Cancer Immunotherapy in Practice: Designing Clinical Trials in Crowded Spaces

Brian I. Rini, MD
Vanderbilt Ingram Cancer Center
Nashville, TN

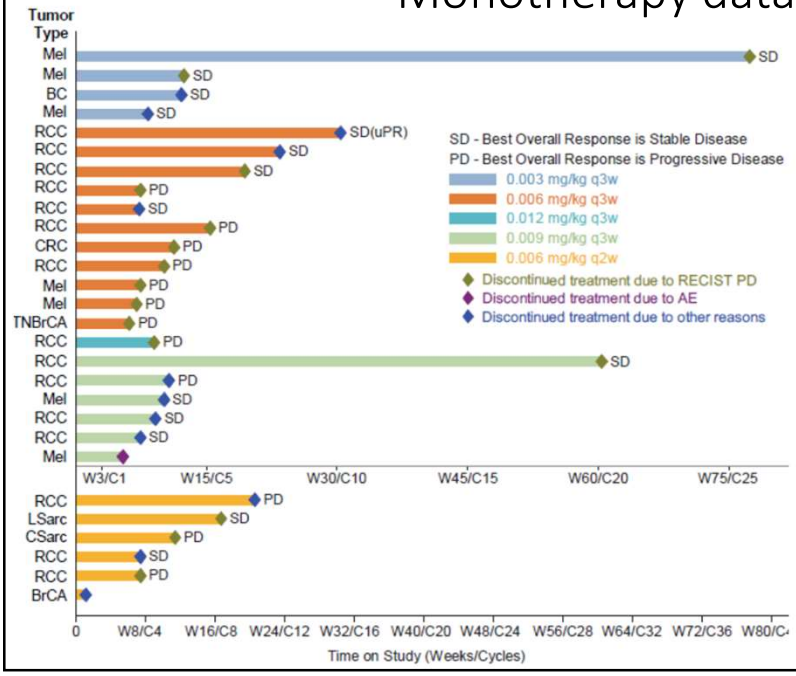
1

Outline

- Is monotherapy activity required and/or how to interpret single-arm combo data?
- What is the best way to study novel IO in disease where IO is standard initial therapy?
- Are biomarker-based approaches viable?

2

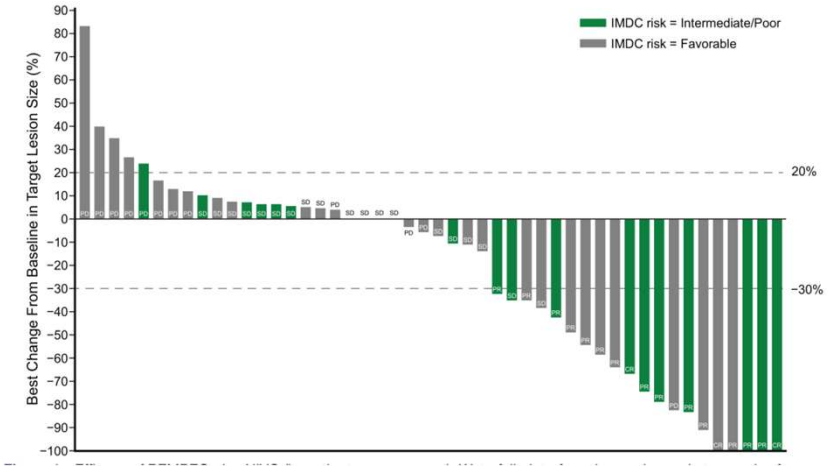
Monotherapy data



- Although no objective responses were observed using RECIST criteria, 9 of 26 patients (35%) experienced maximum tumor reductions ranging from 2% to 30%

3

Novel IO + Nivo in Front-line RCC (n=49)



- ORR 35% (6% CR); PFS 7.7 months
- HCRN nivo trial: ORR 34% (7% CR); PFS 8.3 months (data available later..)

