Cancer Drug Development: Where We Came From & Where We're Headed

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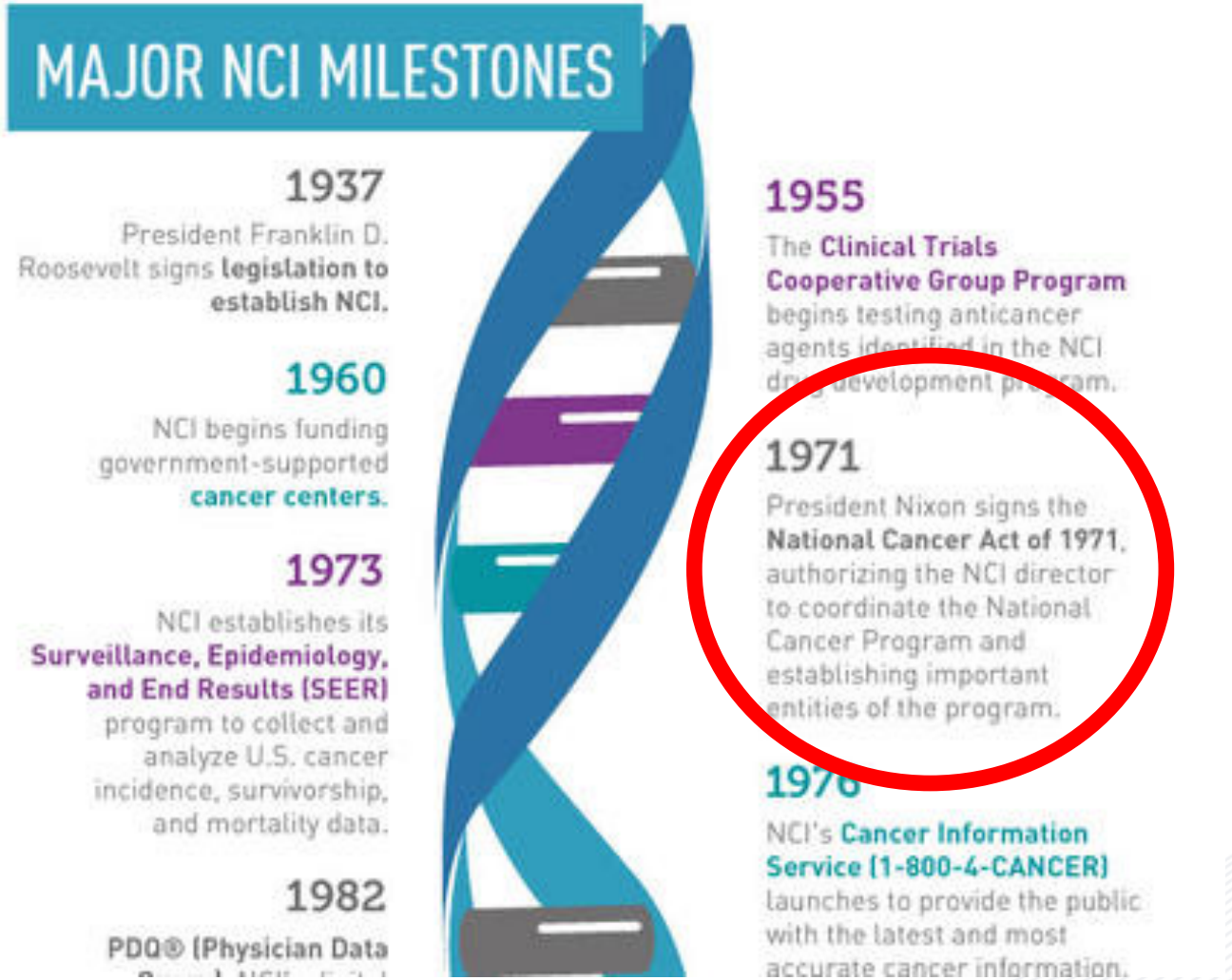
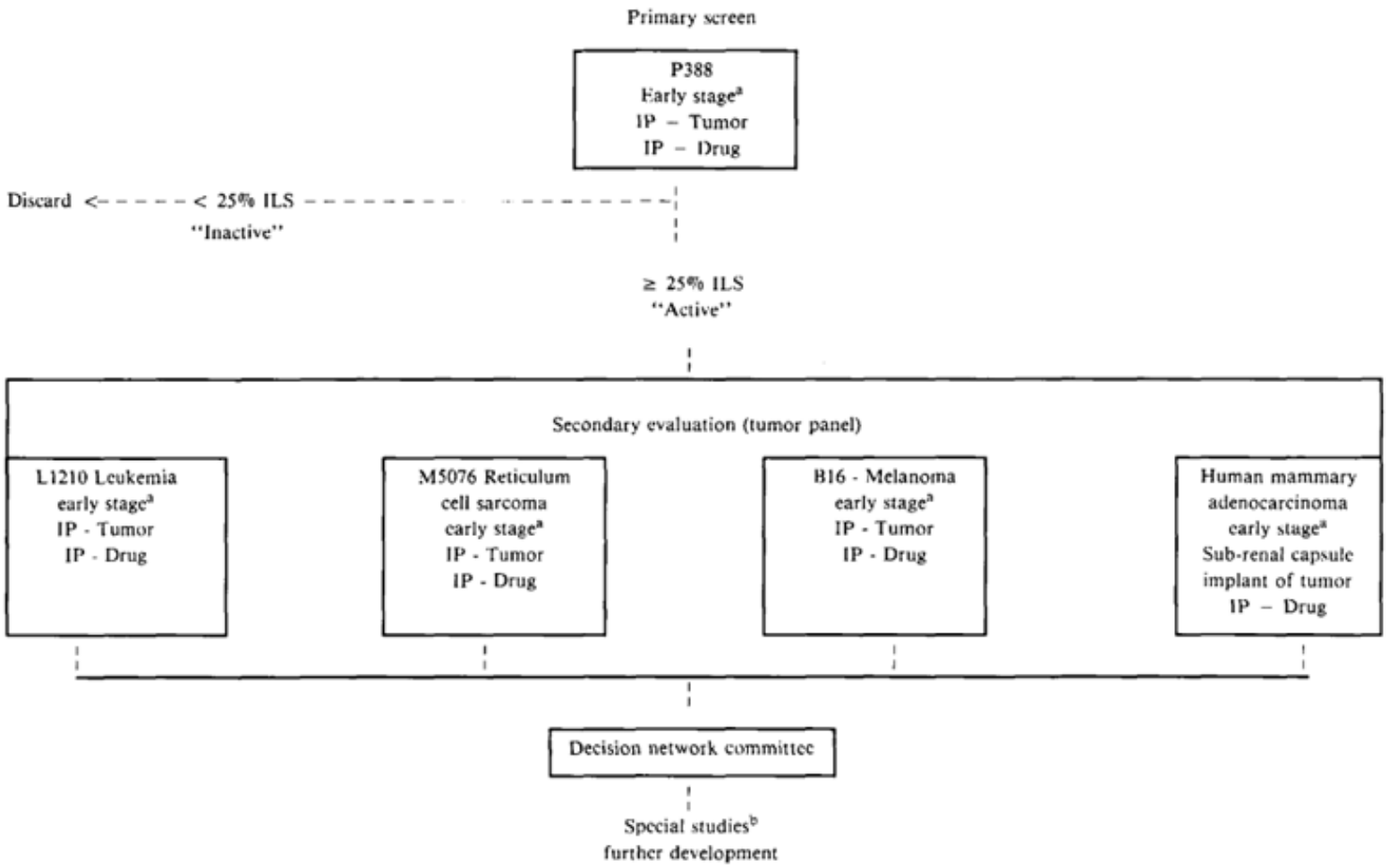

MAJOR NCI MILESTONES
1937
President Franklin D. Roosevelt signs legislation to establish NCI.
1960
NCI begins funding government-supported cancer centers.
1973
NCI establishes its Surveillance, Epidemiology, and End Results (SEER) program to collect and analyze U.S. cancer incidence, survivorship, and mortality data.
1982
PDQ® (Physician Data
1955
The Clinical Trials Cooperative Group Program begins testing anticancer agents
1971
President Nixon signs the National Cancer Act of 1971, authorizing the NCI director to coordinate the National Cancer Program and establishing important entities of the program.
1976
NCI's Cancer Information Service (1-800-4-CANCER) launches to provide the public with the latest and most accurate cancer information.

December 23, 1971

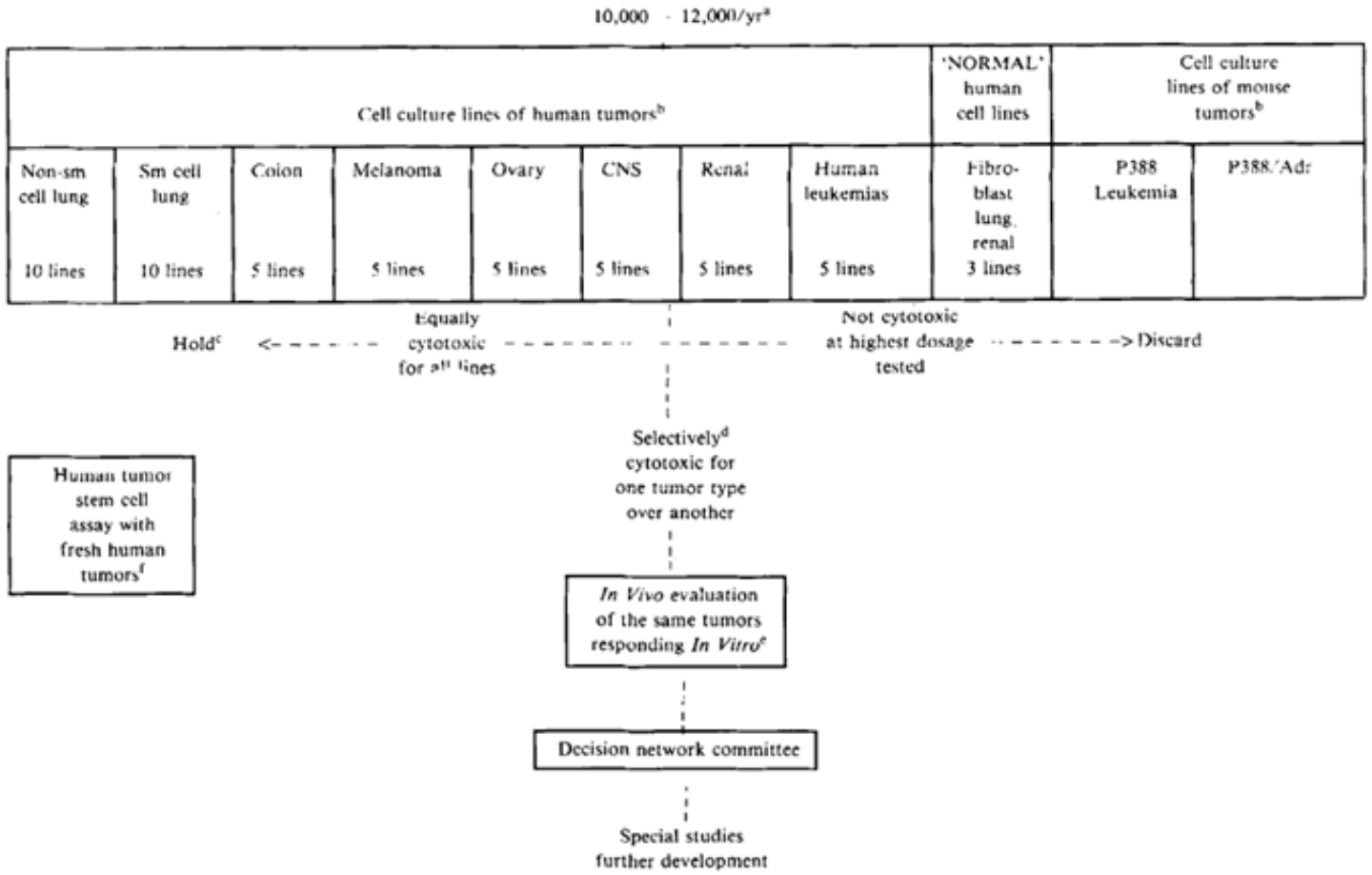
Conceptual

NCI Drug Screening Schema (1985-1986)

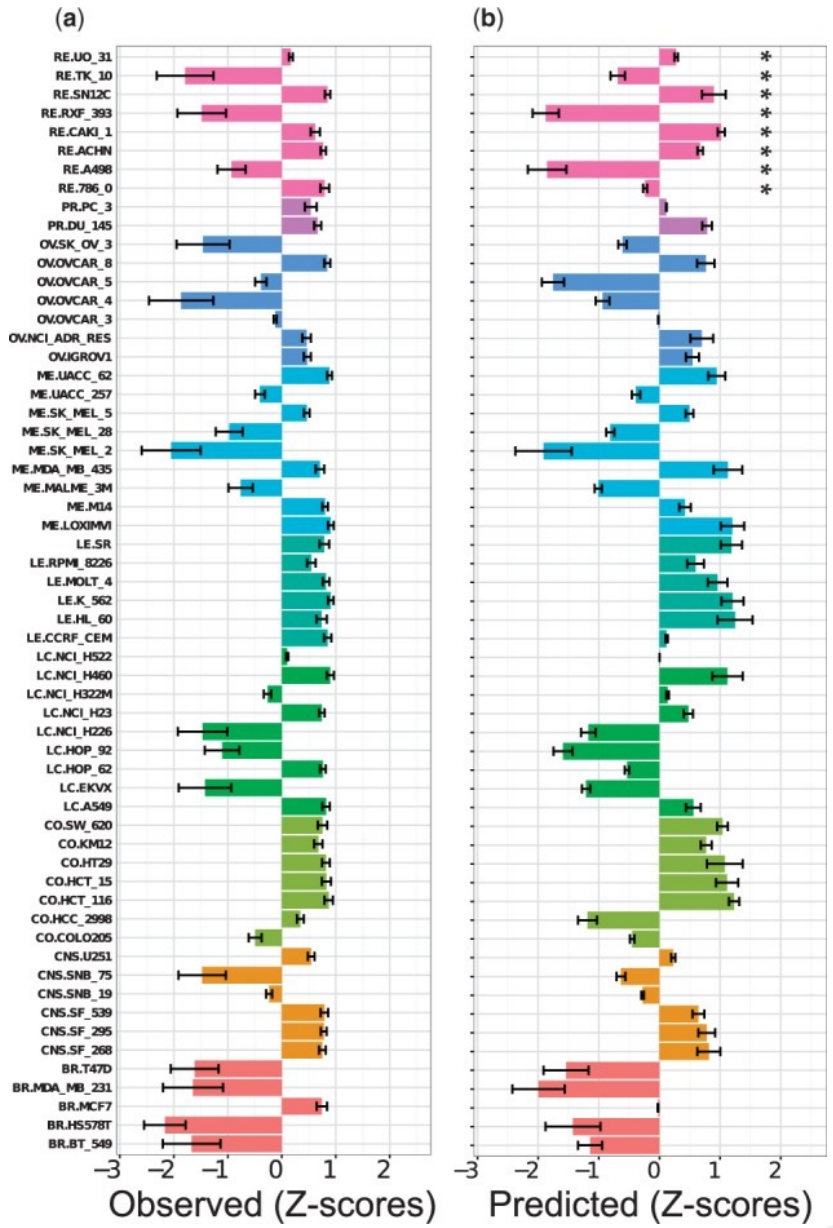


Corbett TH, Valeriote FA, Baker LH. *Invest New Drugs*. 1987;5(1):3-20. PMID: 3298130.

Proposed NCI “Disease Oriented” Drug Screening Schema (1987)



Corbett TH, Valeriote FA, Baker LH. *Invest New Drugs*. 1987;5(1):3-20. PMID: 3298130.



Cortés-Ciriano I, van Westen GJ, Bouvier G, Nilges M, Overington JP, Bender A, Malliavin TE. Improved large-scale prediction of growth inhibition patterns using the NCI60 cancer cell line panel. Bioinformatics. 2016 Jan 1;32(1):85-95. doi: 10.1093/bioinformatics/btv529. Epub 2015 Sep 8. PMID: 26351271; PMCID: PMC4681992.

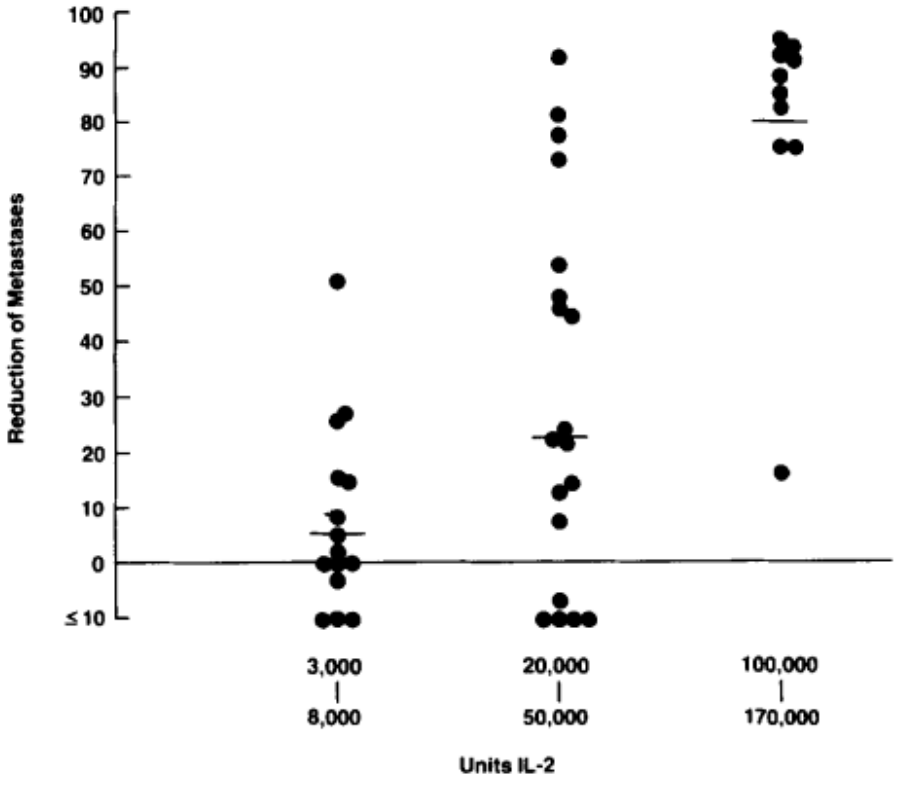
Interleukin-2 (IL-2)

- Discovered in the supernatant of activated T cells in 1976
- Primary role: induce immune responses by stimulating proliferation & differentiation of effector & memory T cells and NK cells
- High-dose IL-2 found to expand cytotoxic lymphocytes
- Tumors do not express IL-2 receptors - any antitumor activity result of IL-2 stimulation of immune cells

Overwijk, WW et al. *Ann Rev of Med.* 2021. Vol. 72:281-311

Early IL-2 *in vivo* Experiments

- administration of rIL-2 to tumor-bearing mice mediated regression of small established pulmonary metastases as well as s.c. tumors in animal models



Rosenberg et al. *J. Exp. Med.* May 1985.

IL-2 First in Human Study

- Twenty patients were reported in 1985 (23 treated) who received a wide variety of different regimens and doses of rIL-2
- Half-life was ~7 min with a later delayed clearance consistent with a two-compartment model as IL-2 was released from extravascular space into the plasma compartment
- Marked depletion of all lymphoid cells was seen almost immediately after IL-2 administration, which rebounded after IL-2 was discontinued
- Significant toxicities became apparent in these early studies, including fever, chills, malaise, arthralgias, and unexpected capillary leak, which led to weight gain from marked fluid retention

No tumor regression observed

Rosenberg, SA. *J Immunol.* 2014. 192 (12): 5451–5458.

IL-2 at higher dose

- 25 patients with metastatic cancer treated with increasing doses of IL-2 until toxicity precluded further dose escalation
- Early phase of study – pts received 60,000 IU/kg every 8 h
- Subsequent doses: 180,000 or 600,000 IU/kg
- 4/7 patients with mMelanoma & 3/3 patients with mRCC exhibited regression
- 1st demonstration of IL-2 mediated tumor regression in humans
- Subsequent explosion of HD IL-2 trials against various metastatic cancers
- Eventual FDA approval: mRCC and melanoma in 1992 and 1998

Rosenberg, SA. *J Immunol.* 2014. 192 (12): 5451–5458
Rosenberg, SA et al., NEJM 1985.

Results of Treatment of 255 Patients With Metastatic Renal Cell Carcinoma Who Received High-Dose Recombinant Interleukin-2 Therapy

By Gwendolyn Fyfe, Richard I. Fisher, Steven A. Rosenberg, Mario Sznol, David R. Parkinson, and Arthur C. Louie

Purpose: **To determine the efficacy and toxicity of a high-dose interleukin-2 (IL-2) regimen in patients with metastatic renal cell carcinoma.**

Patients and Methods: **Two hundred fifty-five assessable patients were entered onto seven phase II clinical trials. Proleukin (aldesleukin; Chiron Corp, Emeryville, CA) 600,000 or 720,000 IU/kg was administered by 15-minute intravenous (IV) infusion every 8 hours for up to 14 consecutive doses over 5 days as clinically tolerated with maximum support, including pressors. A second identical cycle of treatment was scheduled following 5 to 9 days of rest, and courses could be repeated every 6 to 12 weeks in stable or responding patients.**

Results: **The overall objective response rate was 14% (90% confidence interval [CI], 10% to 19%), with 12 (5%) complete responses (CRs) and 24 (9%) partial responses (PRs). Responses occurred in all sites of disease, including bone, intact primary tumors, and visceral metastases, and in patients with large tumor burdens or bulky individual lesions. The median response duration for patients who achieved a CR has not been reached, but was 19.0 months for those who achieved a PR. Baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) was the only predictive prognostic factor for response to IL-2. While treatment was associated with severe acute toxicities, these generally reversed rapidly after therapy was completed. However, 4% of patients died of adverse events judged to be possibly or probably treatment-related.**

Conclusion: **High-dose IL-2 appears to benefit some patients with metastatic renal cell carcinoma by producing durable CRs or PRs. Despite severe acute treatment-associated toxicities, IL-2 should be considered for initial therapy of patients with appropriately selected metastatic renal cell carcinoma.**

J Clin Oncol 13:688-696.

High Dose IL-2 In Metastatic Renal Cell Carcinoma: Summary of Efficacy

	Response Rate		Response Duration (months)	
Response	No.	%	Median	Range†
CR	12	5	NR	5+-62+
PR*	24	9	19	3-57+
PR + CR	36	14	20.3	3-62+

Abbreviation: NR, not yet reached.

*Three partial responders had surgery while in PR and remain disease-free. Duration of response censored from date of surgery.

