Stein et al. ASCO 2018

CANCER IMMUNOTHERAPY

CEA-CD3 T cell engager + atezolizumab in MSS mCRC: novel therapeutic and PDL1 inhibitor atezolizumab

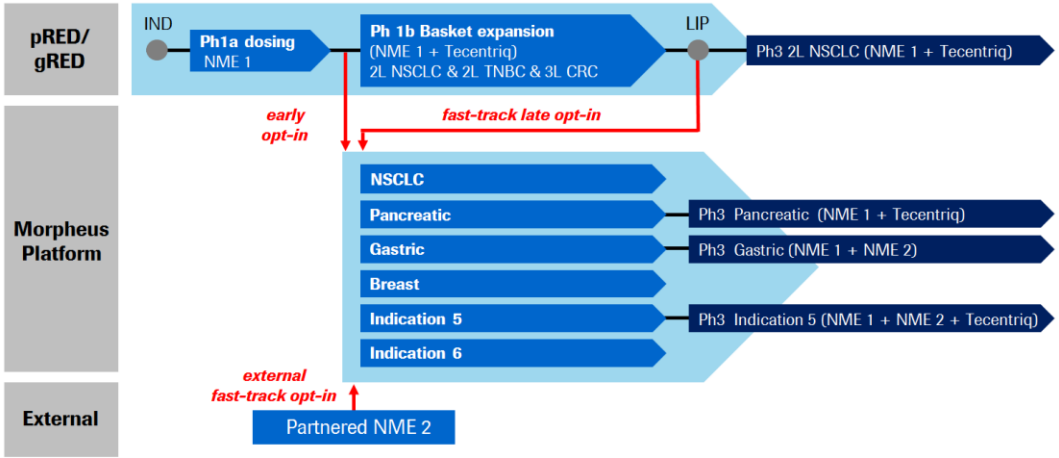
Confirmed best overall response (RECIST v1.1), n (%)	Study 1: CEA-TCB monotherapy	Study 2: CEA-TCB + atezolizumab	
	n = 31, 60-600 mg MSS, n = 28 (90%)[b]	n = 25, 5-160 mg MSS, n = 23 (92%)[c]	n = 11, 80 or 160 mg[a] MSS, n = 11 (100%)
Partial response	2 (6%)	3 (12%)[d]	2 (18%)[d]
Stable disease	12 (39%)	10 (40%)	7 (64%)
Disease control	14 (45%)	13 (52%)	9 (82%)
Progressive disease	16 (52%)	12 (48%)	2 (18%)
Non-evaluable	1 (3%)	-	-

Data reported by investigators, cutoff: March 3, 2017. [a] Sub-group of the column to the left (n = 25 CEA-TCB + atezolizumab patients, treated at doses 5-160 mg).
[b] MMR status unknown for 3 patients. [c] Two patients were MSI-high. [d] One patient had the confirmatory CT scan on March 23, 2017.

Tabernero et. al. ASCO 2017

Rapidly prioritize and Accelerate Transformative Combination Therapies

MORPHEUS
CIT COMBINATIONS PLATFORM



Multi-indication	Multi-basket	Randomized	Longitudinal	Adaptable
Indication specific umbrella protocol with SOC control arm	Biomarker defined subgroups for personalized healthcare	Faster and more confident decisions; potential for accelerated approval	At disease progression patients can reenter other combinations	Fast-track opt-in for external and internal late-stage NMEs

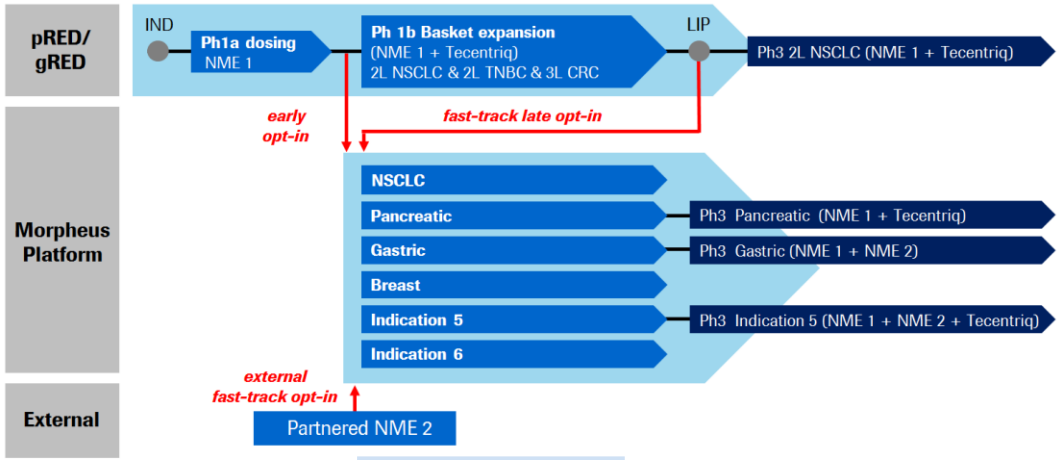
2017 launch in 4 indications including 11 molecules and 22 first-in-disease combinations

CIT=cancer immunotherapy; IND=new investigational drug application; NME=new molecular entity; LIP=late-stage investment point; SOC=standard of care

Ed Cha, Bill Grossman, et al.