4

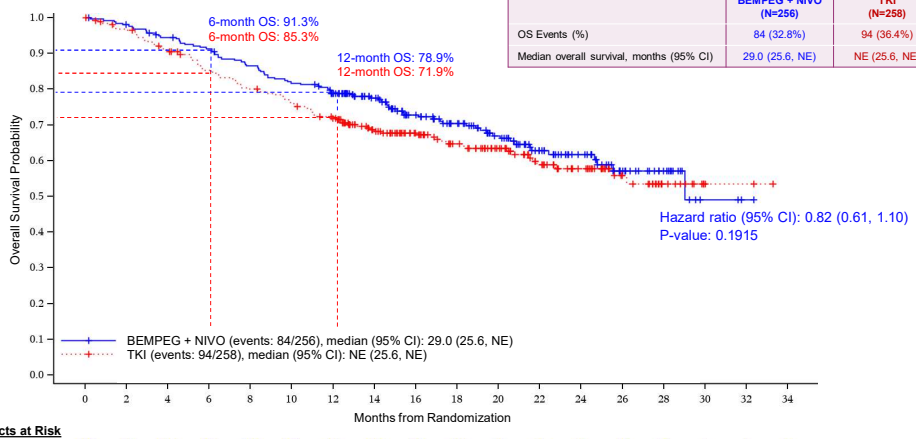
Would you move this combination to a phase 3 trial vs SOC?

- Yes
- No

5

OS in I/P-risk Population

Overall Survival	Intermediate/Poor-risk Population	
	BEMPEG + NIVO (N=256)	TKI (N=258)
OS Events (%)	84 (32.8%)	94 (36.4%)
Median overall survival, months (95% CI)	29.0 (25.6, NE)	NE (25.6, NE)



Number of Subjects at Risk

BEMPEG + NIVO	256	249	238	229	216	204	191	160	129	110	89	64	49	27	15	3	1	0
TKI	258	245	228	211	198	187	173	140	117	100	83	60	45	25	12	2	2	0

PARIS 2022 ESMO congress

Dr. Nizar M. Tannir

Data cutoff, 7 Jan 2022

Phase 1: Bentebibel et al. Cancer Discovery 2109; Phase 2: Tannir et al JITC 2022

6

Is IO-refractory a good/fair place to decipher activity of novel IO agents?

7

What if Ipi or Ipi/Nivo was first studied in IO-refractory RCC?

	HCRN[1]	OMNIVORE[2]	TITAN RCC[3]	FRACTION[4]	Salvage Ipi/Nivo[5]
N	35*	57	49	46	45
Prior TKI allowed	No	Yes	No	Yes	Yes
Timing	Nivo→Ipi (SD at 48 weeks or PD)	Nivo→Ipi (SD or PD at ≤ 6 months)	Nivo→Ipi (SD/PD at week 8 or 16)	Nivo+Ipi in IO-refractory	Nivo+Ipi in IO-refractory
Ipi doses	4	2	2-4	4	4
ORR	11%	4%	14%	17%	20%
PD	63%	40%	67%	30%	62%
CR	3%	0%	2%	0%	0%

Nivo+ipi combo untreated ccRCC ORR 39%, PD 19%, CR 12% (Checkmate 214)
* 87% PD-L1 negative

1. Atkins M et al. JCO 2022 2. McKay et al. JCO 2020 3. Grimm et al. ESMO 2022 4. Choueiri et al. JITC 2022 5. Gul et al. JCO 2020

8

Background and first-in-human phase 1 study of fianlimab + cemiplimab expansion cohorts in patients with advanced melanoma (NCT03005782)

- Combination anti–LAG-3 and anti–PD-1 treatment demonstrated higher median PFS and ORR compared with anti–PD-1 monotherapy in a Phase 2/3 clinical trial of patients with untreated advanced melanoma.[1]
  - RELATIVITY-047 study showed an ORR of 43.1%.[2]
- Fianlimab (REGN3767) and cemiplimab are both high-affinity, human, hinge-stabilised IgG4 mAbs derived using VelocImmune technology.
  - Fianlimab blocks LAG-3/MHC class II–driven T-cell inhibition.[3]
  - Cemiplimab blocks interactions of PD-1 with PD-L1 and PD-L2.[4]
- Initial expansion cohort of fianlimab + cemiplimab in patients with advanced melanoma gave an impressive efficacy of >60% ORR.[5]
- Here we present fianlimab + cemiplimab Phase 1 expansion cohort follow-up data in pts with advanced melanoma, and a confirmatory expansion cohort.