†Plus signs mean ongoing.

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IL-2 Toxicity

Event by Body System	Grade (%) All	3	4
Cardiovascular			
Hypotension	96	59	15
Arrhythmias	14	2	0
Supraventricular	5	2	1
Ventricular	1	0	0
Myocardial ischemia	2	1	<1
Myocardial infarction	2	0	2
Cardiac arrest	2	<1	2
Myocarditis	1	1	0
Gastrointestinal			
Nausea and vomiting	89	24	1
Diarrhea	81	20	2
Stomatitis	32	4	0
Gastrointestinal bleeding	15	3	1
Intestinal perforation	1	0	<1
Neurologic			
Mental status changes	82	23	5
Coma	2	0	2
Seizure (grand mal)	2	1	1
Pulmonary			
Dyspnea	57	16	1
Adult respiratory distress syndrome	1	<1	<1
Respiratory failure	3	<1	2
Hepatic			
Elevated bilirubin level	85	13	8
Elevated transaminase level	72	7	3
Elevated alkaline phosphatase level	77	8	<1
Renal			
Acidosis	19	4	2
Elevated BUN level	85	12	2
Oliguria/anuria	81	40	6
Serum creatinine elevation	81	11	3
General			
Fever and/or chills	97	19	5
Asthenia	39	4	0
Edema	55	2	0
Sepsis	8	4	2
Hematologic			
Thrombocytopenia	83	16	5
Anemia	99	15	3
Other			
Pruritus	53	4	0
Rash	25	1	0
Arthralgia	7	1	0
Myalgia	7	1	0

Fyfe et al. *Journal of Clinical Oncology,* Vol 13, No 3 (March), 1995: pp 688-696

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Fyfe et al. *Journal of Clinical Oncology,* Vol 13, No 3 (March), 1995: pp 688-696

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Fyfe et al. *Journal of Clinical Oncology,* Vol 13, No 3 (March), 1995: pp 688-696

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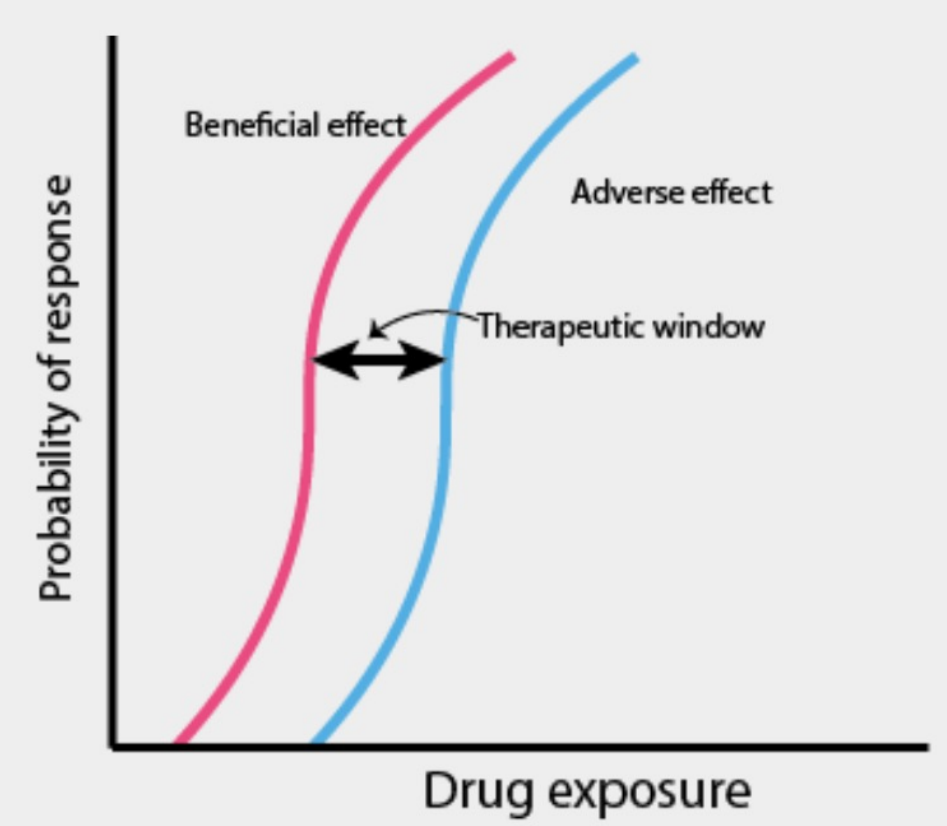
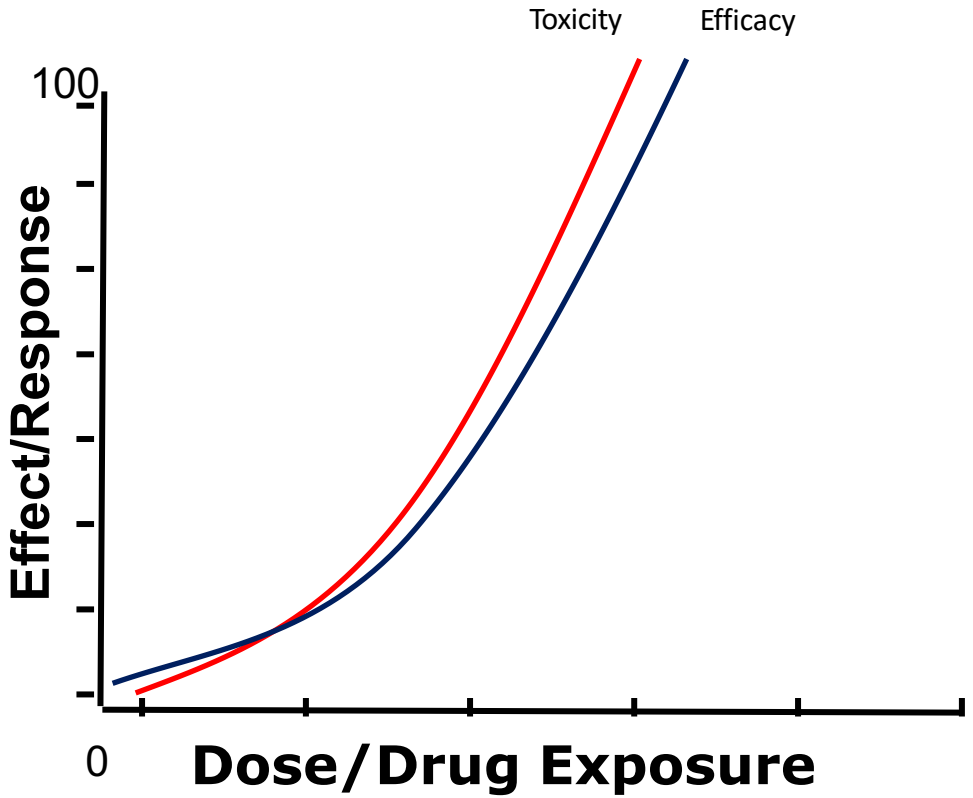
Narrow Therapeutic Window

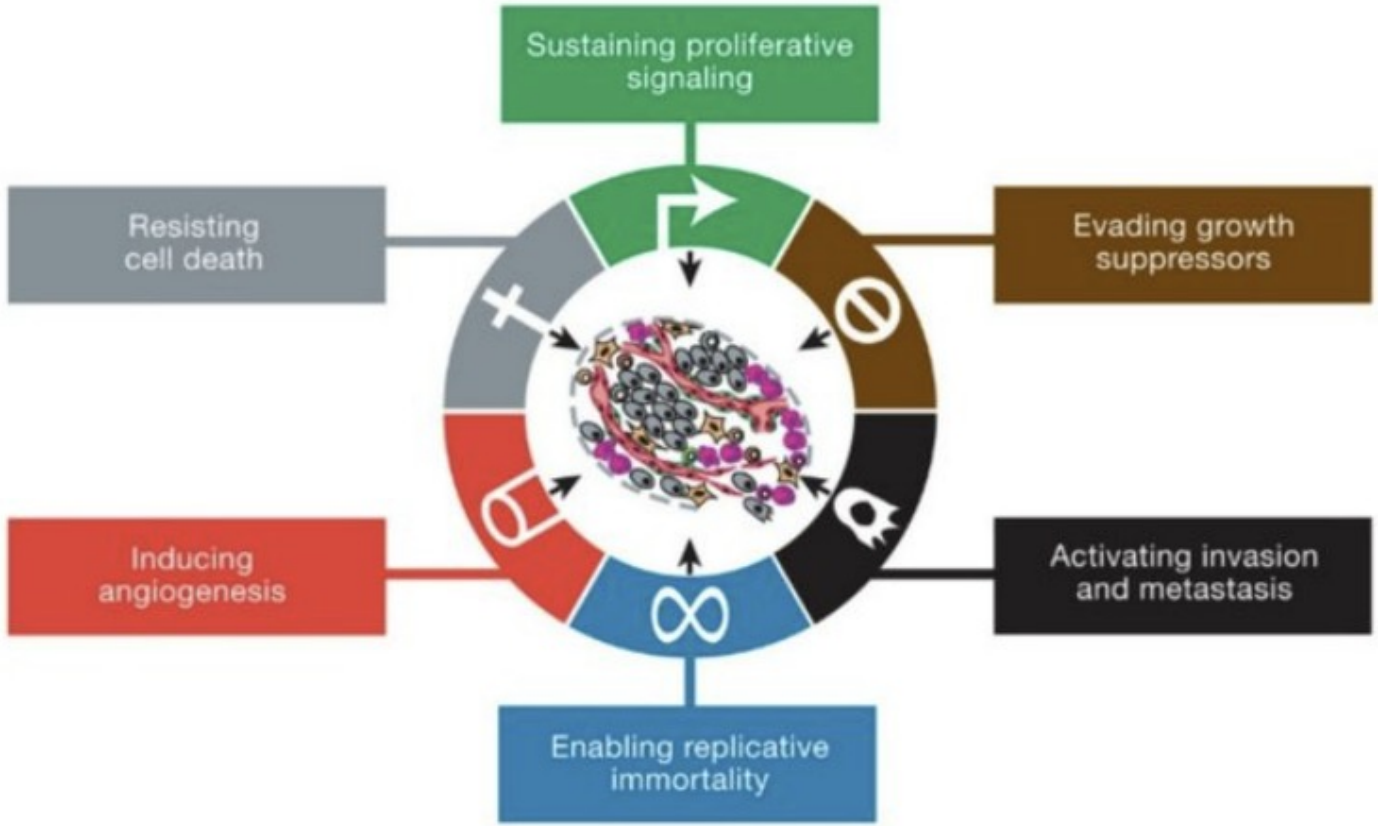




https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-information-april-21-22-2022-meeting-oncologic-drugs-advisory-committee-meeting-announcement

Biology

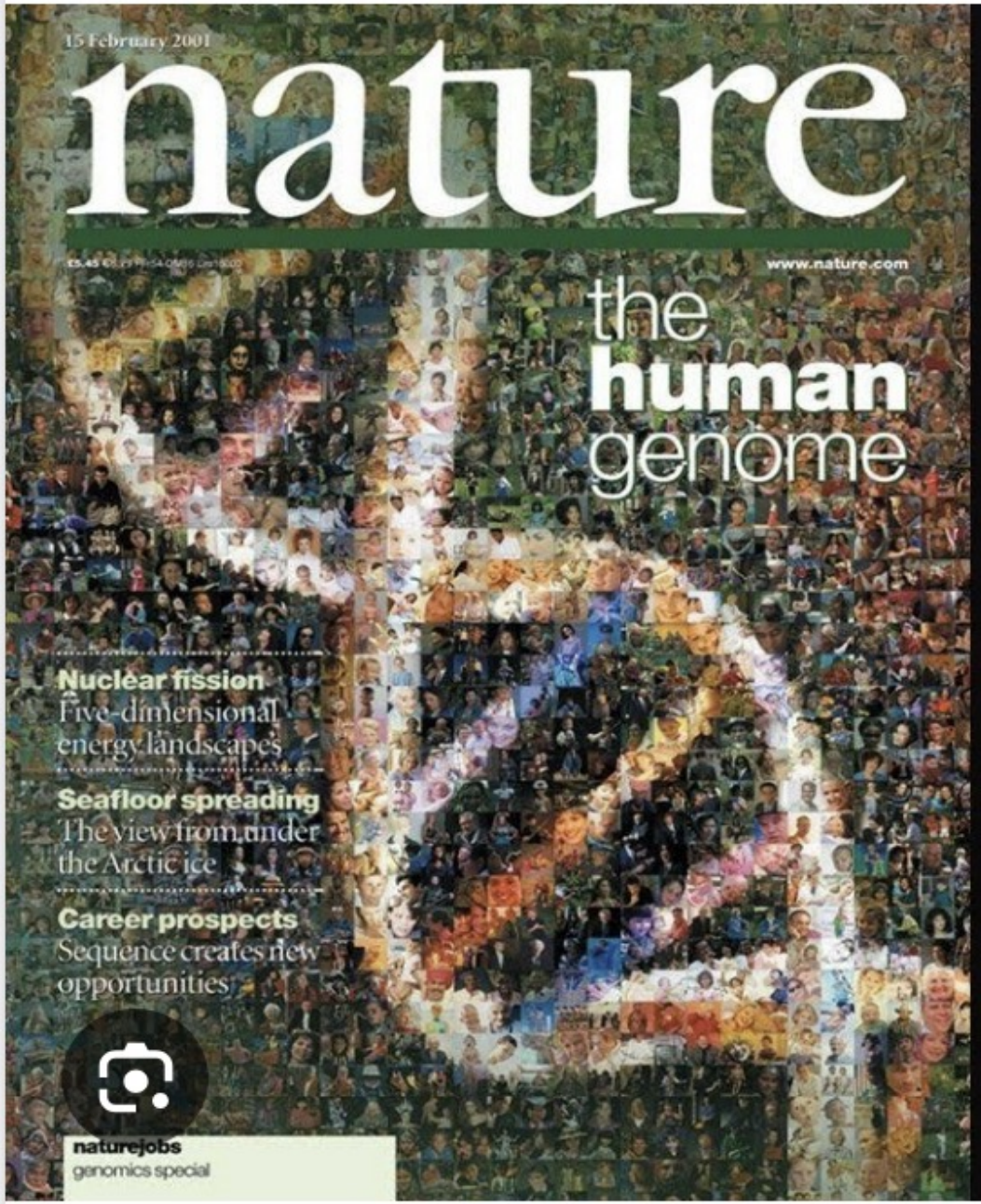
Hallmarks of Cancer

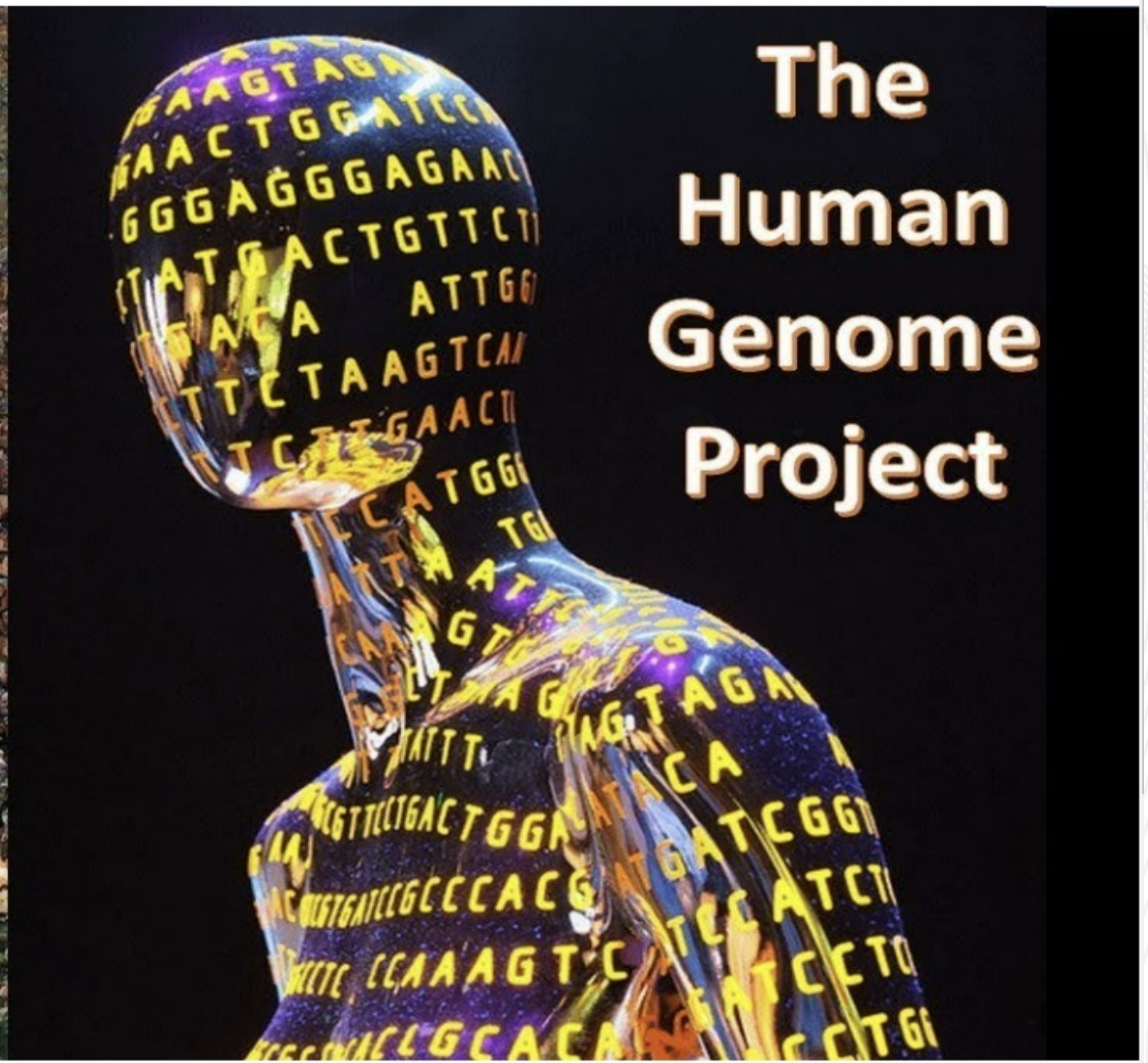


2000

2022

Hannahan & Weinberg, 2000, 2022

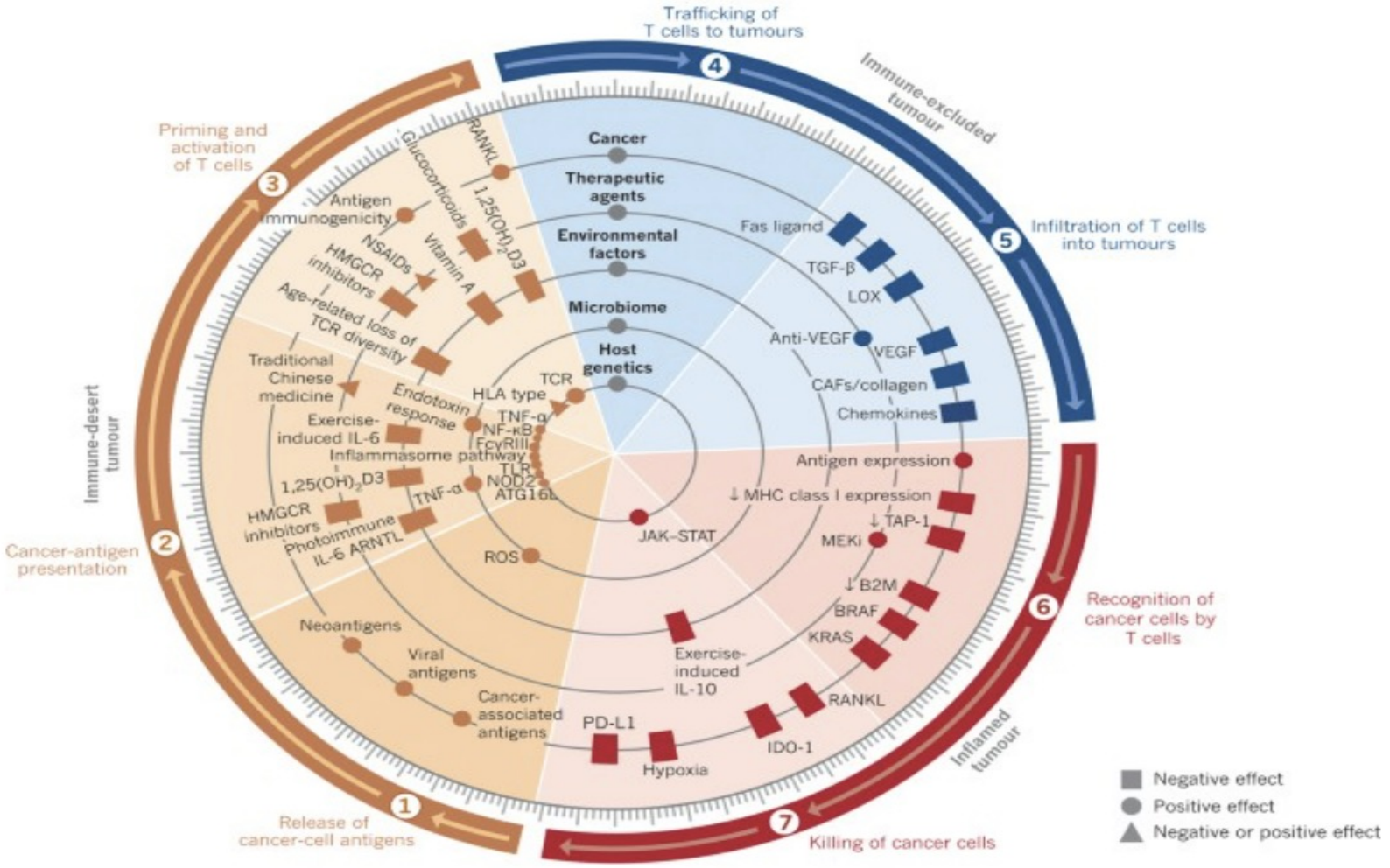

15 February 2001
nature
www.nature.com
the human genome
Nuclear fission
Five-dimensional energy landscapes
Seafloor spreading
The view from under the Arctic ice
Career prospects
Sequence creates new opportunities
naturejobs
genomics special


The Human Genome Project

Cancer-immune phenotypes.