Chen DS, FDA-AACR 2017

Rapid and reliable estimation of benefit over SOC



Real World Data

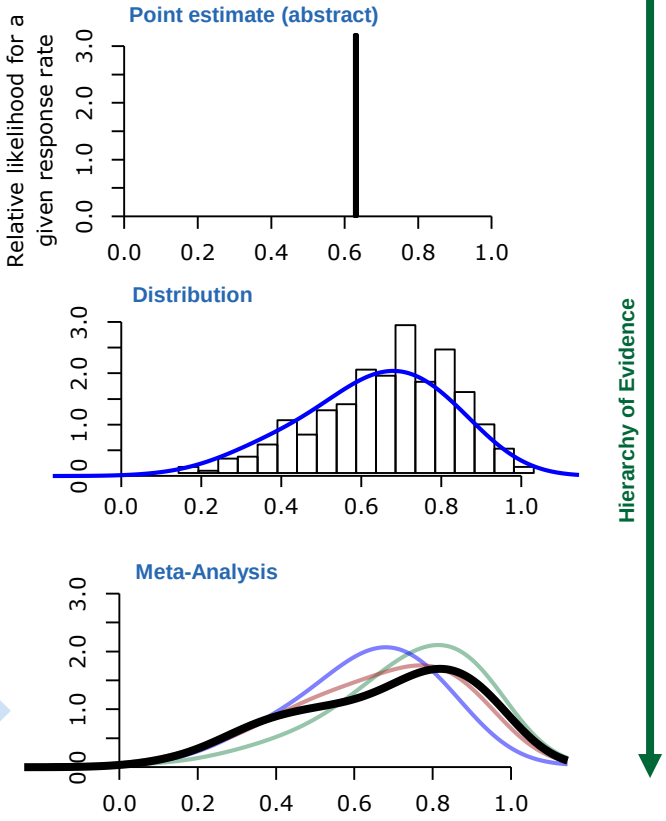
- *Create a **synthetic control arm** based on RWD using similar inclusion/exclusion criteria as RCT, with patients treated by the SOC*
- *Outcomes from RWD cohort can complement or replace those from the CT SOC arm*

Contempory randomized Control Arm

+*individual* patient characteristics

+*individua*l patient biomarker data

+Real world data* linked to NGS



Chen DS, FDA AACR 2017

Discussion

- There are a multitude of scenarios in which CIT drugs can be developed in combination with other products (SOC, investigational drug[s], novel combinations)
- Individual contribution of each component of the combination could be leveraged from historical studies, demonstrated in Phase Ib/II, or demonstrated in a multi-arm randomized Phase III study.

- ***Outstanding Questions:***
  - Can real world data be leveraged to demonstrate individual contribution of a component or SOC?
  - Given level of existing data on PD-1/PD-L1 drugs, what is the level of evidence needed to establish B/R of new CIT in NME + CIT combinations?
  - What are additional considerations when developing novel-novel CIT combinations?

Acknowledgements

Gregg Fine
Alan Sandler
Amreen Husain
Marjorie Green
Daniel Waterkamp
Marcella Fasso
Carol O'Hear
Marcus Ballinger
Roel Funke
Hila Barak
Jing Yi
Ed Cha
Aney Vasisht
Cathi Ahearn
Robin Taylor
Priti Hegde
Marcin Kowanetz
Sanjeev Mariathasan
Luciana Molinero
Meghna Das Thakur
Mahrukh Huseni
Sami Mahrus

Mahesh Yadav
Dustin Smith
Richard Bourgon
Wei Zou
Craig Cummings
Lukas Amler
Ira Mellman
Shannon Turley
Matthew Albert
Jane Grogan
Lelia Delamarre
Scott Holden
Stuart Lutzker
Friedrich Graf-Finkenstein
Jose Saro
Vaios Karanikas
Fabien Giere
Pablo Umana
William Pao
Weilan Ye
Alex Ritter
Wei Lin

Wayne Chu
Herb Hurwitz
Daniel Waterkamp
Domink Ruettinger
Christian Rommel
Christian Klein
Marina Bacac
Jerry Hsu
Mark Arundine
Geri Jermy
Mark Velligan
Hartmut Koeppen
Mika Derynck
Sandra Horning

CITC
Tecentriq Teams
gRED CIT Teams
pRED CIT Teams
PD Oncology LT
Disease Franchises & JOLT

Steve Hodi

Jedd Wolchok

Gordon Freeman

Josep Tabernero

Omid Hamid

Tom Powles

Naiyer Rizvi

Ignacio Melero

George Coukos

Scott Gettinger

Matthew Hellmann

Roy Herbst

Toni Ribas

Genentech/Roche investigators

Patients and their families