Expansion cohorts 6 and 15†
Anti–PD-1/PD-L1 naive

Expansion cohort 7
Anti–PD-1/PD-L1 experienced‡

Fianlimab 1600 mg + cemiplimab 350 mg IV every 3 weeks, for up to 51 weeks§

- **Tumour response assessed by investigators**
- **Response assessments every 6 or 9¶ weeks (RECIST 1.1) to determine ORR**

Primary endpoint
- ORR per RECIST 1.1 criteria

Secondary endpoints
- Safety, PK and ADA

Key inclusion criteria
- ≥18 years of age
- ECOG PS of 0 or 1
- At least one lesion measurable by RECIST 1.1
- Metastatic or inoperable locally advanced nonuveal melanoma

Key exclusion criteria
- Prior treatment with LAG-3–targeting biologic or small molecule
- Radiation therapy within 2 weeks prior to enrolment

†Prior systemic therapies, including prior adjuvant therapies, excluded for cohort 15.
‡Defined as patients who had progressed on prior anti–PD-1/PD-L1 treatment within 3 months of screening. Patients must have tolerated therapy for a ≥6 weeks and must not have discontinued treatment due to toxicity.
§With an option for an additional 51 weeks.
¶Response assessments were every 6 weeks for the first 24 weeks, then 9 weeks for the subsequent 27 weeks.

1. Tawbi HA et al. *N Engl J Med.* 2022;386:24–34. 2. Long GV et al. *J Clin Oncol.* 2022;40(suppl 36): 360385. 3. Burova E et al. *Mol Cancer.* 2019;18:2051–2062. 4. Burova E et al. *Mol Cancer.* 2017;16:861–870. 5. Hamid O et al. *J Clin Oncol.* 2021;39(suppl 15):9515.

ADA, antidrug antibody; ECOG PS, Eastern Cooperative Oncology Group performance score; IV, intravenous; LAG-3, lymphocyte activation gene-3; mAb, monoclonal antibody; MHC, major histocompatibility complex; ORR, objective response rate; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PD-L2, programmed cell death-ligand 2; PK, pharmacokinetics; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

PARIS 2022 ESMO congress

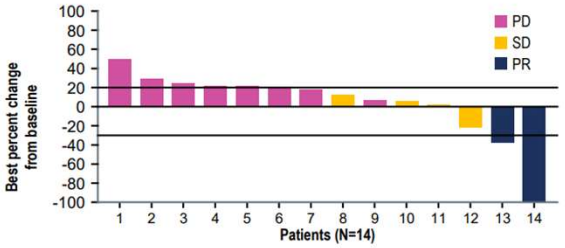
Dr Omid Hamid

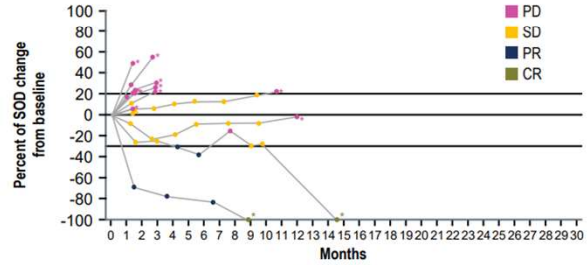
9

Clinical activity among anti–PD-(L)1–experienced patients (cohort 7)