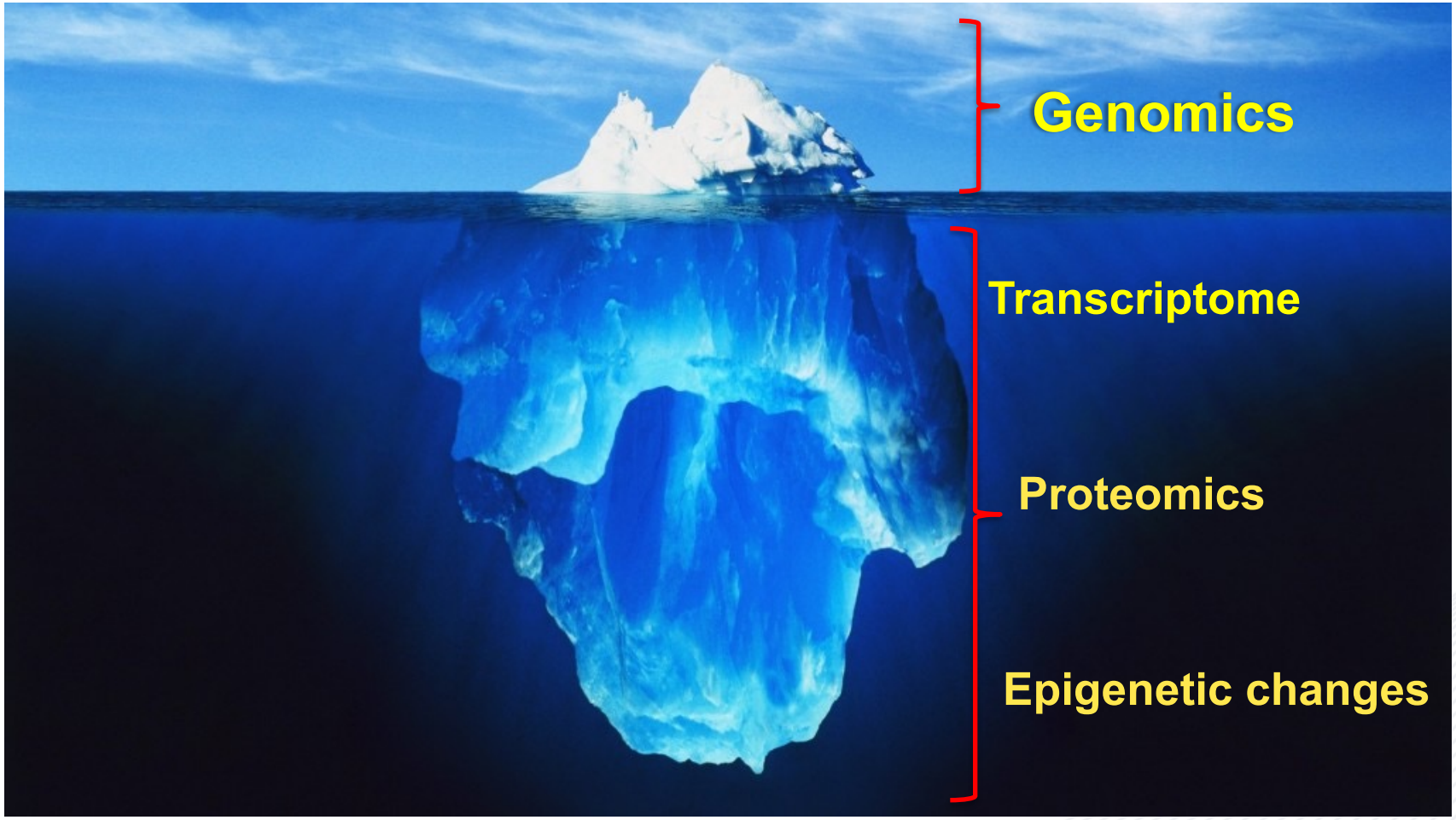
Chen & Mellman, Nature 2017

Factors Influencing the Cancer Immune Set Point



Chen & Mellman Nature 2017

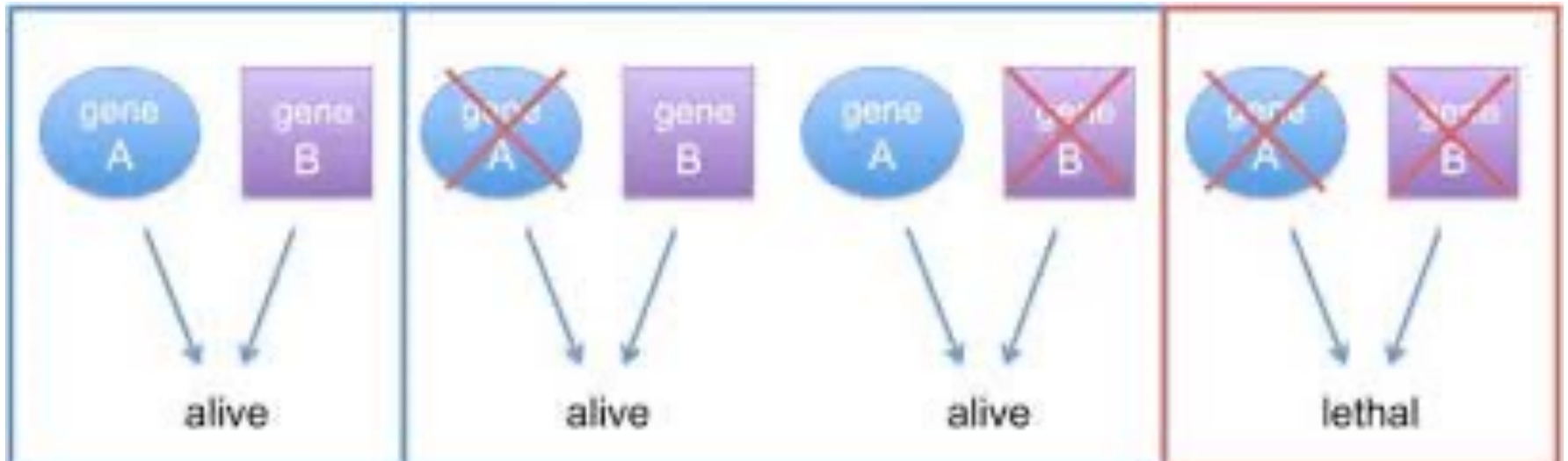
Major Scientific Tools



Integrating Genetic Approaches into the Discovery of Anticancer Drugs

Leland H. Hartwell, Philippe Szankasi, Christopher J. Roberts,
Andrew W. Murray, Stephen H. Friend*

Science (1997), 278: 1064 - 1068



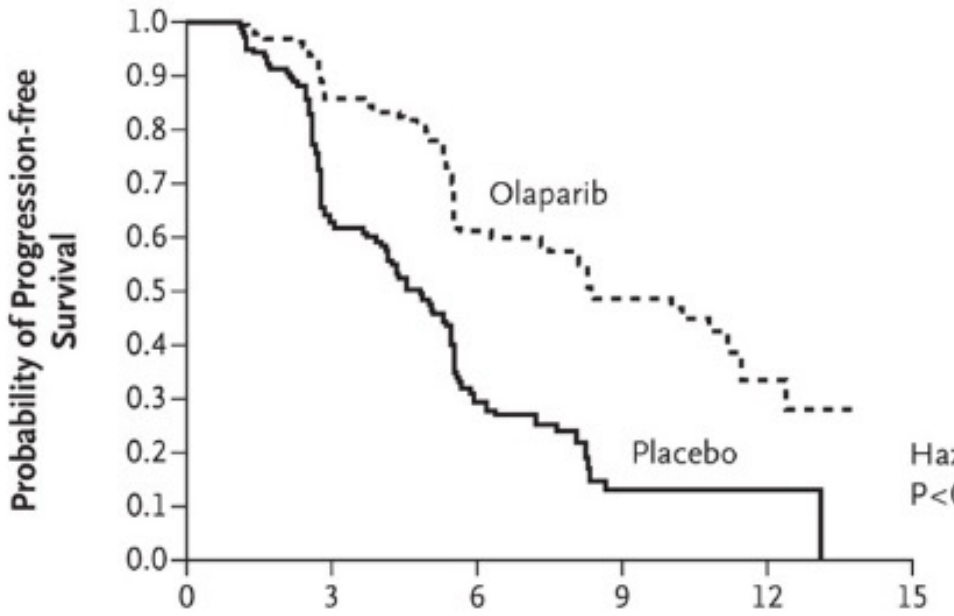
Tuesday, 20 December 2011

Company *updates on olaparib development program*

Company today announced that its investigational compound olaparib will not progress into Phase III development for the maintenance treatment of serous ovarian cancer.

The decision to discontinue olaparib's development in serous ovarian cancer was made following a review of an interim analysis of a Phase II study (study 19) which indicated that the previously reported progression free survival benefit is unlikely to translate into an overall survival benefit, the definitive measure of patient benefit in ovarian cancer. In addition, attempts to identify a suitable tablet dose for use in Phase III studies have not been successful.

Olaparib Maintenance in Platinum-sensitive Relapsed Ovarian Cancer: PFS



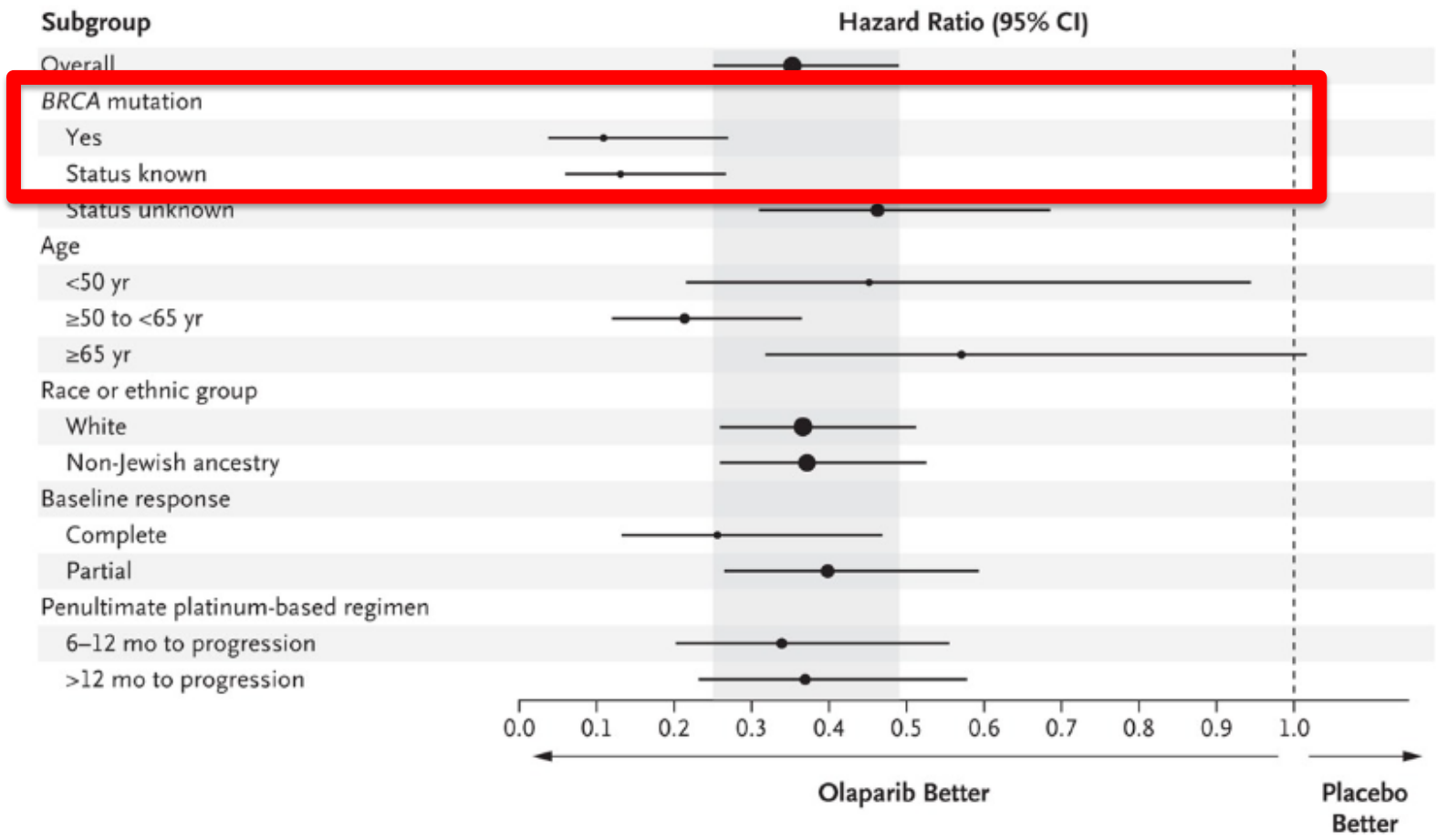
Hazard ratio, 0.35 (95% CI, 0.25–0.49)
P<0.001

No. at Risk						
Olaparib	136	104	51	23	6	0
Placebo	129	72	23	7	1	0

	No. of Patients/ Total No. (%)	Median Progression-free Survival (mo)
Olaparib	60/136 (44.1)	8.4
Placebo	93/129 (72.1)	4.8

Ledermann et al. NEJM 2012; 366:1382-1392

Olaparib Maintenance in Platinum-sensitive Relapsed Ovarian Cancer: Subgroup Analysis of PFS



Ledermann et al. NEJM 2012; 366:1382-1392

Gynecologic Oncology 140 (2016) 199–203

Contents lists available at ScienceDirect

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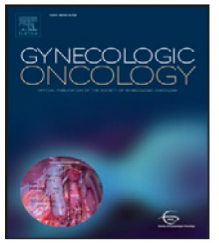
journal homepage: www.elsevier.com/locate/ygyno



Efficacy and safety of olaparib monotherapy in germline *BRCA1/2* mutation carriers with advanced ovarian cancer and three or more lines of prior therapy

Susan M. Domchek [a,*], Carol Aghajanian [b], Ronnie Shapira-Frommer [c], Rita K. Schmutzler [d], M. William Audeh [e], Michael Friedlander [f], Judith Balmaña [g], Gillian Mitchell [h,i], Georgeta Fried [j], Salomon M. Stemmer [k], Ayala Hubert [l,m], Ora Rosengarten [n], Niklas Loman [o], Jane D. Robertson [p,1], Helen Mann [p], Bella Kaufman [c]

[a] *Basser Research Center and Abramson Cancer Center, Philadelphia, PA, USA*
[b] *Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA*
[c] *Sheba Medical Center, Tel Hashomer, Israel*
[d] *Center for Familial Breast and Ovarian Cancer and Center of Integrated Oncology, Cologne, Germany*
[e] *Samuel Oschin Cancer Institute, Los Angeles, CA, USA*
[f] *Prince of Wales Clinical School, University of New South Wales, Sydney, Australia*
[g] *Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain*
[h] *Peter MacCallum Cancer Centre, Melbourne, Australia*
[i] *Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia*
[j] *Institute of Oncology, Rambam Health Care Campus, Haifa, Israel*
[k] *Rabin Medical Center, Petah Tikva, Israel*
[l] *Hadassah-Hebrew University Hospital Sharett Institute of Oncology, Jerusalem, Israel*
[m] *Sharett Institute of Oncology, Jerusalem, Israel*
[n] *Shaare Zedek Medical Centre, Jerusalem, Israel*
[o] *Skånes universitetssjuk Lund, Lund, Sweden*
[p] *AstraZeneca, Macclesfield, UK*

Objective response rate and duration of response stratified by platinum sensitivity status in patients with g*BRCA1/2*m ovarian cancer and measurable disease at baseline who had received ≥3 prior chemotherapy regimens (n = 137).

Platinum sensitivity status[a] (N = total patients with measurable disease)	Confirmed responders[b] n	ORR, % (95% CI)	Median DoR, months (95% CI)
Total (N = 137)	46	34 (26–42)	7.9 (5.6–9.6)
Platinum sensitive (N = 39)[c]	18	46 (30–63)	8.2 (5.6–13.5)
Platinum resistant (N = 81)	24	30 (20–41)	8.0 (4.8–14.8)
Platinum refractory (N = 14)	2	14 (2–43)	6.4 (5.4–7.4)
Platinum status unknown (N = 3)	2	67 (9–99)	6.3 (4.7–7.9)

Domchek, et al
GYN Onc 2016

SOLO1: Phase III trial of maintenance olaparib following platinum-based chemotherapy in newly diagnosed patients with advanced ovarian cancer and a *BRCA1/2* mutation

Kathleen Moore,[1] Nicoletta Colombo,[2] Giovanni Scambia,[3] Byoung-Gie Kim,[4] Ana Oaknin,[5] Michael Friedlander,[6] Alla Lisyanskaya,[7] Anne Floquet,[8] Alexandra Leary,[9] Gabe S. Sonke,[10] Charlie Gourley,[11] Susana Banerjee,[12] Amit Oza,[13] Antonio González-Martín,[14] Carol Aghajanian,[15] William Bradley,[16] Elizabeth S. Lowe,[17] Ralph Bloomfield,[18] Paul DiSilvestro[19]

[1]Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK, USA; [2]University of Milan-Bicocca and IEO, European Institute of Oncology IRCCS, Milan, Italy; [3]Fondazione Policlinico Universitario A. Gemelli IRCCS Università Cattolica, Rome, Italy; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [5]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [6]University of New South Wales Clinical School, Prince of Wales Hospital, Randwick, Australia; [7]St Petersburg City Oncology Dispensary, St Petersburg, Russia; [8]Institut Bergonié, Comprehensive Cancer Centre, Bordeaux, France; [9]Gustave-Roussy Cancer Campus, Villejuif, France; [10]The Netherlands Cancer Institute, Amsterdam, The Netherlands; [11]Cancer Research UK Edinburgh Centre, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK; [12]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [13]Princess Margaret Cancer Centre, Toronto, ON, Canada; [14]Clínica Universidad de Navarra, Madrid, Spain; [15]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [16]Froedtert and the Medical College of Wisconsin, Milwaukee, WI, USA; [17]AstraZeneca, Gaithersburg, MD, USA; [18]AstraZeneca, Cambridge, UK; [19]Women & Infants Hospital, Providence, RI, USA

esmo.org

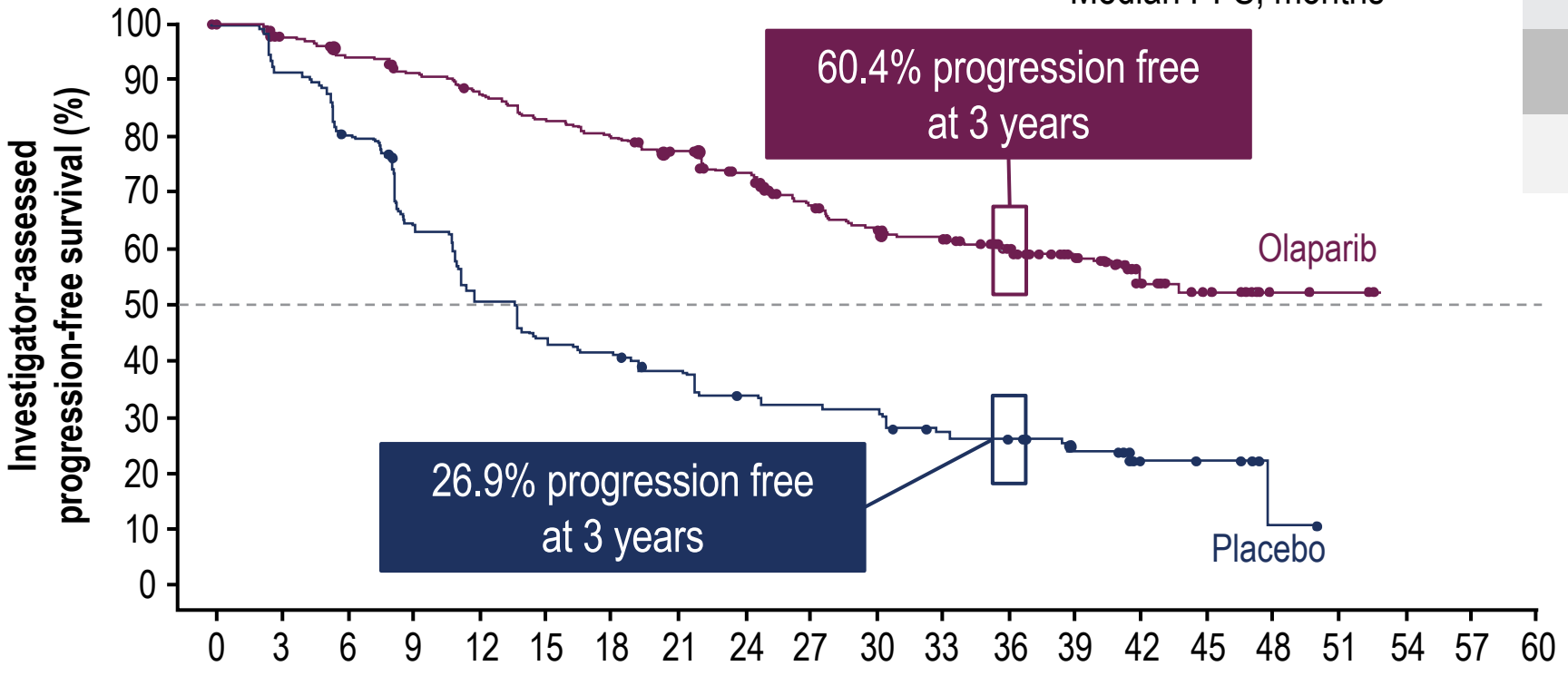
ClinicalTrials.gov identifier: NCT01844986

This study was sponsored by AstraZeneca; part of an alliance between AstraZeneca and Merck & Co., Inc.

Conducted in partnership with the Gynecologic Oncology Group (GOG-3004)

PFS by investigator assessment

	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		



No. at risk

Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

MUNICH 2018 ESMO congress

CI, confidence interval; NR, not reached

AACR American Association for Cancer Research®
ANNUAL MEETING 2022 New Orleans
APRIL 8-13, 2022 • #AACR22

PETRA: A first-in-class, first-in-human trial of the next-generation PARP1-selective inhibitor AZD5305 in patients with *BRCA1/2*, *PALB2* or *RAD51C/D* mutations

CT007

Presenter: Timothy Yap, M.D.

Discussant: Patricia Mucci LoRusso, D.O., Ph.D.(h)

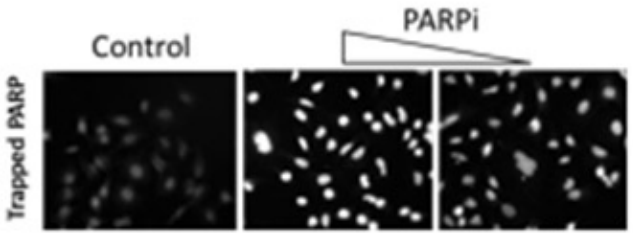
Professor of Medicine
Associate Center Director: Experimental Therapeutics
Yale University/Yale Cancer Center

Trapping: AZD5305 selectively traps PARP1 onto the chromatin

Novel PARP-trapping assay developed

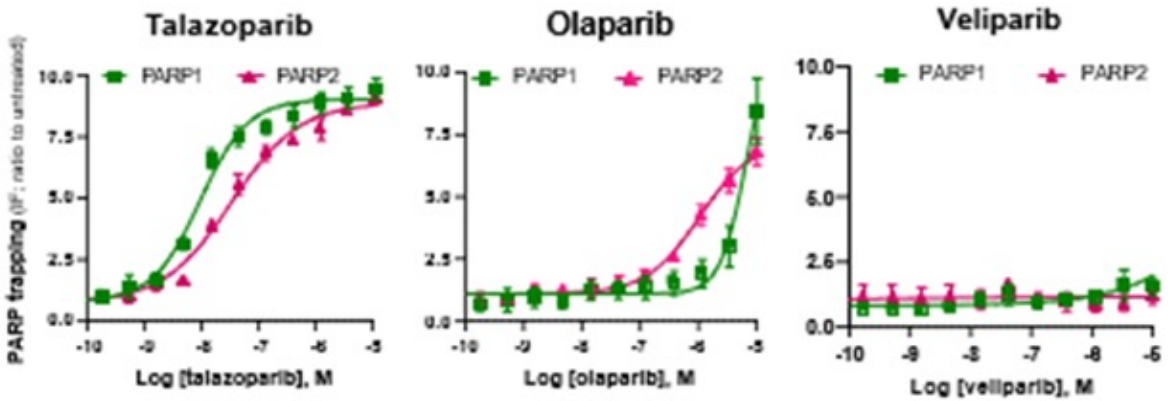
Method:

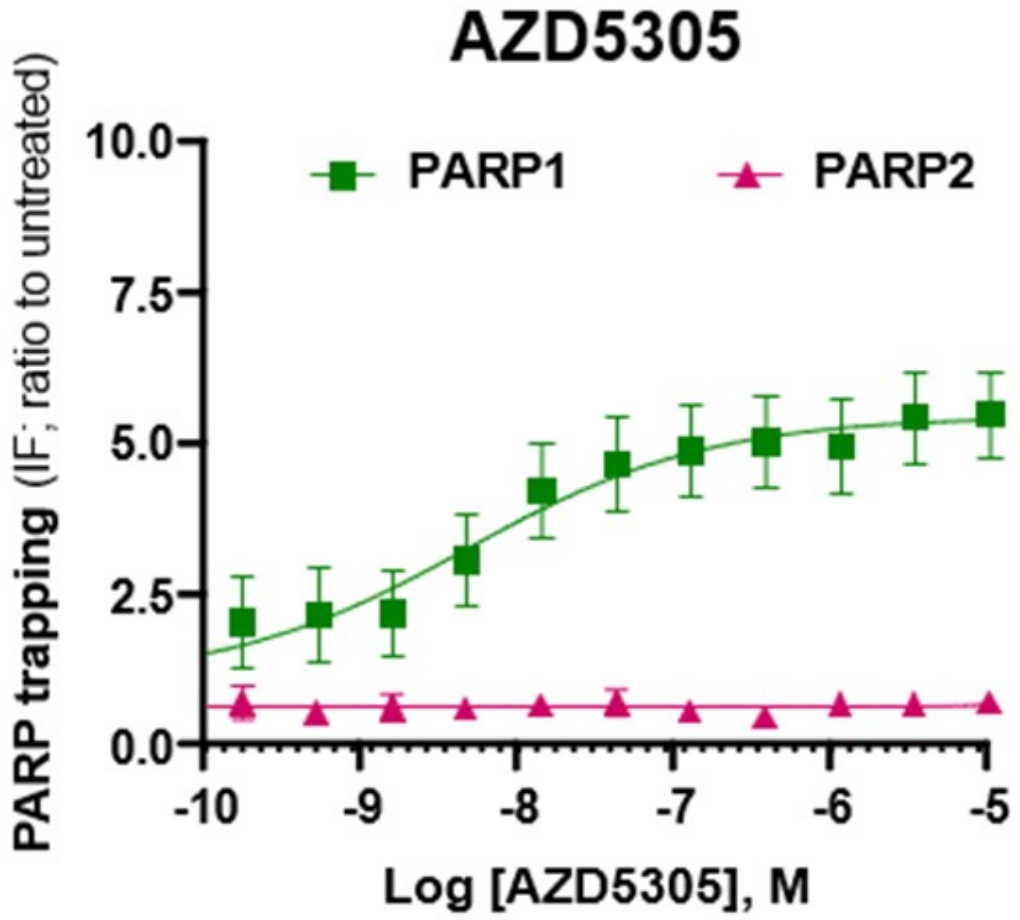
- Seed cells in 96 well plate
- Drug treatments
- In-Situ Extraction
- Fixation and IF staining



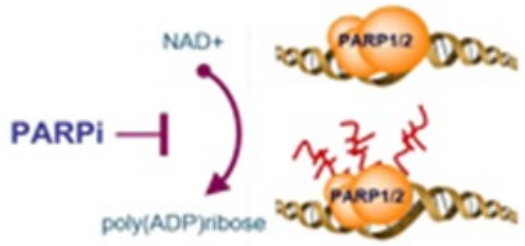
High throughput; quantitative

Trapping profiles of clinical PARPi



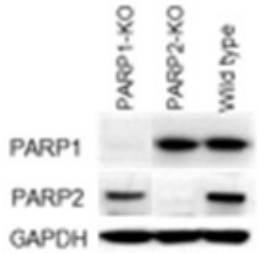


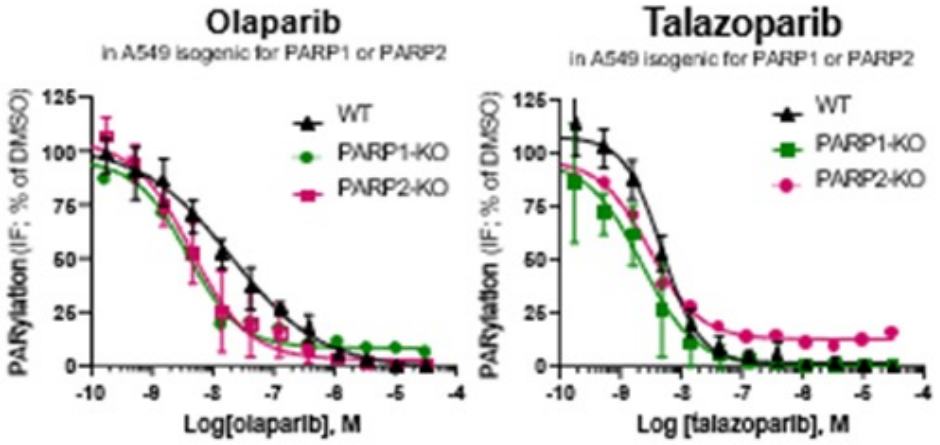
PARylation: AZD5305 selectively inhibits PARP1 in cells

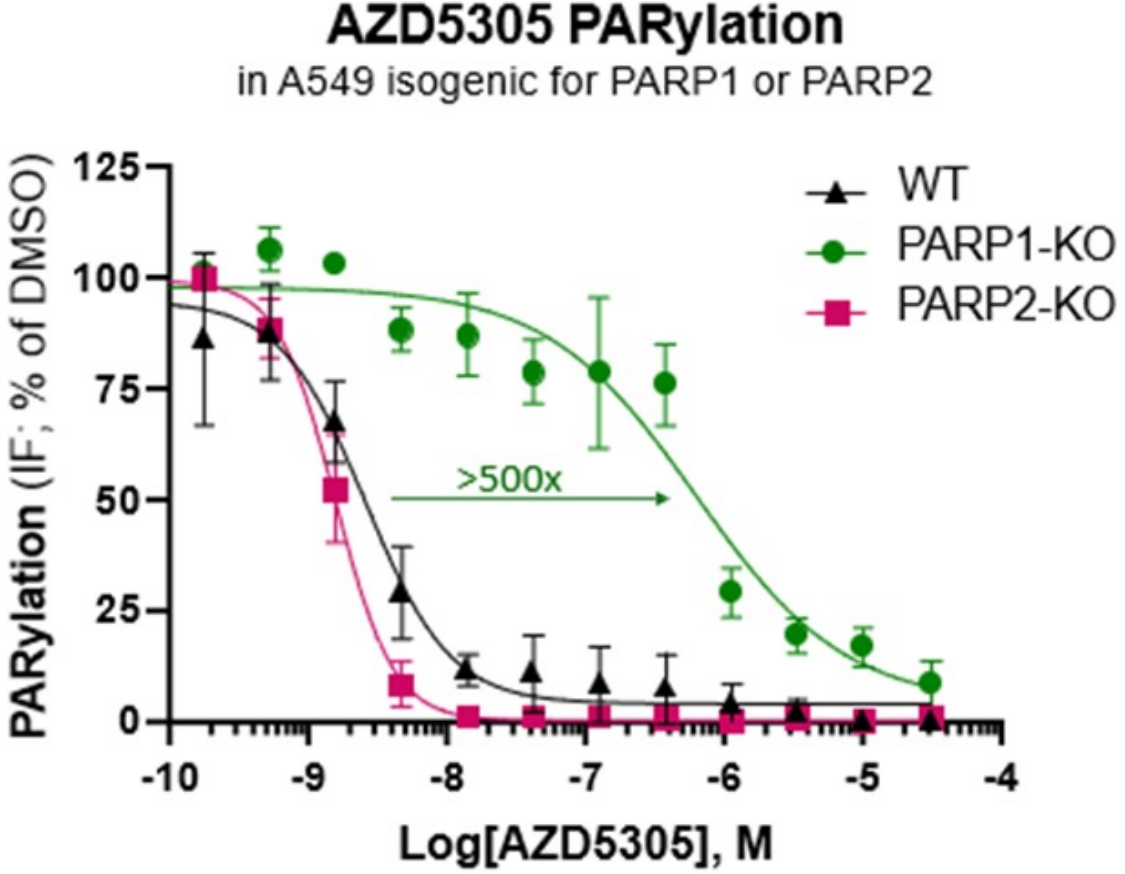


PARylation inhibition is most proximal biomarker for PARPi

	PARylation contribution	
WT	PARP1	PARP2
PARP1-KO	/	PARP2
PARP2-KO	PARP1	/



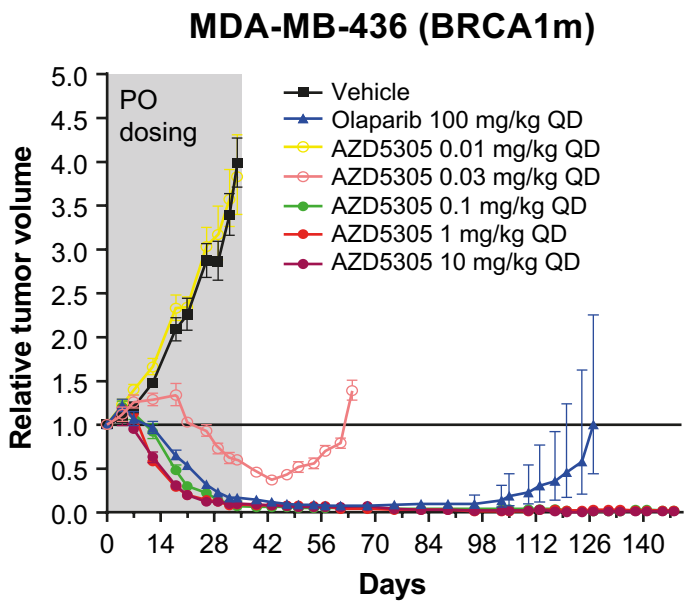


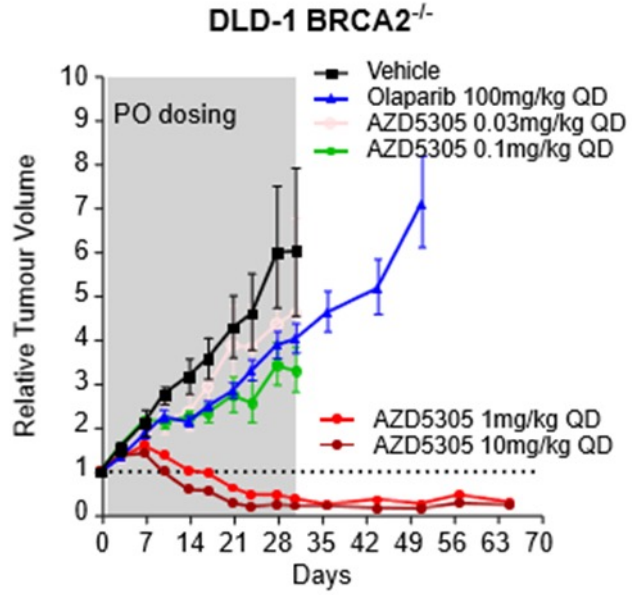


Johannes, et al., AACR 2021

AZD5305 - more efficacious than first generation PARPi

- Durable regression observed following
- cessation of AZD5305 dosing[4]





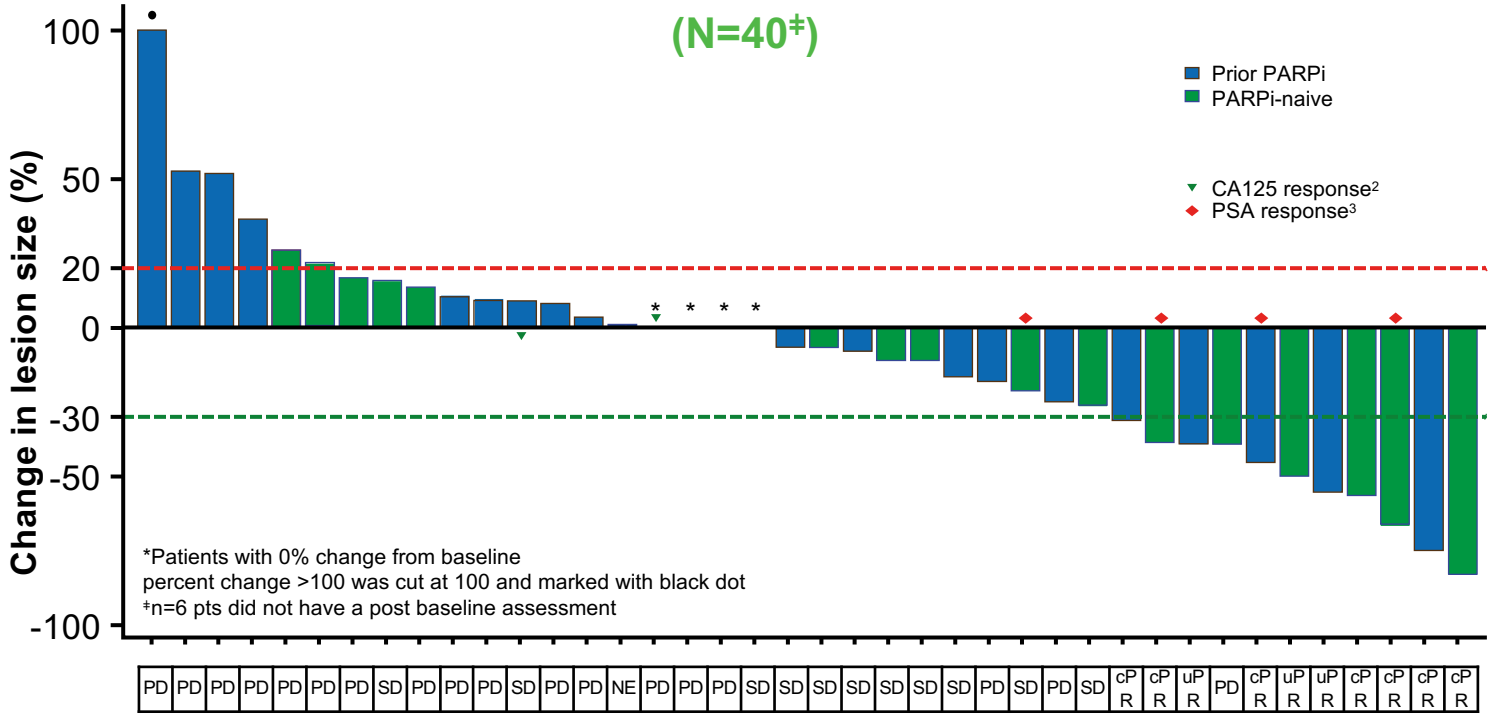
[1] https://doi.org/10.1021/acs.jmedchem.1c01012; [2] Johannes J, AACR 2021, Abstract #ND05; [3] Illuzzi G. AACR 2021, poster 1272; [4] Staniszewska AD. AACR 2021, poster 1270.

Response vs Prior PARP Inhibitor Exposure

- 46 patients were included in the interim response analysis set[1]
- 6 patients were not evaluable[2] for RECIST v1.1 assessment
- Responses seen regardless of prior PARPi
- Few CRs at time of data cutoff
- Should we focus on response duration rather than response type?
- Were those PARPi exposed patients truly resistant to 1st generation inhibitors or was it drug exposure/pharmacologic resistance?
- Will combination strategies lead to improvement

Best % change in target lesions size by prior PARPi

(N=40‡)



[1]All dosed subjects who had measurable disease at baseline and who received their first dose at least 13 weeks prior to data extract [2]n=5 did not have a follow up scan and n=1 had SD<7 weeks [2]GCIG CA125 response [3]PCWG3 PSA_{50} response [4]n=2 can be confirmed
cPR, confirmed Partial Response; uPR, unconfirmed Partial Response; SD, Stable disease; PD, progressive disease

AZD5305 Achieves Higher Fold Coverage over the TEC Compared to First Generation PARPi

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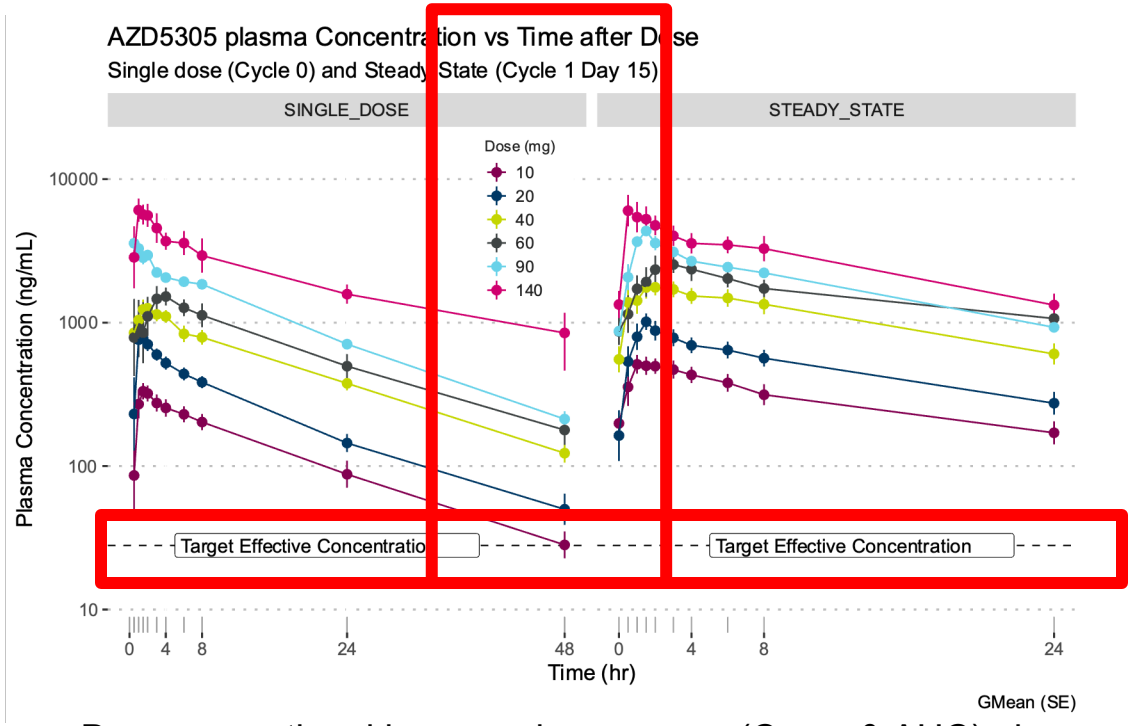
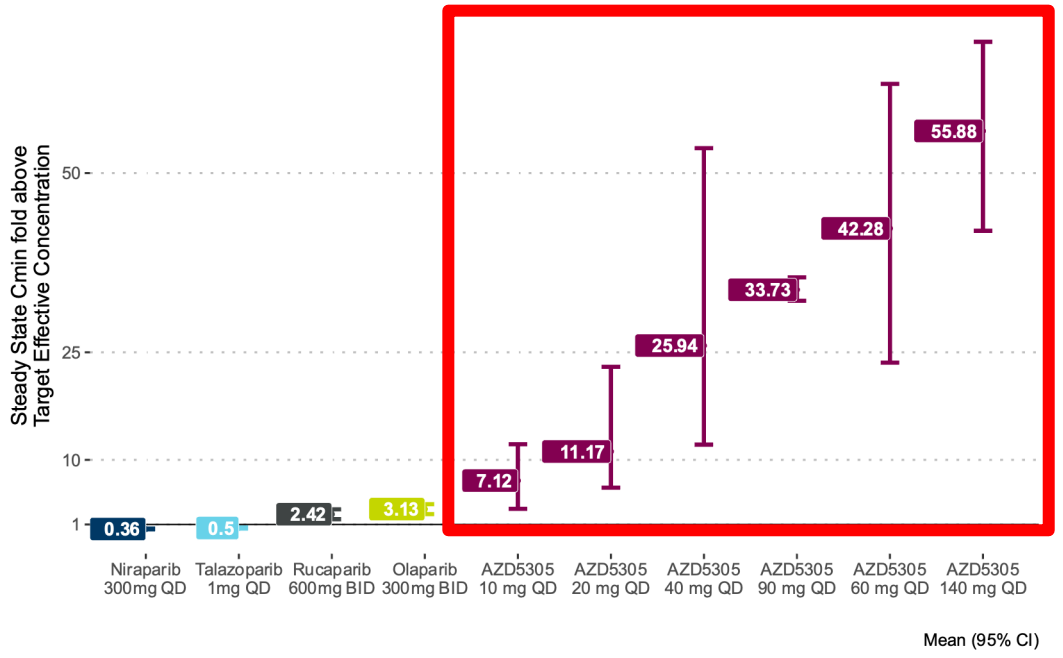
AZD5305 plasma concentration vs time after dose



First-generation PARPi and AZD5305 C_{min} fold above TEC



- Dose proportional increase in exposure (Cmax & AUC) observed with increase in dose (10 – 140 mg QD)
- Quick onset (Tmax 0.5-3 h) with mean terminal elimination half-life 13.1–16.4 h across cohorts
- Steady state Cmin above target effective concentration (TEC) in all patients with mean fold Cmin/TEC 7.12 and 55.88 at 10 mg and 140 mg QD, respectively