% (n), unless otherwise stated	Total (N=15)
ORR, % (95% CI)	**13.3 (1.7–40.5)**
Complete response	0
Partial response	13.3 (2)
Stable disease	26.7 (4)
Progressive disease	53.3 (8)
NE	6.7 (1)
DCR	40.0 (6)
KM-estimated PFS, median (95% CI), months	1.5 (1.3–7.7)
DOR, median (95% CI), months	NR (3.4–NE)
ORR by LAG-3 expression, %	
<1%	NA
≥1%	18.2
ORR by PD-L1 expression, %	
<1%	18.2
≥1%	0

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; KM, Kaplan-Meier; LAG-3, lymphocyte activation gene-3; NA, not available; NE, not evaluable; NR, not reached; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; SOD, sum of diameters.





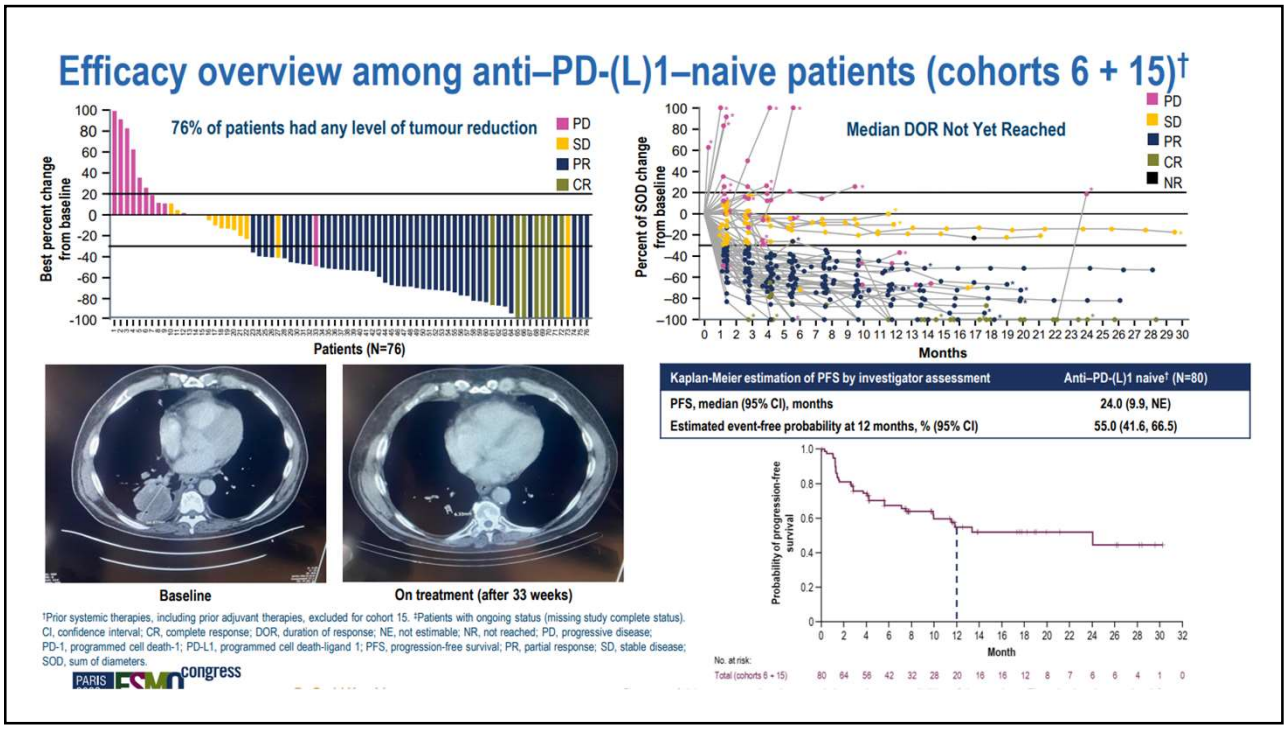
- Both patients that experienced CR had PD-L1 expression <1% and LAG-3 expression >1%.