AUC, area under the curve; TEC, target effective concentration; TEC: IC95 in DLD-1 BRAC2-/-

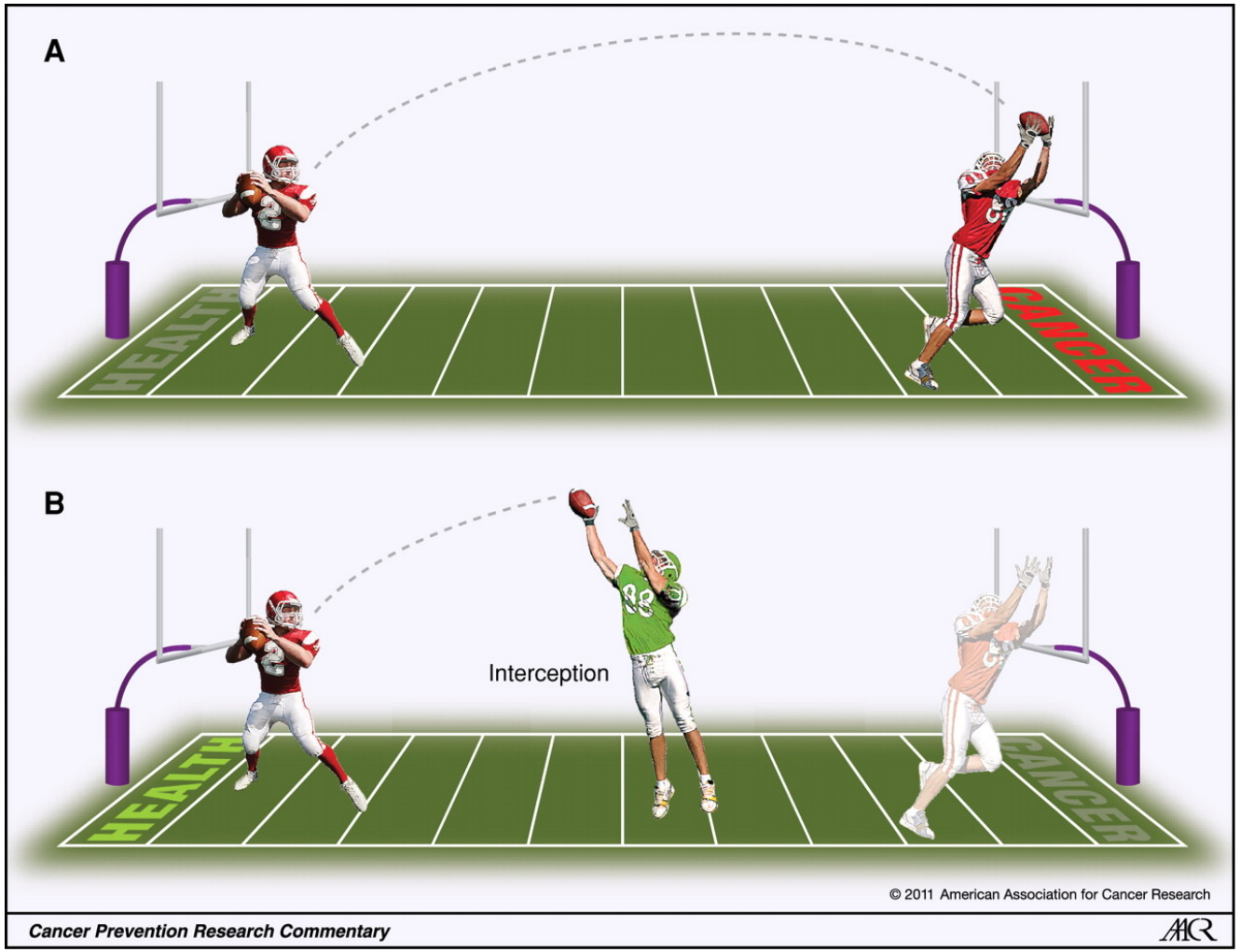
Results: Overall Safety Summary

AE category, n (%)	AZD5305 10 mg QD (n=8)	AZD5305 20 mg QD (n=19)	AZD5305 40 mg QD (n=17)	AZD5305 60 mg QD (n=10)	AZD5305 90 mg QD (n=3)	AZD5305 140 mg QD (n=4)	Total (N=61)
Duration of therapy (months), median (range)	4.8 (1.8-14.9)	2.8 (0.9-11.5)	2.0 (0.4-9.6)	1.95 (0-3.8)	4.8 (4.6-4.9)	0.7 (0.6-1.6)	2.1 (0-14.9)
All TEAEs	8 (100.0)	19 (100.0)	17 (100.0)	8 (80.0)	3 (100.0)	0	55 (90.2)
Grade ≥3 AEs	3 (37.5)	10 (52.6)	6 (35.3)	3 (30.0)	2 (66.7)	0	24 (39.3)
Serious TEAEs	0	9 (47.4)	5 (29.4)	2 (20.0)	0	0	16 (26.2)
Discontinuations	0	0	0	1 (10.0)	0	0	1 (1.6)
Dose reductions	1 (12.5)	0	1 (5.9)	0	0	0	2 (3.3)
AZD5305-related TEAEs	5 (62.5)	11 (57.9)	9 (52.9)	4 (40.0)	3 (100.0)	0	32 (52.5)
Grade ≥3 AEs	3 (37.5)	3 (15.8)	1 (5.9)	0	2 (66.7)	0	9 (14.8)
Serious TEAEs	0	0	0	0	0	0	0
Discontinuations	0	0	0	0	0	0	0
Dose reductions	1 (12.5)	0	1 (5.9)	0	0	0	2 (3.3)

- AZD5305 was well tolerated across doses
- Only 2 patients (3.3%) had dose reductions (for grade 3 neutropenia and grade 1 thrombocytopenia related to AZD5305)
- At DCO there have been no DLTs and no AZD5305-related serious AEs or treatment discontinuations

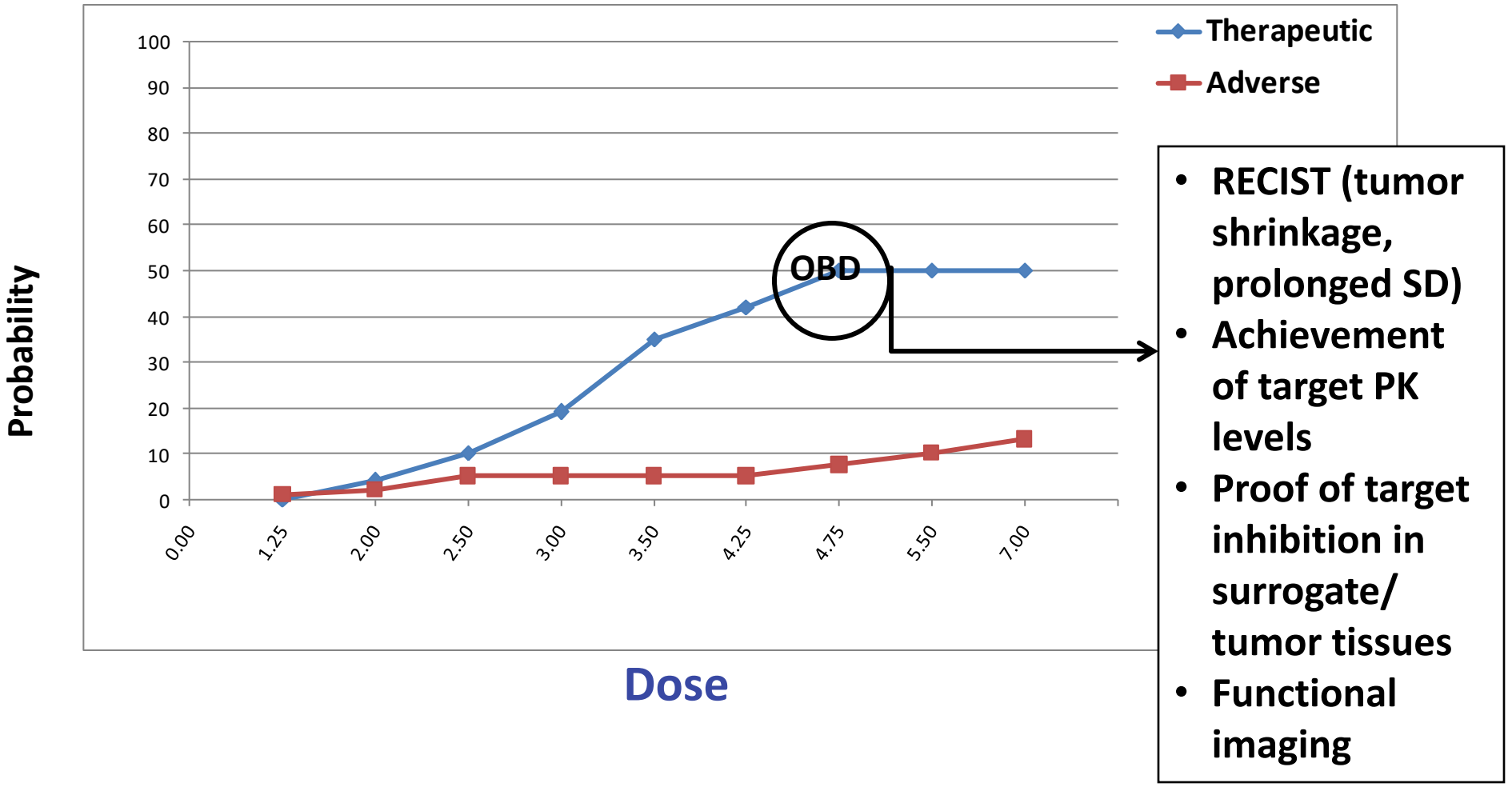
DLT, dose-limiting toxicity; TEAE, treatment emergent adverse event

Cancer Interception



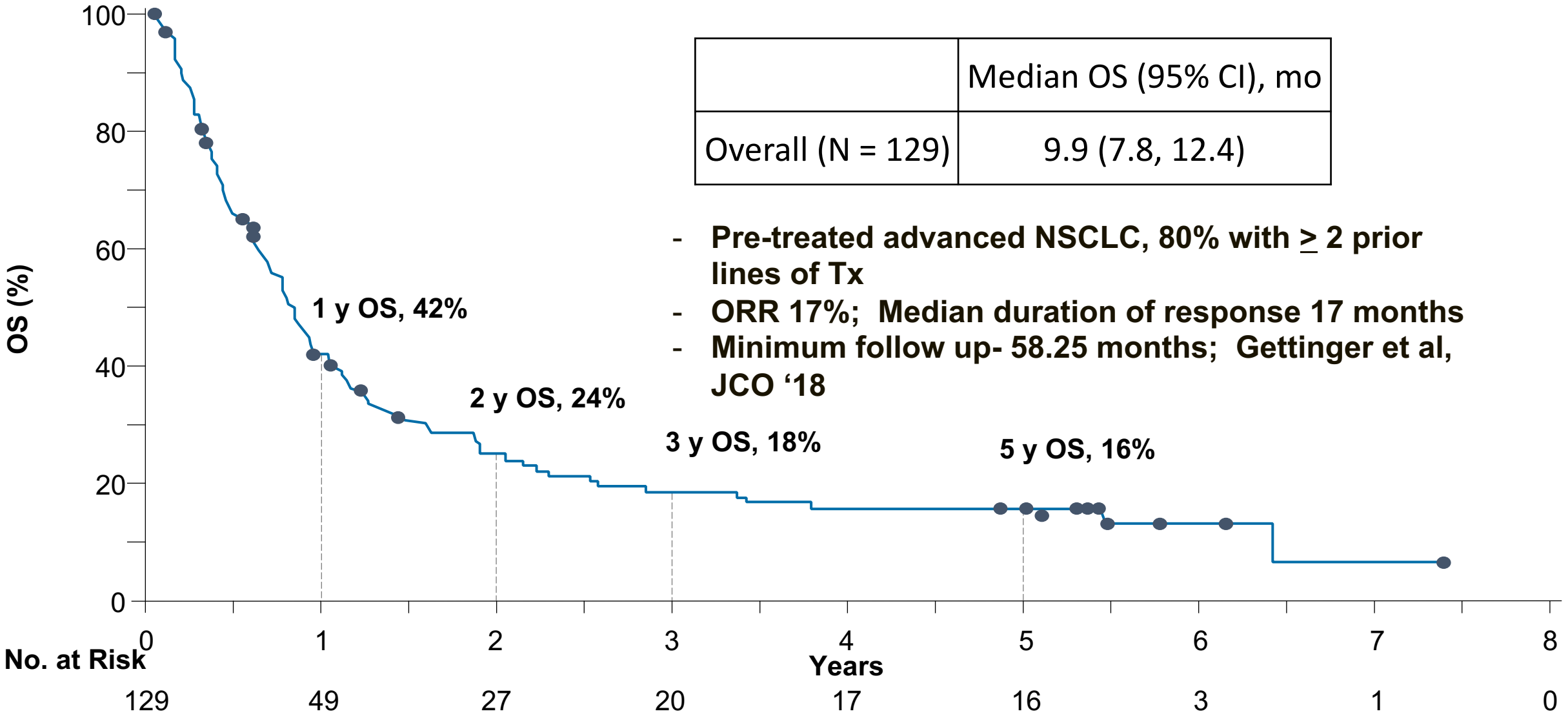
Blackburn. *Cancer Prev Res*. 2011;4(6):787-792.

Dose-Response: Efficacy and Toxicity



Earlier Intervention

CA209-003, Salvage Nivolumab for Adv NSCLC



	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

- **Pre-treated advanced NSCLC, 80% with ≥ 2 prior lines of Tx**
- **ORR 17%; Median duration of response 17 months**
- **Minimum follow up- 58.25 months; Gettinger et al, JCO '18**

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Gettinger et al, J Clin Oncol 2018

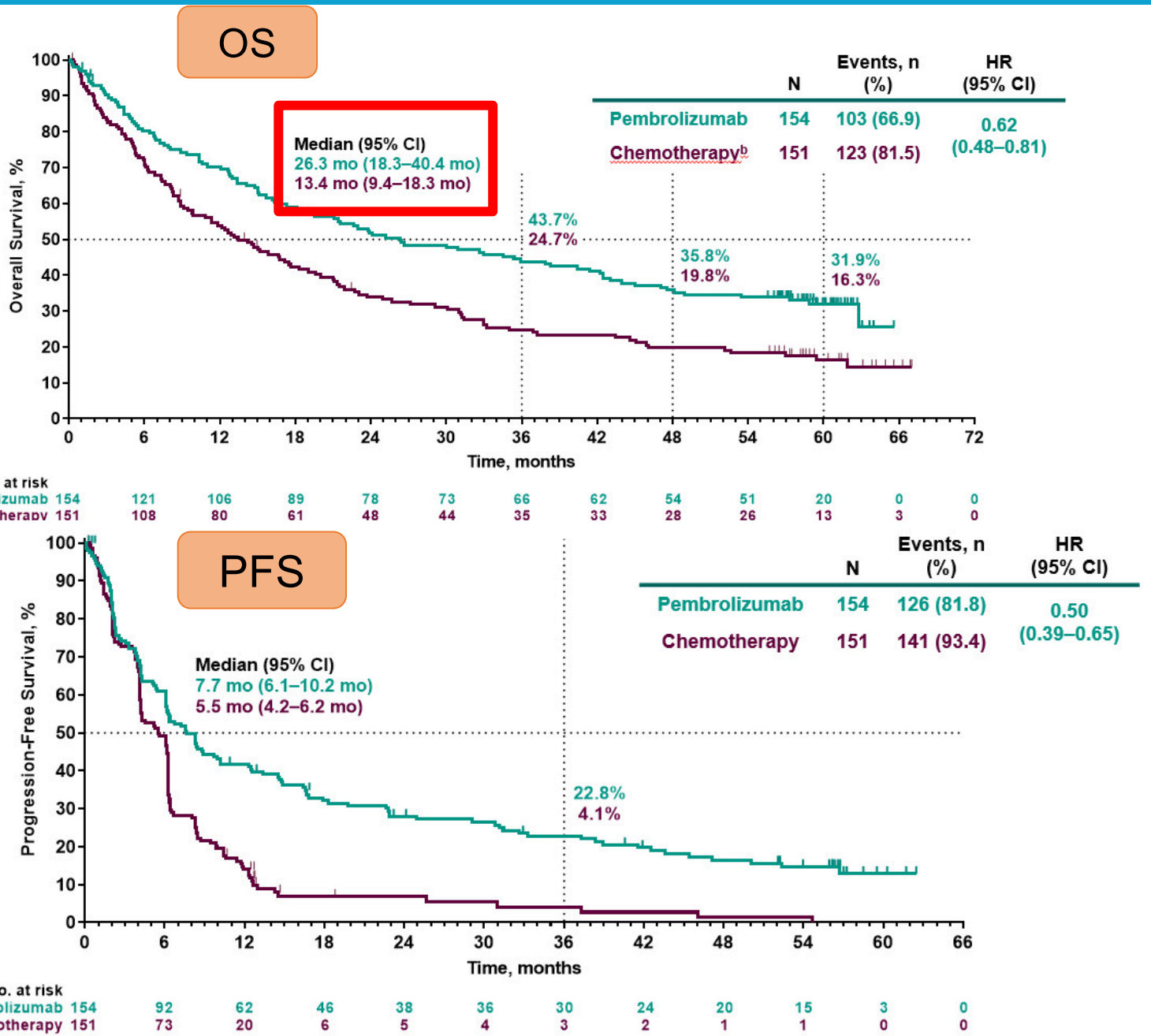
Keynote 24- Front Line

(biomarker driven)

5 year OS:
Median
26.3 mo (18.3-40.4 mo) 31.9% vs.
13.4 mo (94-18.3 mo) 16.3%
HR: 0.62 (0.48-0.81)

3 Year PFS:
Median
7.7 mo (6.1-10.2 mos) 22.8% vs.
5.5 mo (4.2-6.2 mo) 4.1%
HR: 0.50 (0.39-0.65)

Overall Response Rate:
46.1% vs. 31.1%
Partial Response:
41.6% vs. 31.1%
Complete Response:
4.5% vs. 0



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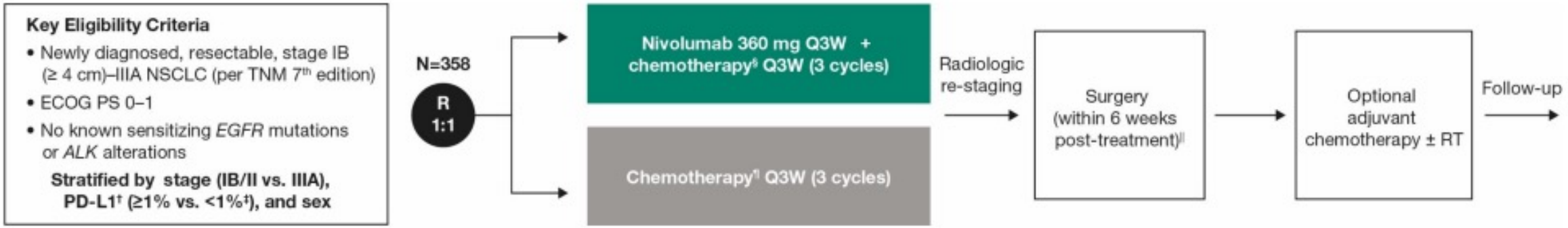
J.R. Brahmer KEYNOTE-024 *ESMO 2020: LBA 51*

CHECKPOINT 816 STUDY DESIGN

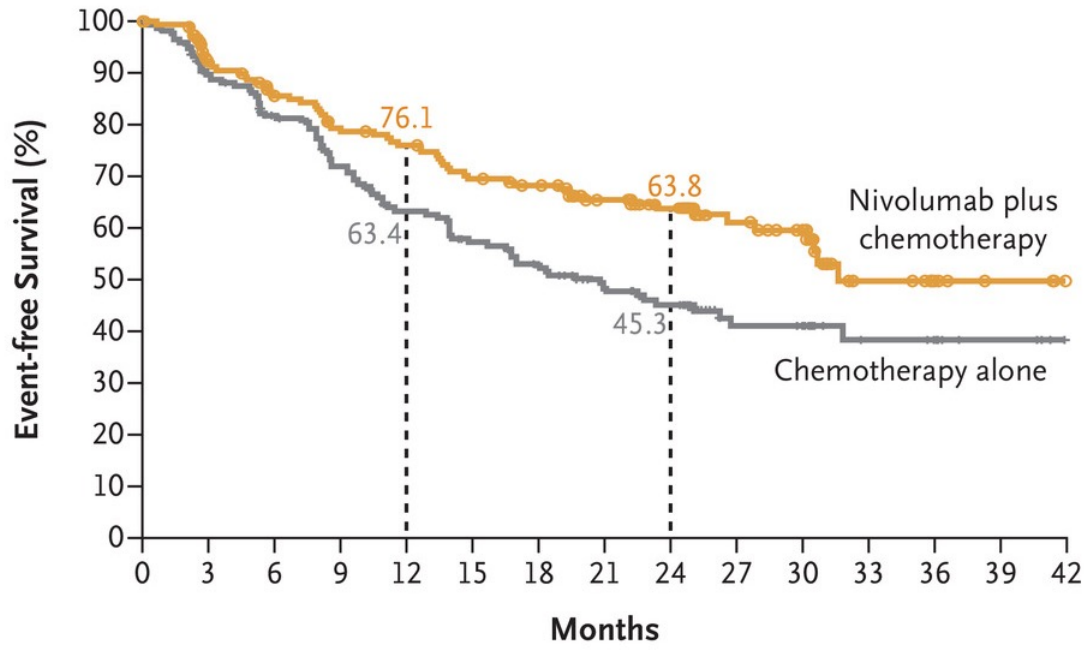


Primary Endpoints
- pCR by BIPR
- EFS by BICR

Key Secondary Endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key Exploratory Endpoints Included
- ORR by BICR
- Feasibility of surgery; peri- and post-operative surgery-related AEs
- Predictive biomarkers (PD-L1, TMB, ctDNA**)

EVENT-FREE SURVIVAL ACCORDING TO BLINDED INDEPENDENT CENTRAL REVIEW



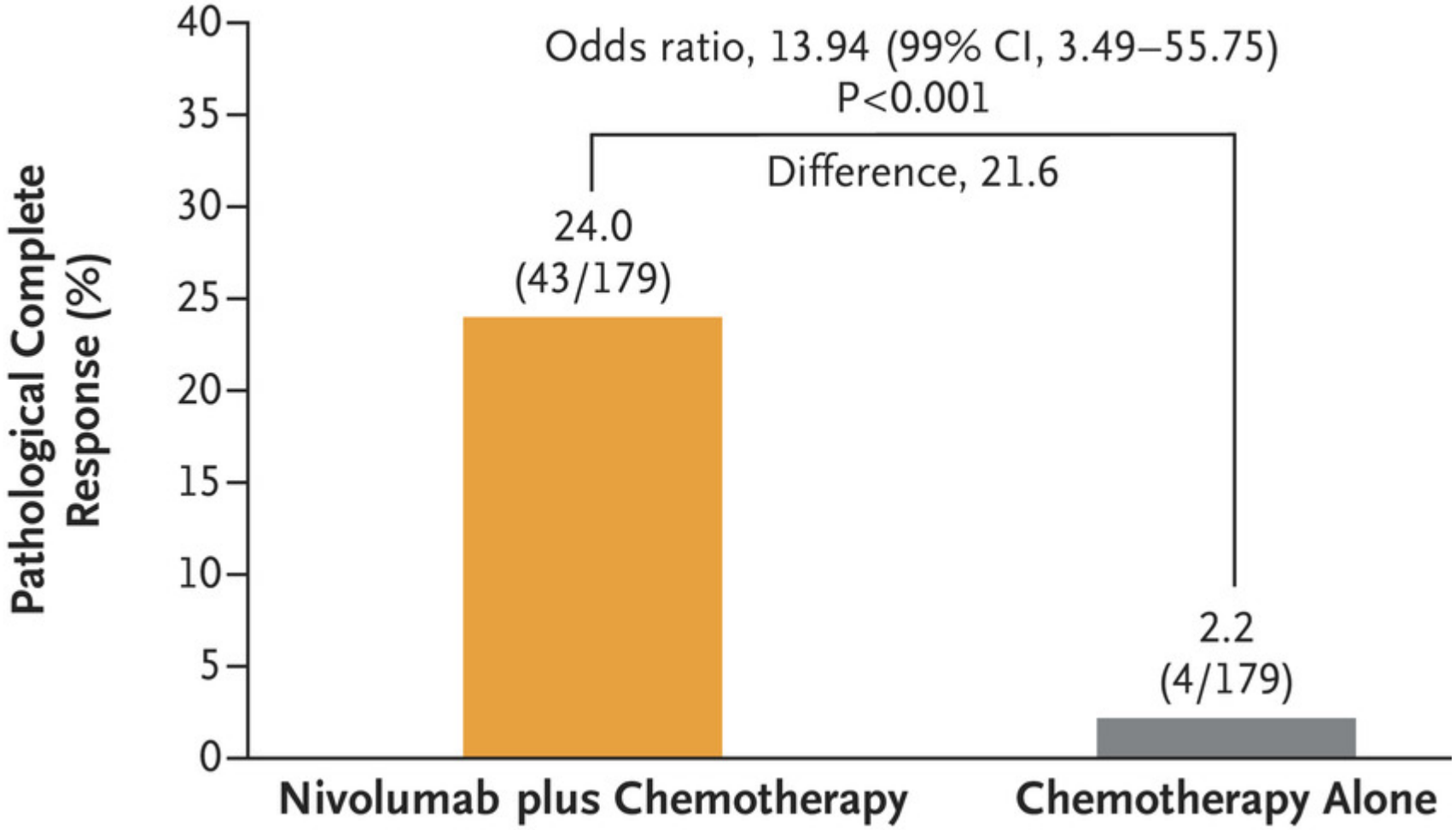
	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

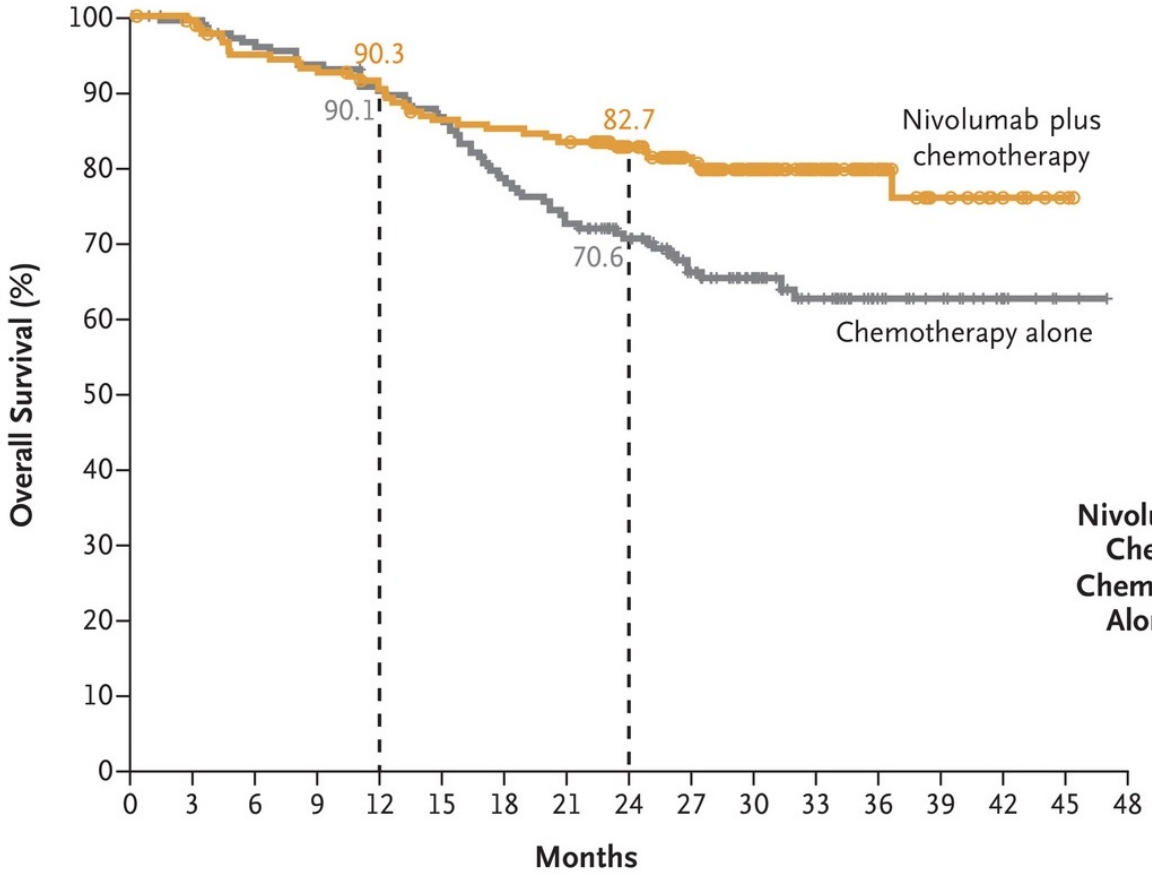
No. at Risk

Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

PATHOLOGICAL COMPLETE RESPONSE ACCORDING TO BLINDED INDEPENDENT PATHOLOGICAL REVIEW



OVERALL SURVIVAL



	No. of Patients	Median Overall Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	NR (NR–NR)
Chemotherapy Alone	179	NR (NR–NR)

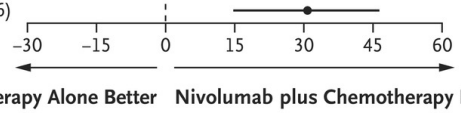
Hazard ratio for death, 0.57 (99.67% CI, 0.30–1.07)
P=0.008

No. at Risk

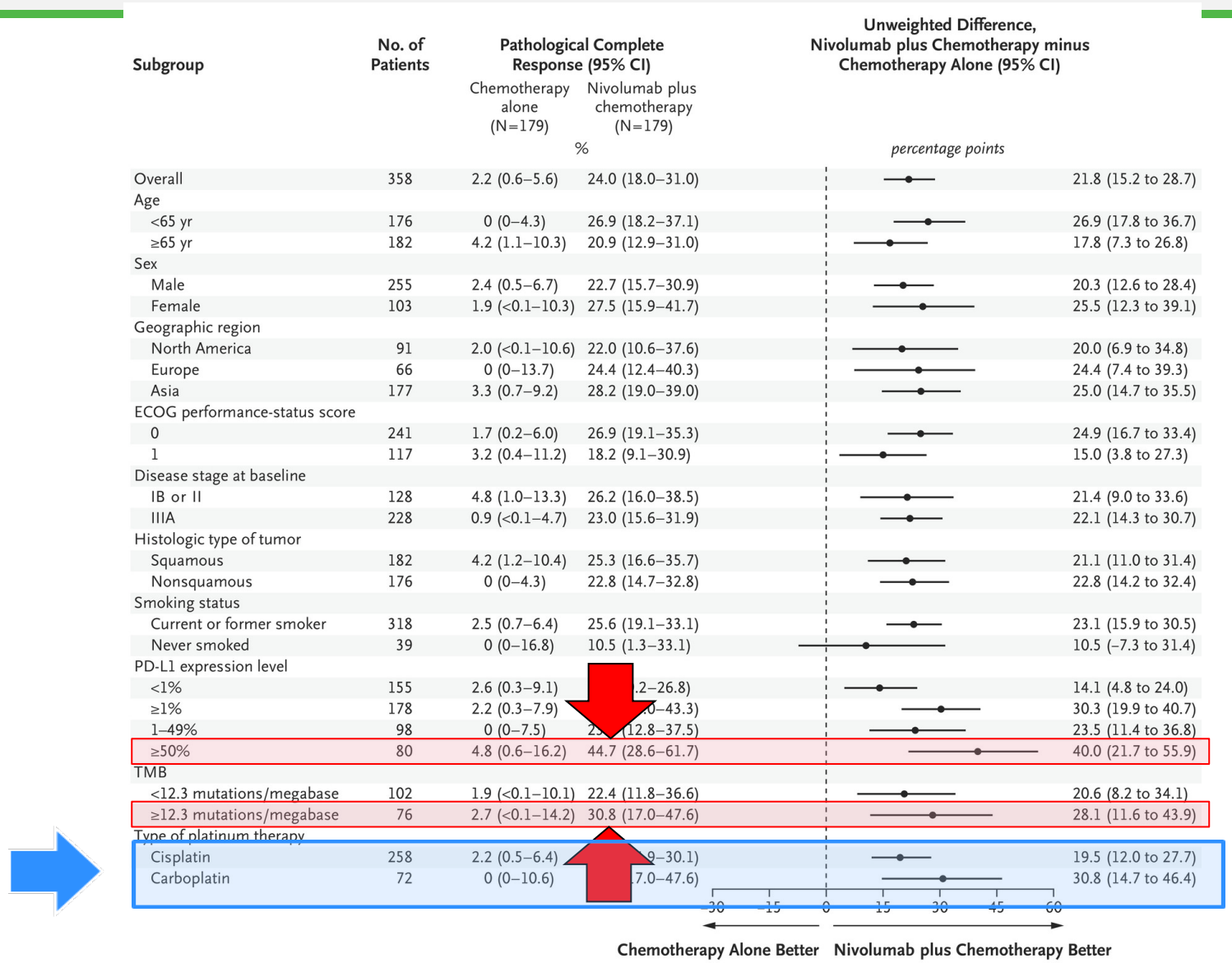
Nivolumab plus chemotherapy	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemotherapy alone	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

PATHOLOGICAL COMPLETE RESPONSE ACCORDING TO BLINDED INDEPENDENT PATHOLOGICAL REVIEW

Subgroup	No. of Patients	Pathological Complete Response (95% CI)		Unweighted Difference, Nivolumab plus Chemotherapy minus Chemotherapy Alone (95% CI)
		Chemotherapy alone (N=179)	Nivolumab plus chemotherapy (N=179)	
		%		*percentage points*
Overall	358	2.2 (0.6–5.6)	24.0 (18.0–31.0)	21.8 (15.2 to 28.7)
Age				
<65 yr	176	0 (0–4.3)	26.9 (18.2–37.1)	26.9 (17.8 to 36.7)
≥65 yr	182	4.2 (1.1–10.3)	20.9 (12.9–31.0)	17.8 (7.3 to 26.8)
Sex				
Male	255	2.4 (0.5–6.7)	22.7 (15.7–30.9)	20.3 (12.6 to 28.4)
Female	103	1.9 (<0.1–10.3)	27.5 (15.9–41.7)	25.5 (12.3 to 39.1)
Geographic region				
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)	20.0 (6.9 to 34.8)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)	24.4 (7.4 to 39.3)
Asia	177	3.3 (0.7–9.2)	28.2 (19.0–39.0)	25.0 (14.7 to 35.5)
ECOG performance-status score				
0	241	1.7 (0.2–6.0)	26.9 (19.1–35.3)	24.9 (16.7 to 33.4)
1	117	3.2 (0.4–11.2)	18.2 (9.1–30.9)	15.0 (3.8 to 27.3)
Disease stage at baseline				
IB or II	128	4.8 (1.0–13.3)	26.2 (16.0–38.5)	21.4 (9.0 to 33.6)
IIIA	228	0.9 (<0.1–4.7)	23.0 (15.6–31.9)	22.1 (14.3 to 30.7)
Histologic type of tumor				
Squamous	182	4.2 (1.2–10.4)	25.3 (16.6–35.7)	21.1 (11.0 to 31.4)
Nonsquamous	176	0 (0–4.3)	22.8 (14.7–32.8)	22.8 (14.2 to 32.4)
Smoking status				
Current or former smoker	318	2.5 (0.7–6.4)	[illegible]9.1–33.1)	23.1 (15.9 to 30.5)
Never smoked	39	0 (0–16.8)	[illegible]3.3–33.1)	10.5 (–7.3 to 31.4)
PD-L1 expression level				
<1%	155	2.6 (0.3–9.1)	16.7 (9.2–26.8)	14.1 (4.8 to 24.0)
≥1%	178	2.2 (0.3–7.9)	32.6 (23.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23.5 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)
TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)
Type of platinum therapy				
Cisplatin	258	2.2 (0.5–6.4)	[illegible]9–30.1)	19.5 (12.0 to 27.7)
Carboplatin	72	0 (0–10.6)	[illegible]7.0–47.6)	30.8 (14.7 to 46.4)



PATHOLOGICAL COMPLETE RESPONSE ACCORDING TO BLINDED INDEPENDENT PATHOLOGICAL REVIEW



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Geographic region				
North America	91	2.0 (<0.1–10.6)	22.0 (10.6–37.6)	20.0 (6.9 to 34.8)
Europe	66	0 (0–13.7)	24.4 (12.4–40.3)	24.4 (7.4 to 39.3)
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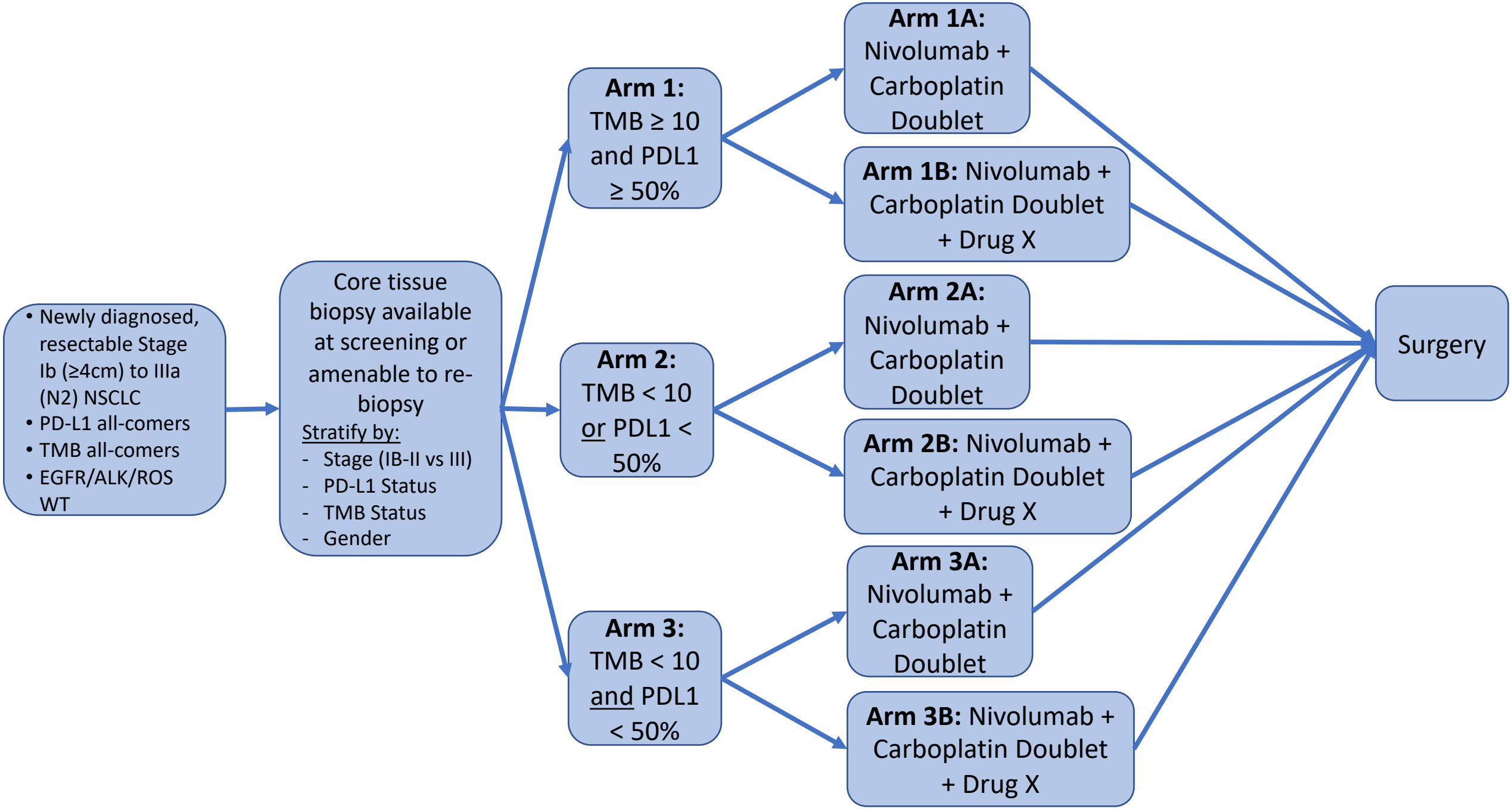
≥1%	178	2.2 (0.3–7.9)	.0–43.3)	30.3 (19.9 to 40.7)
1–49%	98	0 (0–7.5)	23 (12.8–37.5)	23.5 (11.4 to 36.8)
≥50%	80	4.8 (0.6–16.2)	44.7 (28.6–61.7)	40.0 (21.7 to 55.9)
TMB				
<12.3 mutations/megabase	102	1.9 (<0.1–10.1)	22.4 (11.8–36.6)	20.6 (8.2 to 34.1)
≥12.3 mutations/megabase	76	2.7 (<0.1–14.2)	30.8 (17.0–47.6)	28.1 (11.6 to 43.9)
Type of platinum therapy				
Cisplatin	258	2.2 (0.5–6.4)	.9–30.1)	19.5 (12.0 to 27.7)
Carboplatin	72	0 (0–10.6)	.7.0–47.6)	30.8 (14.7 to 46.4)

Forde et al. NEJM. 2022;386(21):1973-1985

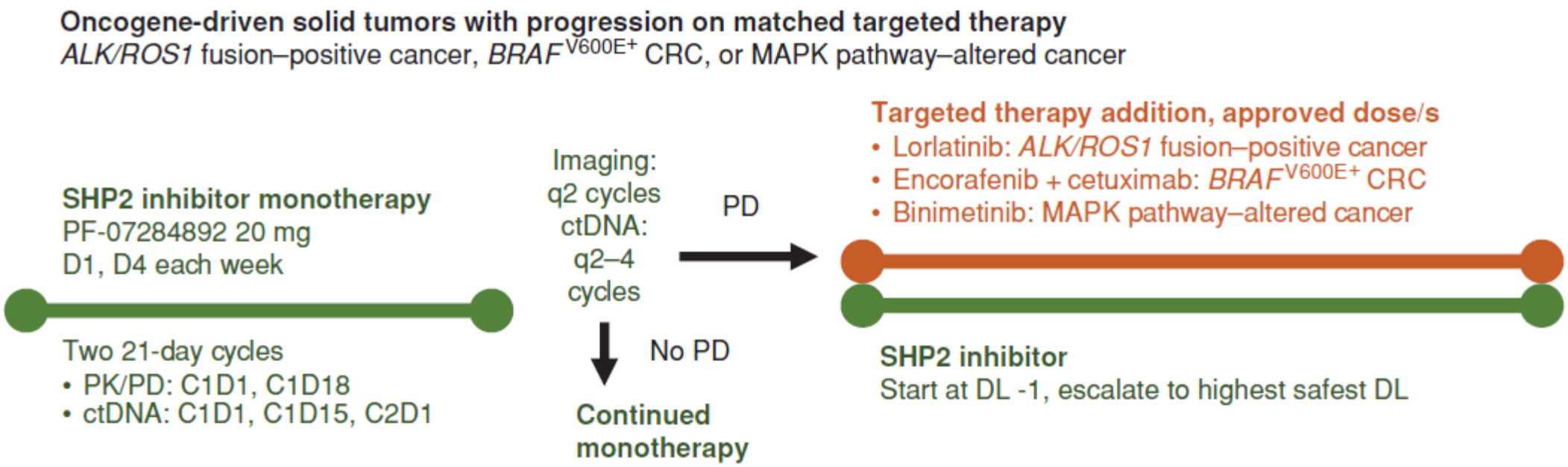

• Newly diagnosed, resectable Stage Ib (≥4cm) to IIIa (N2) NSCLC
• PD-L1 all-comers
• TMB all-comers
• EGFR/ALK/ROS WT
Core tissue biopsy available at screening or amenable to re-biopsy
Stratify by:
- Stage (IB-II vs III)
- PD-L1 Status
- TMB Status
- Gender
Arm 1: TMB ≥ 10 and PDL1 ≥ 50%
Arm 2: TMB < 10 or PDL1 < 50%
Arm 3: TMB < 10 and PDL1 < 50%
Arm 1A: Nivolumab + Carboplatin Doublet
Arm 1B: Nivolumab + Carboplatin Doublet + Drug X
Arm 2A: Nivolumab + Carboplatin Doublet
Arm 2B: Nivolumab + Carboplatin Doublet + Drug X
Arm 3A: Nivolumab + Carboplatin Doublet
Arm 3B: Nivolumab + Carboplatin Doublet + Drug X
Surgery

RESEARCH BRIEF

SHP2 Inhibition Sensitizes Diverse Oncogene-Addicted Solid Tumors to Re-treatment with Targeted Therapy