PARIS 2022 ESMO congress

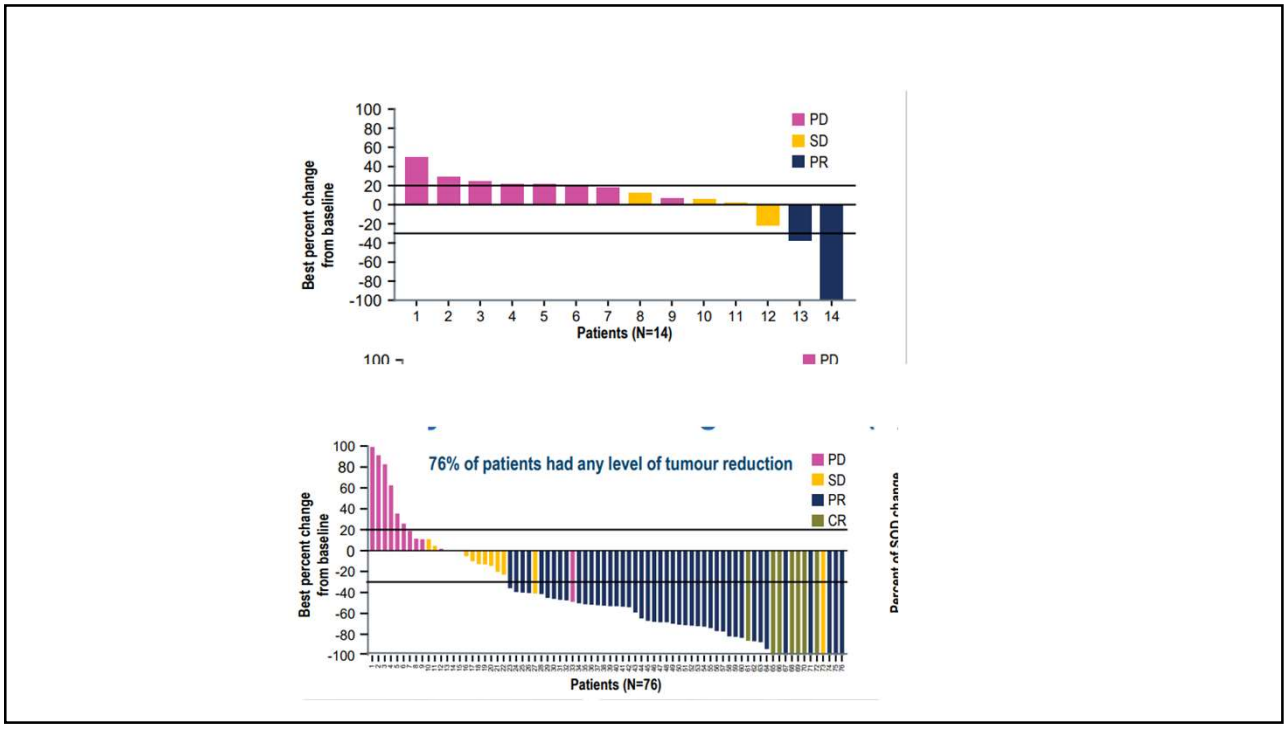
Dr Omid Hamid

Data cut-off date: 1 Jul 2022

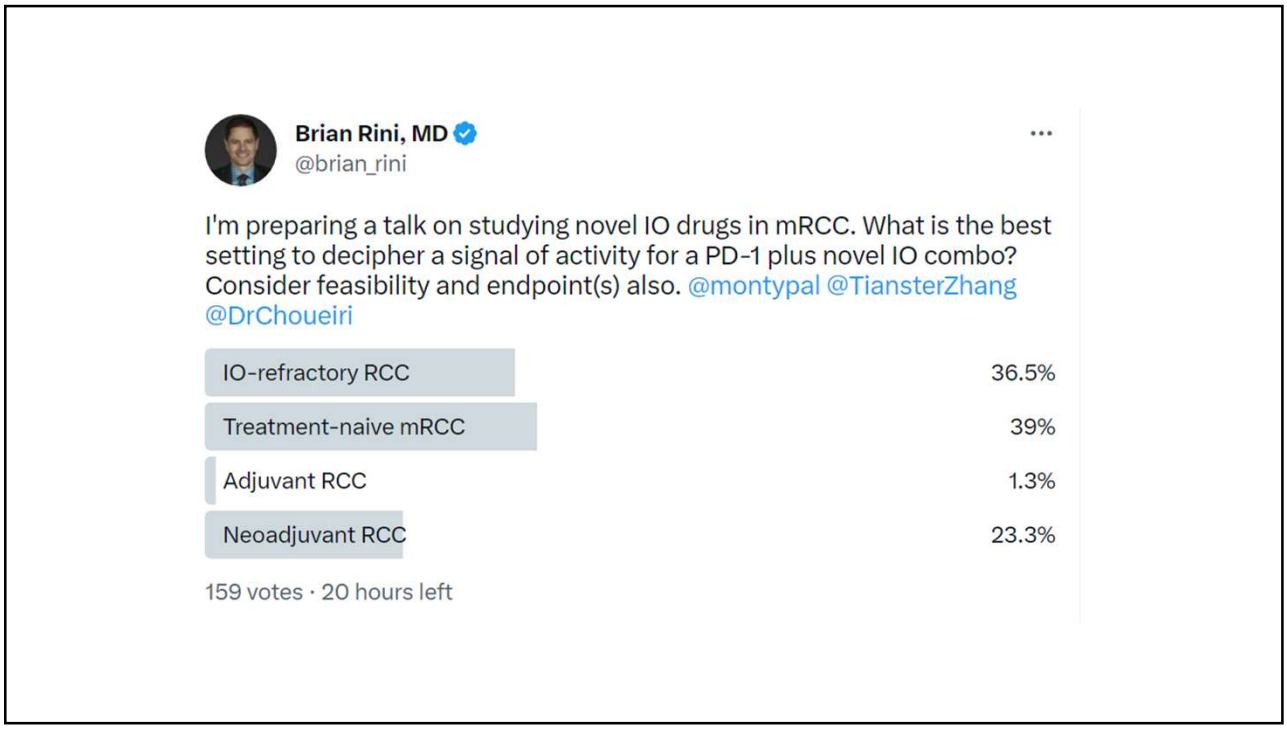
10


Efficacy overview among anti–PD-(L)1–naive patients (cohorts 6 + 15)†
76% of patients had any level of tumour reduction
PD
SD
PR
CR
Best percent change from baseline
Patients (N=76)
Median DOR Not Yet Reached
NR
Percent of SOD change from baseline
Months
Kaplan-Meier estimation of PFS by investigator assessment
Anti–PD-(L)1 naive† (N=80)
PFS, median (95% CI), months
24.0 (9.9, NE)
Estimated event-free probability at 12 months, % (95% CI)
55.0 (41.6, 66.5)
Probability of progression-free survival
Month
No. at risk:
Total (cohorts 6 + 15)
80 64 56 42 32 28 20 16 16 12 8 7 6 6 4 1 0
Baseline
On treatment (after 33 weeks)
†Prior systemic therapies, including prior adjuvant therapies, excluded for cohort 15. ‡Patients with ongoing status (missing study complete status).
CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; NR, not reached; PD, progressive disease;
PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease;
SOD, sum of diameters.
PARIS ESMO congress

11


PD
SD
PR
Best percent change from baseline
Patients (N=14)
76% of patients had any level of tumour reduction
CR
Patients (N=76)

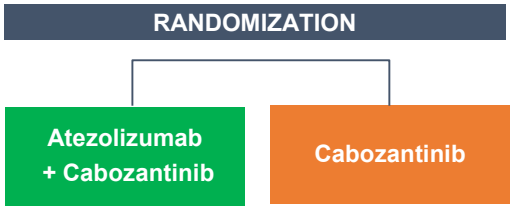
12



13

CONTACT-03 (NCT04338269)
mRCC 2/3L (clear cell, papillary, unclassified)
VEGFRTKI ± PD-L1 inhibition

Phase 3 (N = 500)
Primary endpoint: PFS, OS



14

Exelixis Provides Update on Phase 3 CONTACT-03 Trial Evaluating Cabozantinib in Combination with Atezolizumab in Patients with Previously Treated Advanced Kidney Cancer

March 2, 2023

ALAMEDA, Calif.--(BUSINESS WIRE)--Mar. 2, 2023-- Exelixis, Inc. (Nasdaq: EXEL) today announced that the phase 3 CONTACT-03 study did not meet its primary endpoint of progression-free survival (PFS). CONTACT-03 evaluated cabozantinib in combination with atezolizumab versus cabozantinib alone in patients with locally advanced or metastatic clear cell or non-clear cell (papillary or unclassified only) renal cell carcinoma (RCC) who progressed during or after immune checkpoint inhibitor therapy (either combination or monotherapy).

The safety profile of the combination of cabozantinib and atezolizumab observed in the trial was consistent with the known safety profiles for each single agent, and no new safety signals were identified with the combination.

Detailed findings will be presented at an upcoming medical meeting.

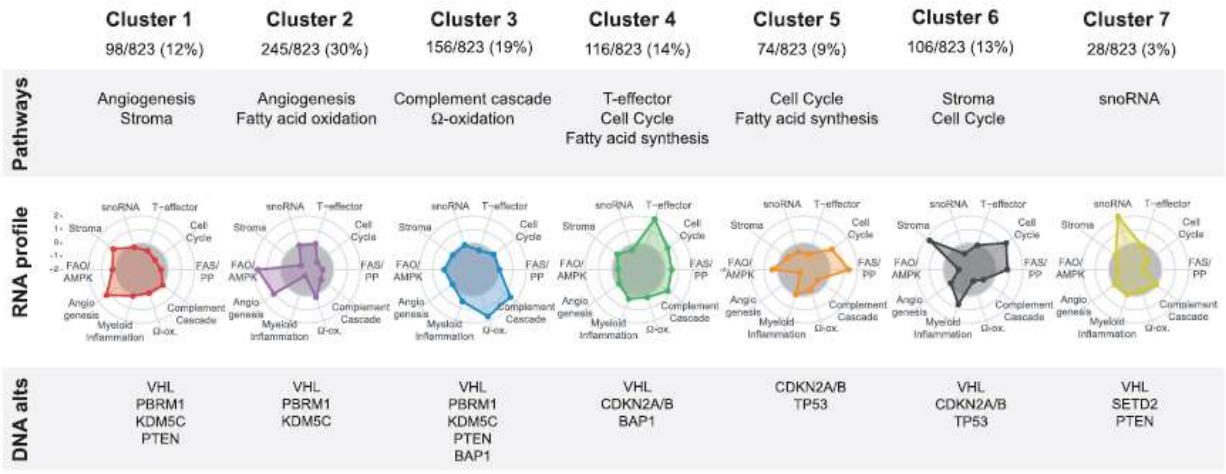
- The data suggests that patients maybe initially hard-wired as IO responders or non-responders, at least to PD-X and CTLA-4-based approaches.
- Whether this will apply to PD-1 inhibitors in this setting (which have had greater clinical effect than PD-L1 inhibitors) awaits the results of the ongoing TiNivo-2 trial (tivozanib +/- nivolumab in IO-refractory RCC).
- Checkpoint inhibitors have long-term immunological effects (>6 months based on both drug half-life and persistence of stimulated T cells), and thus rechallenge within 6 months may be too soon. Whether rechallenging responders who stopped ICI therapy in the more distant past would be of benefit is not known. Switching to drugs which target alternative immune pathways may still be of benefit.
- The effect in ICI patients who initially respond to therapy and are then rechallenged > 6 months after stopping is unknown.

15

How about investigating IO in a biomarker-selected population?