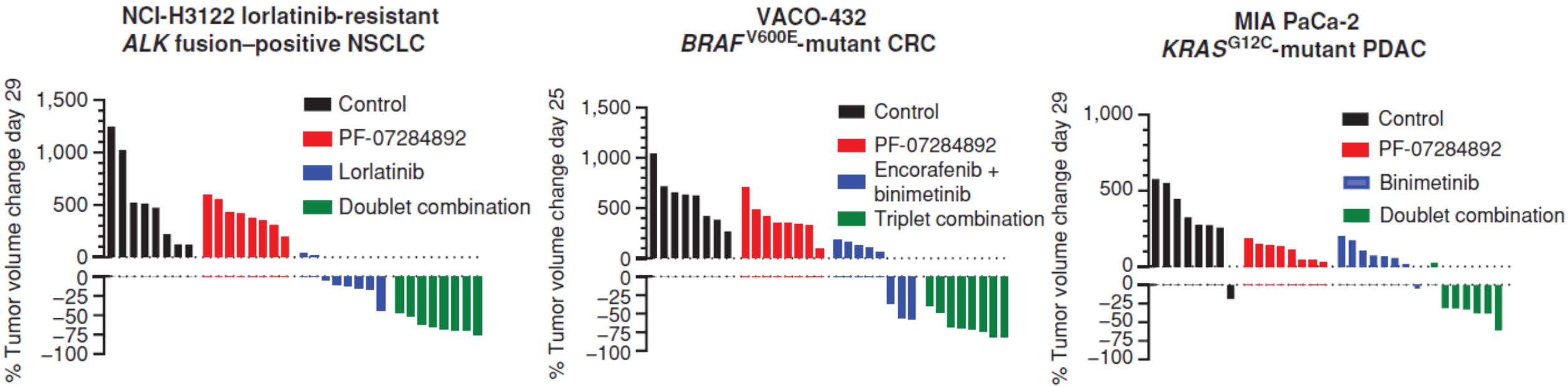
Alexander Drilon[1], Manish R. Sharma[2], Melissa L. Johnson[3], Timothy A. Yap[4], Shirish Gadgeel[5], Dale Nepert[6], Gang Feng[7], Micaela B. Reddy[6], Allison S. Harney[6], Mohamed Elsayed[6], Adam W. Cook[6], Christina E. Wong[6], Ronald J. Hinklin[6], Yutong Jiang[6], Eric N. Brown[6], Nickolas A. Neitzel[6], Ellen R. Laird[6], Wen-I Wu[6], Anurag Singh[6], Ping Wei[8], Keith A. Ching[8], John J. Gaudino[6], Patrice A. Lee[6], Dylan P. Hartley[6], and S. Michael Rothenberg[6,8]

SHP2 inhibitor PF-07284892 Phase I Study Schema



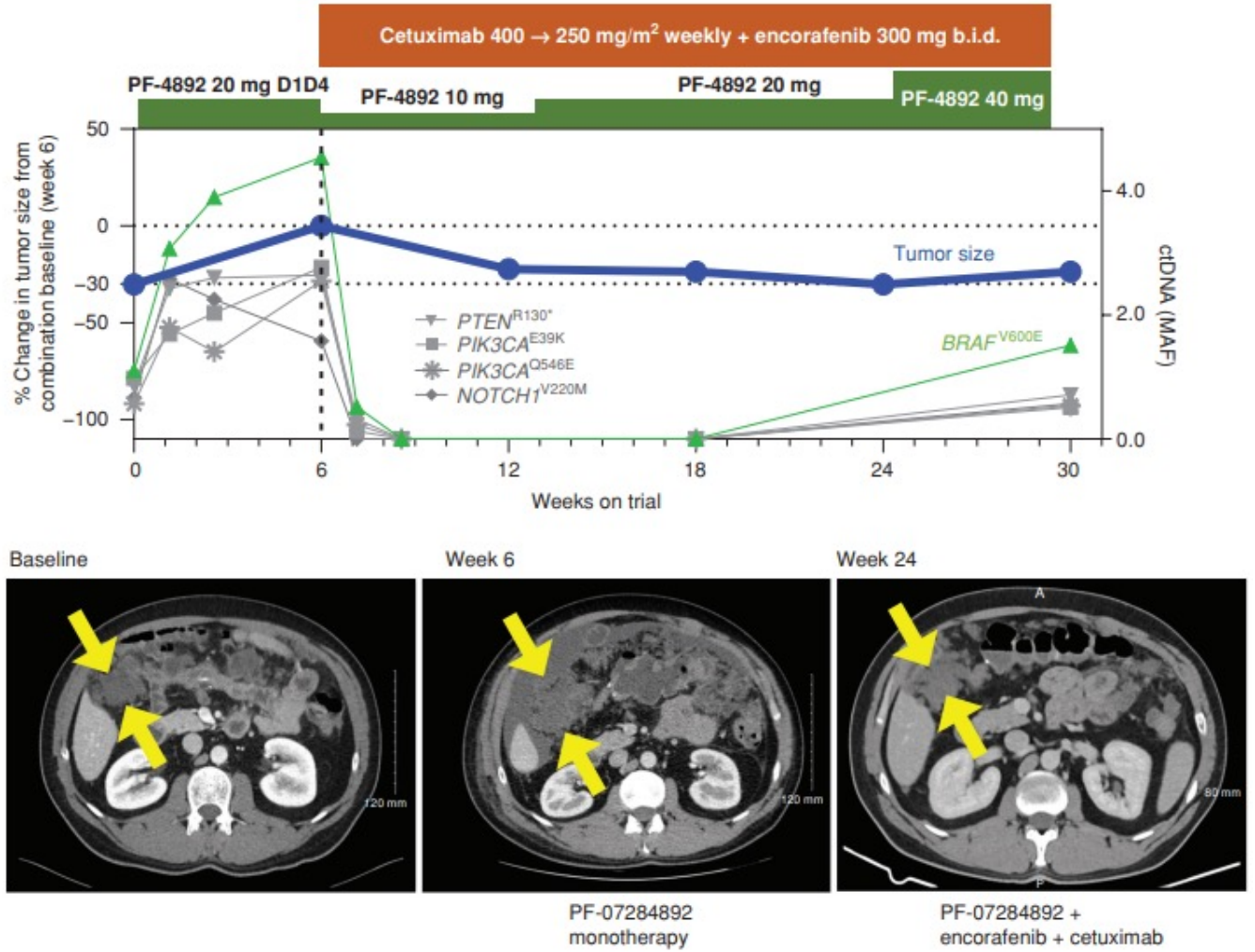
Drilon et al. *Cancer Discov.* 2023;13:1789–801

PF-07284892 *In Vitro* Efficacy



Drilon et al. *Cancer Discov.* 2023;13:1789–801

PF-07284892 overcomes intrinsic resistance to encorafenib + cetuximab in a BRAFV600E-mutant CRC patient



Drilon et al. *Cancer Discovery*. 2023. 1789

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Novel Technologies

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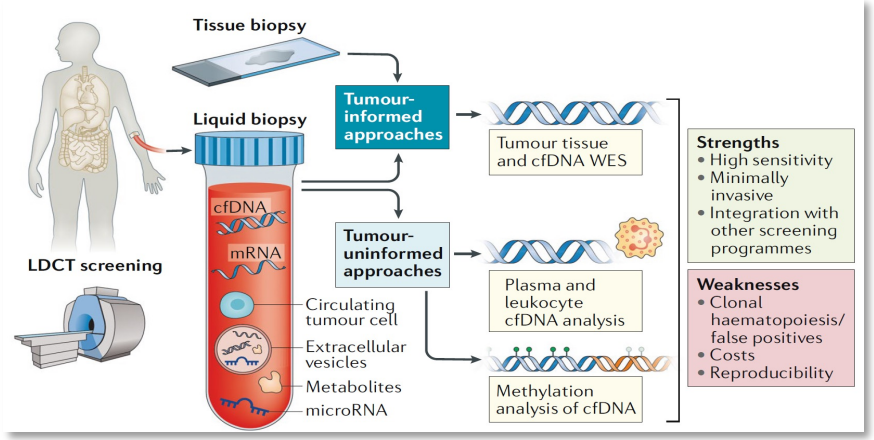
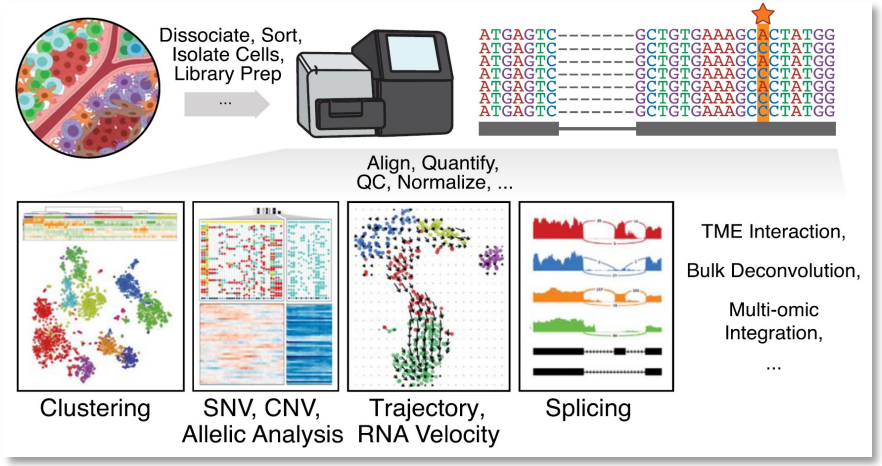
Liquid biopsy



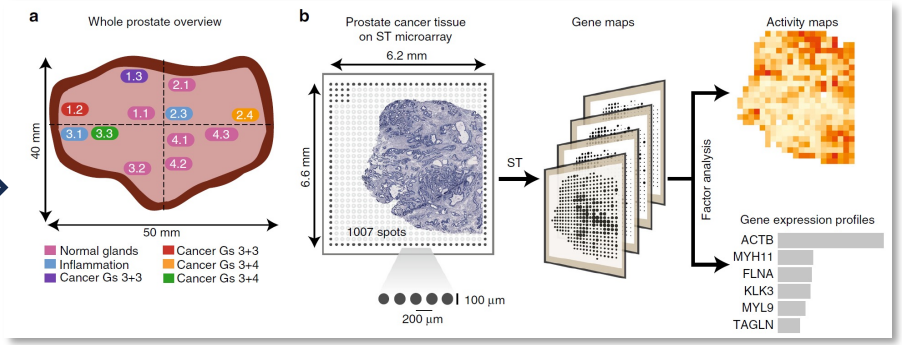
Rolfo and Russo., 2020. Nature Reviews Clinical Oncology

Single-cell transcriptomics



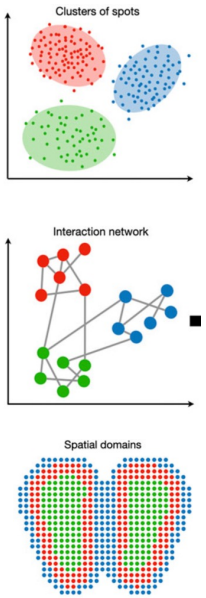
Fan et al., 2020. Experimental & Molecular Medicine volume

Spatial transcriptomics & proteomics



Berglund et al., 2080. Nature Communications

Advanced integrative computational analysis & AI



nature medicine

Article

https://doi.org/10.1038/s41591-023-02399-0

Camonsertib in DNA damage response-deficient advanced solid tumors: phase 1 trial results

Received: 14 October 2022

Accepted: 12 May 2023

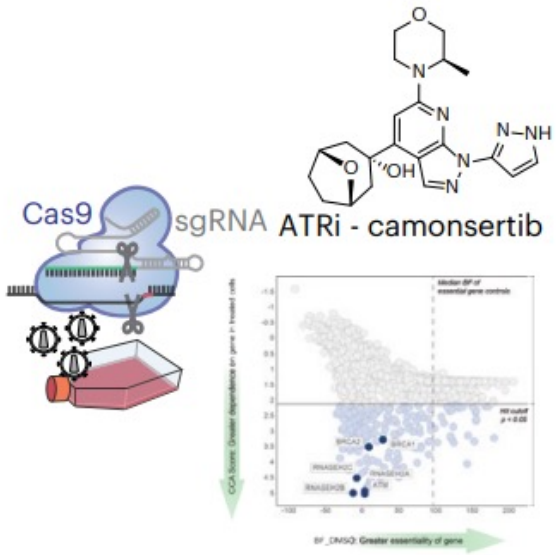
Published online: 5 June 2023

Check for updates

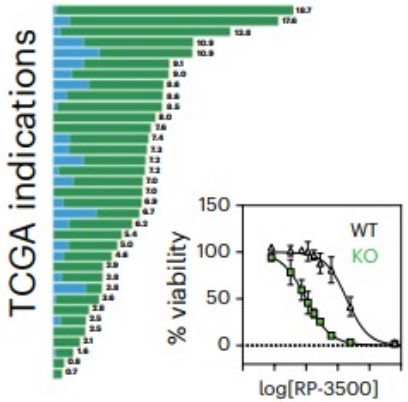
Timothy A. Yap[1], Elisa Fontana[2], Elizabeth K. Lee[3], David R. Spigel[4], Martin Højgaard[5], Stephanie Lheureux[6], Niharika B. Mettu[7], Benedito A. Carneiro[8], Louise Carter[9], Ruth Plummer[10], Gregory M. Cote[11], Funda Meric-Bernstam[1], Joseph O'Connell[12], Joseph D. Schonhoft[12], Marisa Wainszelbaum[12], Adrian J. Fretland[12], Peter Manley[12,15], Yi Xu[12], Danielle Ulanet[12], Victoria Rimkunas[12], Mike Zinda[12], Maria Koehler[12], Ian M. Silverman[12], Jorge S. Reis-Filho[13] & Ezra Rosen[14]

SNIPRx CRISPR–Cas9-enabled chemogenomic screen to identify ATRi-sensitizing and synthetic lethal alterations for patient selection

Chemogenomic CRISPR screen to identify synthetic lethal gene LoF



Cancer prevalence, experimental validation and biomarker feasibility



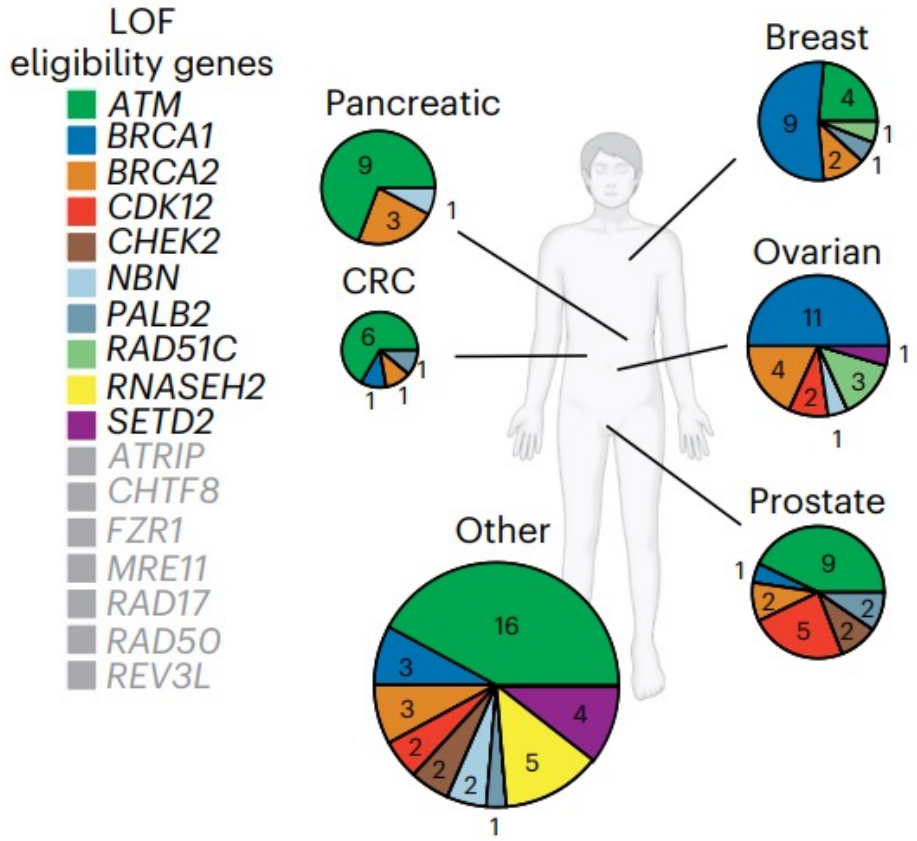
List of prioritized gene alterations

Patients with advanced or metastatic solid tumors with LoF in the following genes: *ATM, ATRIP, BRCA1, BRCA2, CDK12, CHTF8, FZR1, MRE11, NBN, PALB2, RAD17, RAD50, RAD51B/C/D, REV3L, RNASEH2A/B or SETD2*

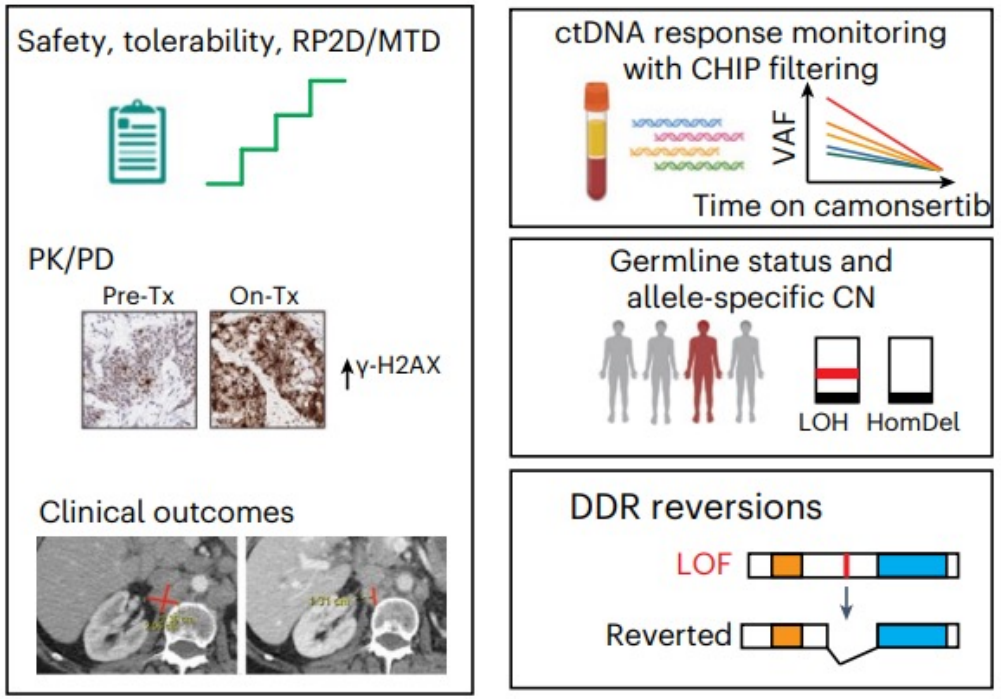
Yap et al. *Nature Medicine*. Vol 29. June 2023

Patient enrollment by gene and tumor type and overview of pre-planned analyses

TRESR enrollment for camonsertib monotherapy based on CRISPR screen (*n* = 120)