16

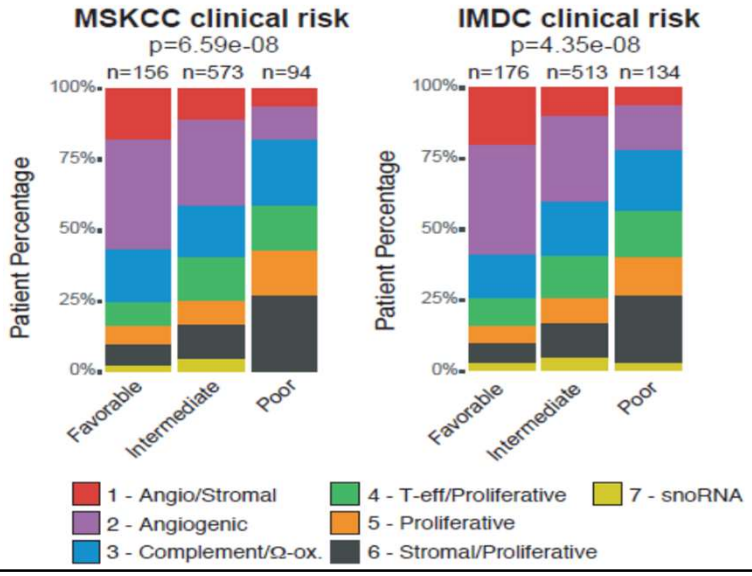
RCC is not biologically uniform and deciphering a signal for novel agents may require better patient selection



Motzer, Rini et al. *Cancer Cell* 2020

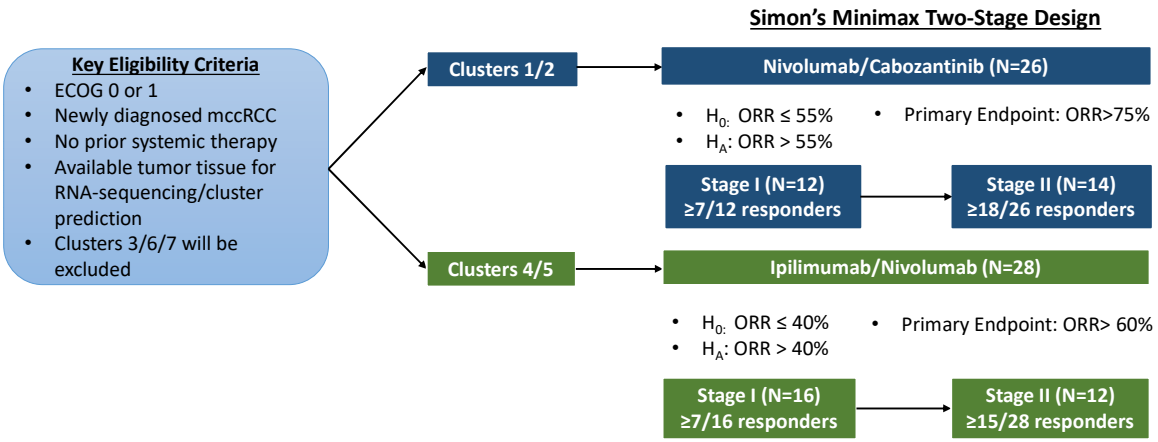
17

Patient groups defined by clinical characteristics display heterogeneous biology



18

OPtimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC) (NCT 05361720)



19

Principles of IO Development in RCC

- Mechanism(s) of additivity/synergy must exist based on pre-clinical data.
- Monotherapy activity is desirable.
- Single arm combination trials should have robust alternative hypotheses.
- Regimens should be studied in IO-naïve, advanced RCC patients. This may require novel 'window of opportunity' trials with acceptance from investigators, patients and IRBs.
- The neoadjuvant setting is appealing but lacks validated clinical endpoints.
- RCC is not a 'crowded' space. We have a long way to go to cure 100% of patients. Stacking IO drugs for initial advanced disease will lead to more cures.

20