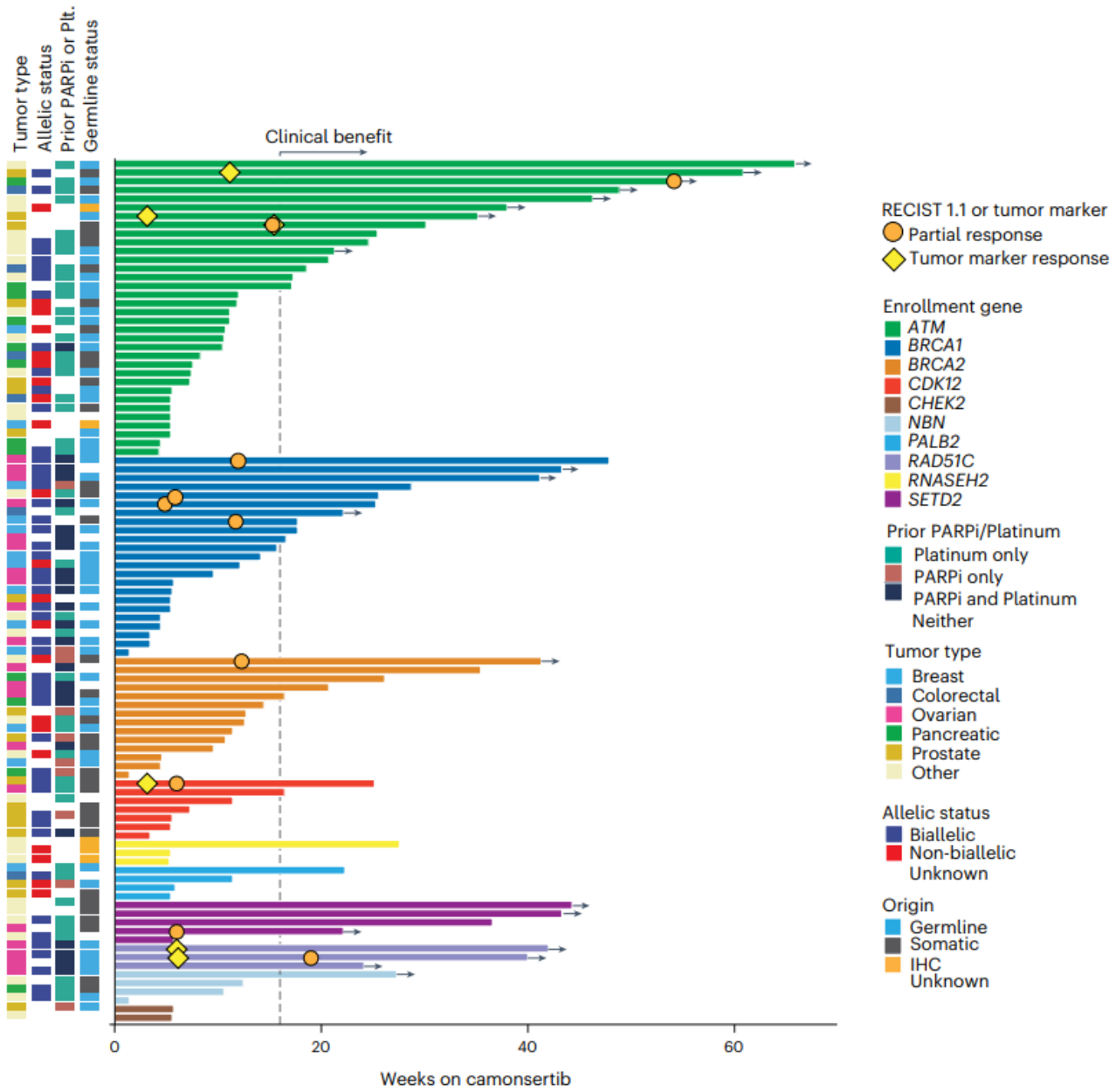


Phase 1 objectives and pre-planned genomic analysis



Yap et al. *Nature Medicine*. Vol 29. June 2023

Clinical outcomes in TRESR: Duration of treatment by genotype



Yap et al. *Nature Medicine*. Vol 29. June 2023

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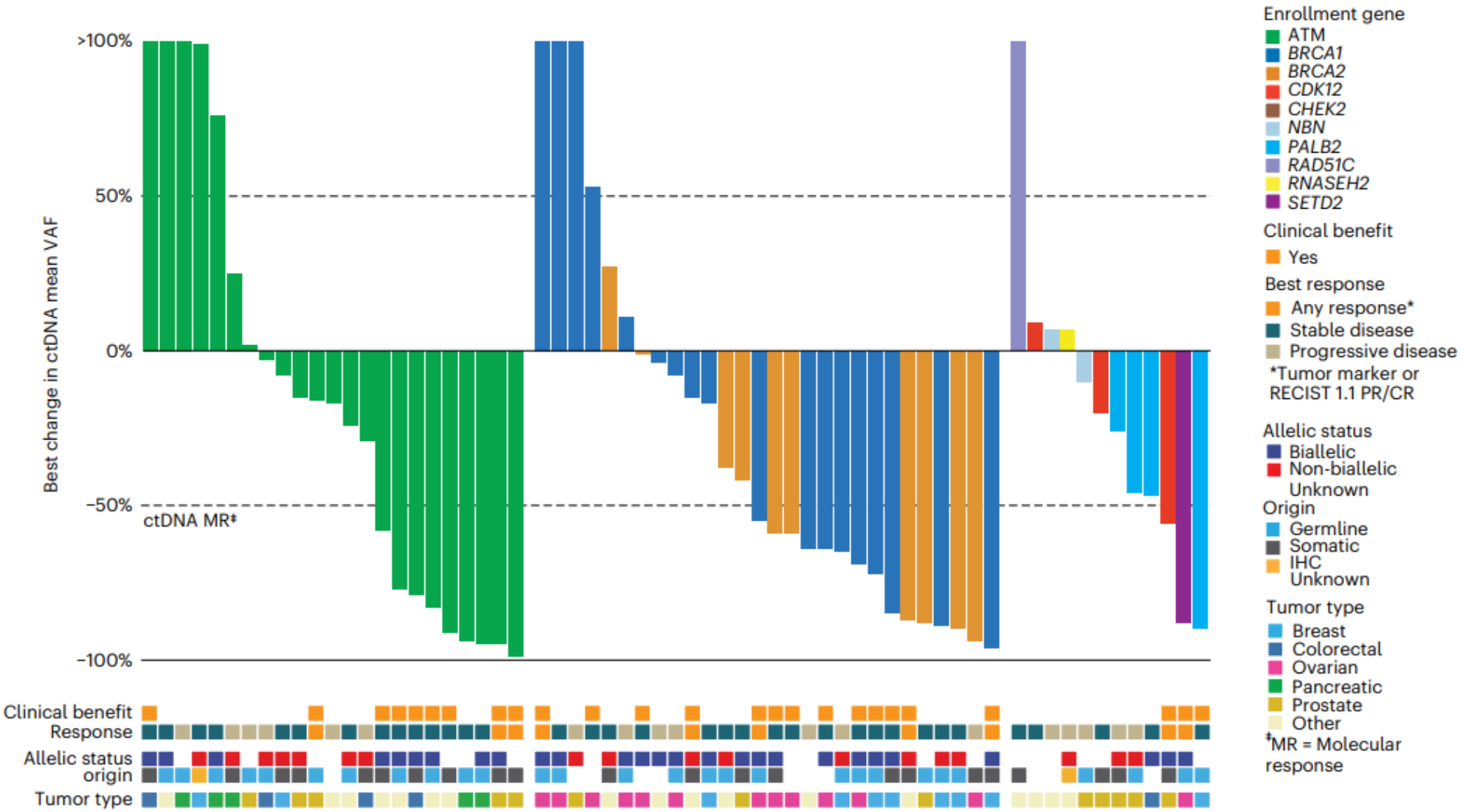
ctDNA MRs in TRESR: Best ctDNA response by enrollment gene



Yap et al. *Nature Medicine*. Vol 29. June 2023

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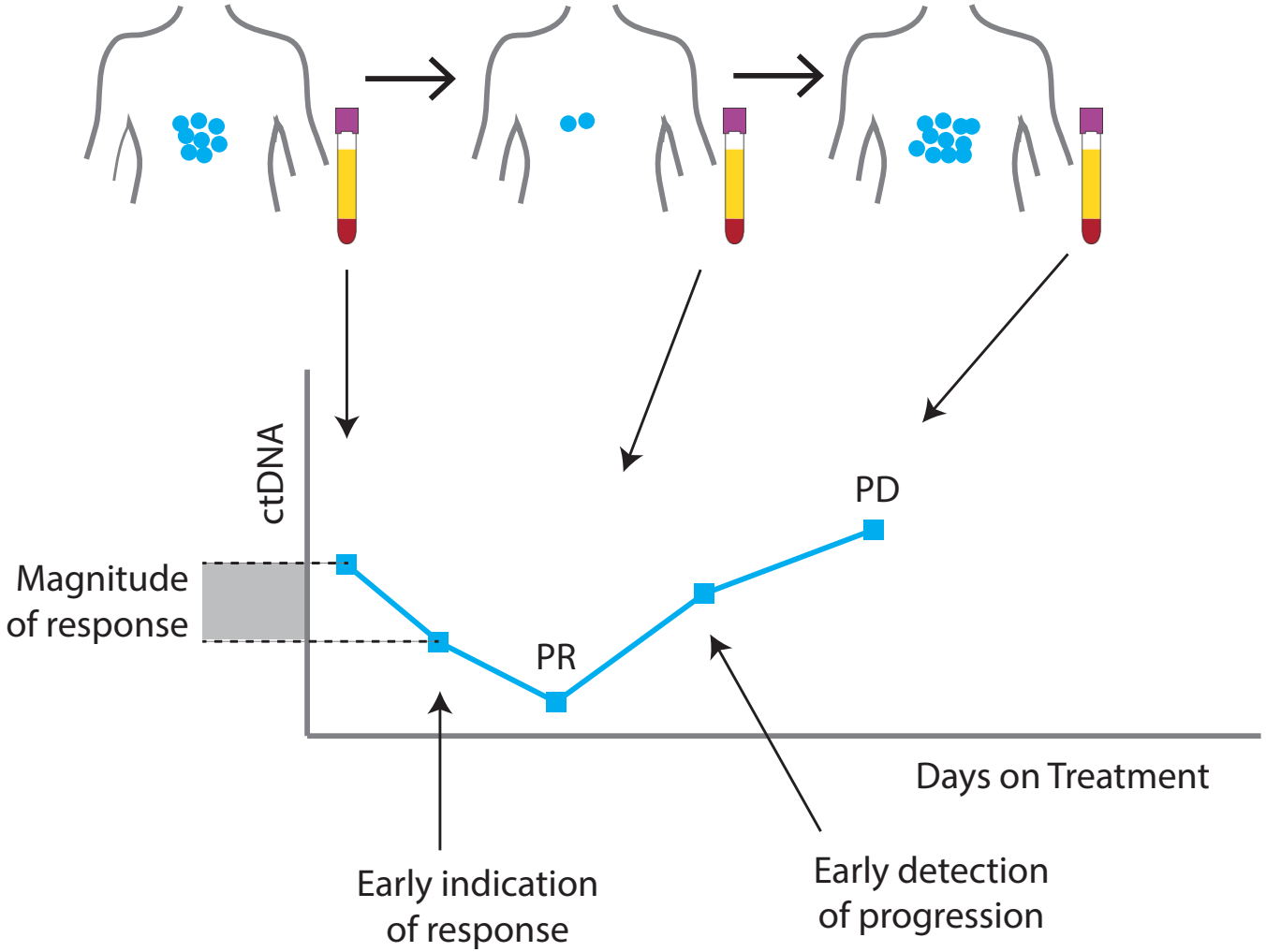
Can we monitor metastatic cancer patients more frequently than every two months using a ctDNA blood test?



What would it need to be?

- A pan-cancer treatment monitoring test
- Weekly testing
- Low cost, fast turnaround
- Low sample requirement
- Logistically straightforward

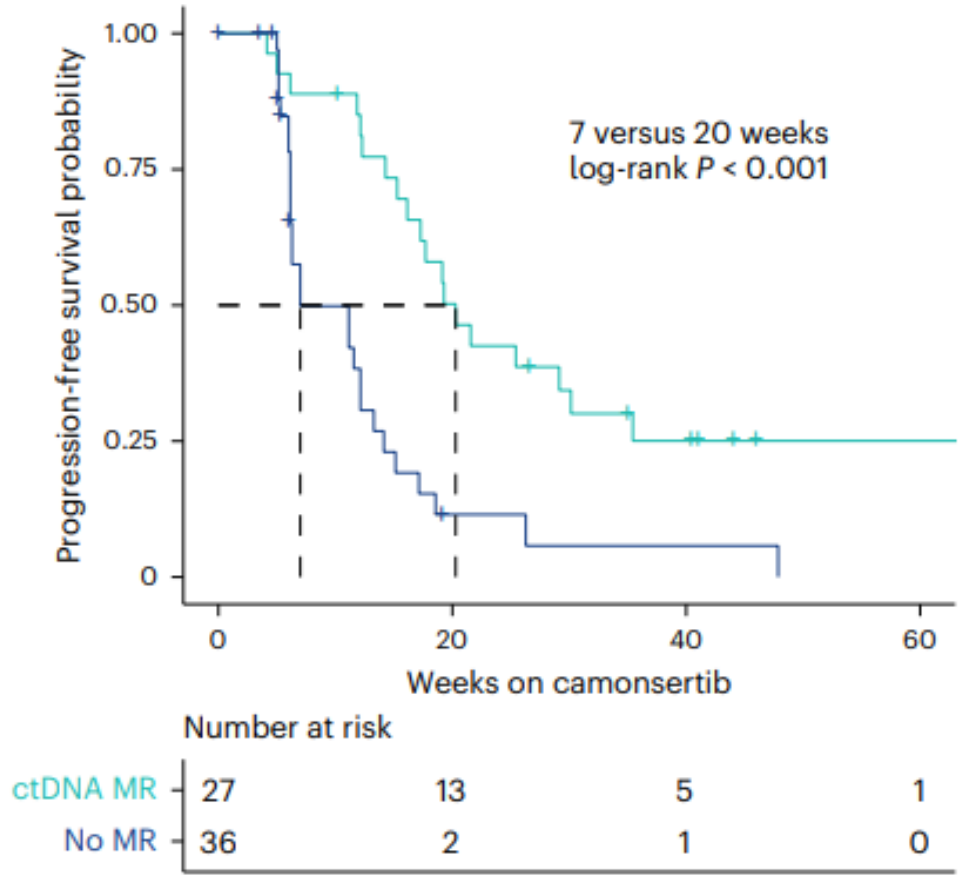
Why do we need it?

- To individualize treatment decisions for each patient in real-time
- To improve clinical trial design and read-out, move away from average response across a group of patients

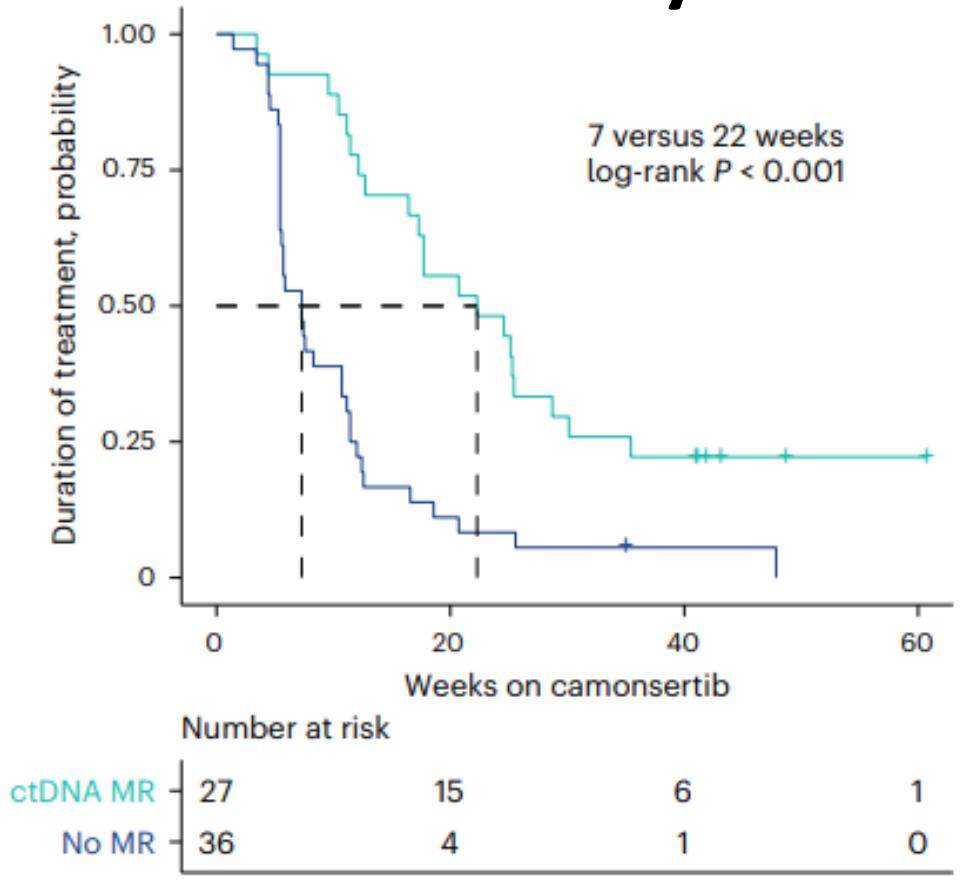
Budhraja et al. Science Translational Medicine 2023 – Murtaza Lab

ctDNA MRs in TRESR: PFS and DOT

PFS



DOT by MR



Yap et al. *Nature Medicine*. Vol 29. June 2023

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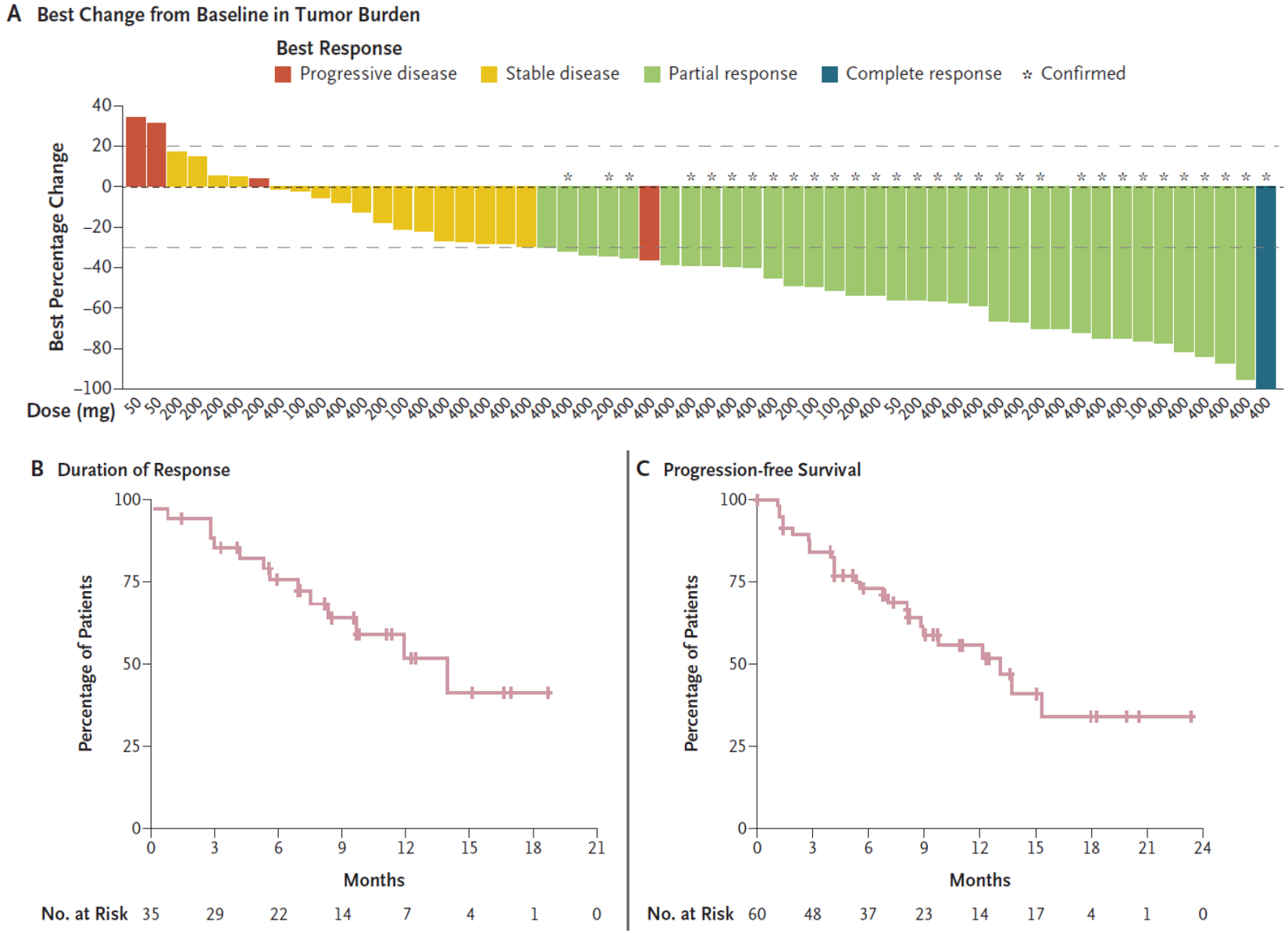
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Single-Agent Divarasib (GDC-6036) in Solid Tumors with a *KRAS* G12C Mutation

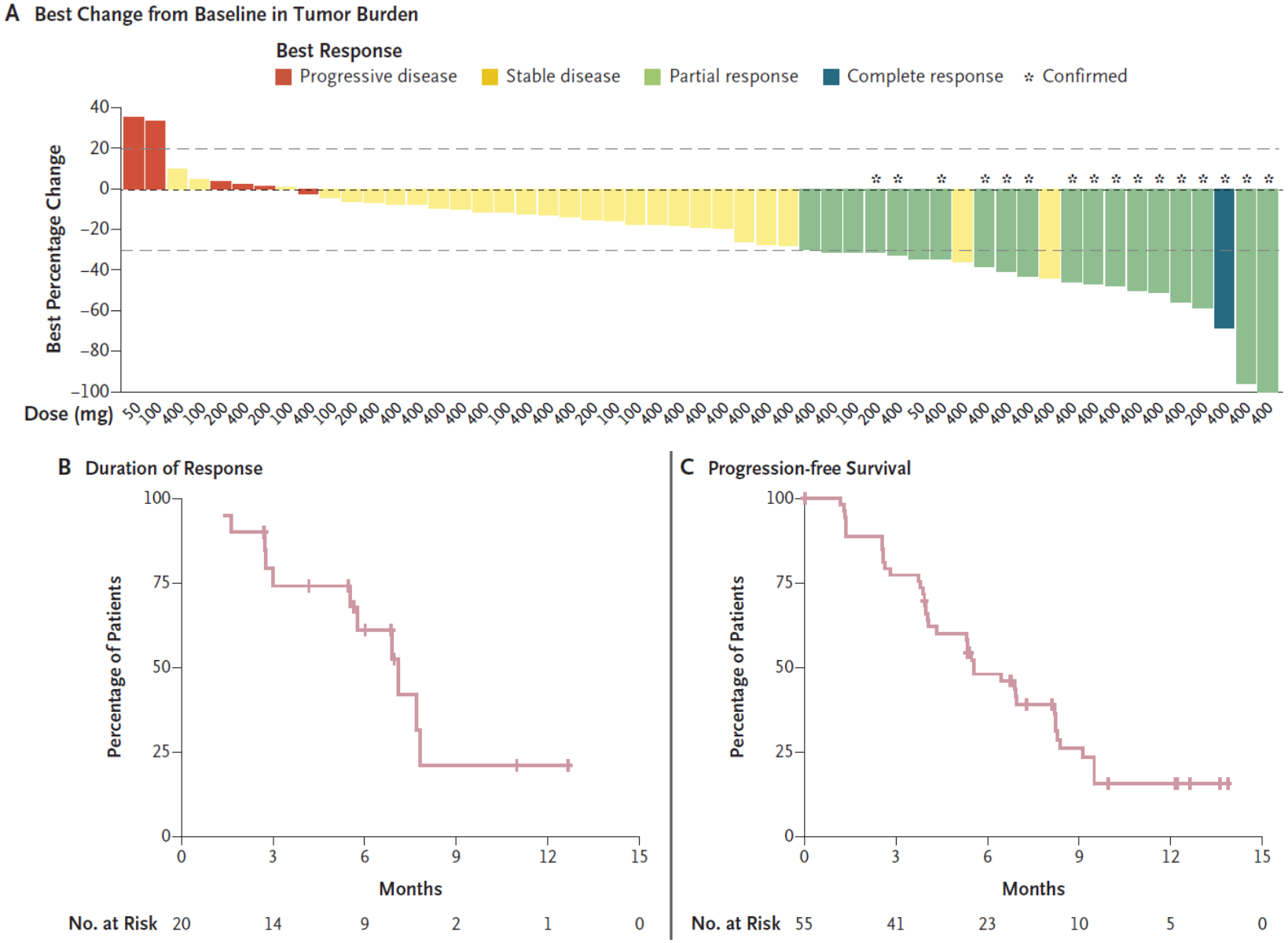
Adrian Sacher, M.D., Patricia LoRusso, D.O., Manish R. Patel, M.D., Wilson H. Miller, Jr., M.D., Ph.D., Elena Garralda, M.D., Martin D. Forster, M.D., Ph.D., Armando Santoro, M.D., Alejandro Falcon, M.D., Tae Won Kim, M.D., Ph.D., Luis Paz-Ares, M.D., Samantha Bowyer, M.B., B.Ch., M.P.H., Maria de Miguel, M.D., Sae-Won Han, M.D., Ph.D., Matthew G. Krebs, M.B., Ch.B., Ph.D., Jong-Seok Lee, M.D., Michael L. Cheng, M.D., Kathryn Arbour, M.D., Erminia Massarelli, M.D., Ph.D., Yoonha Choi, Ph.D., Zhen Shi, Ph.D., Sandhya Mandlekar, Ph.D., Mark T. Lin, M.D., Ph.D., Stephanie Royer-Joo, Engr., Julie Chang, Ph.D., Neekesh V. Dharia, M.D., Ph.D., Jennifer L. Schutzman, M.D., Ph.D., and Jayesh Desai, M.B., B.S., for the GO42144 Investigator and Study Group*

Divarasib Antitumor Activity in Patients with NSCLC



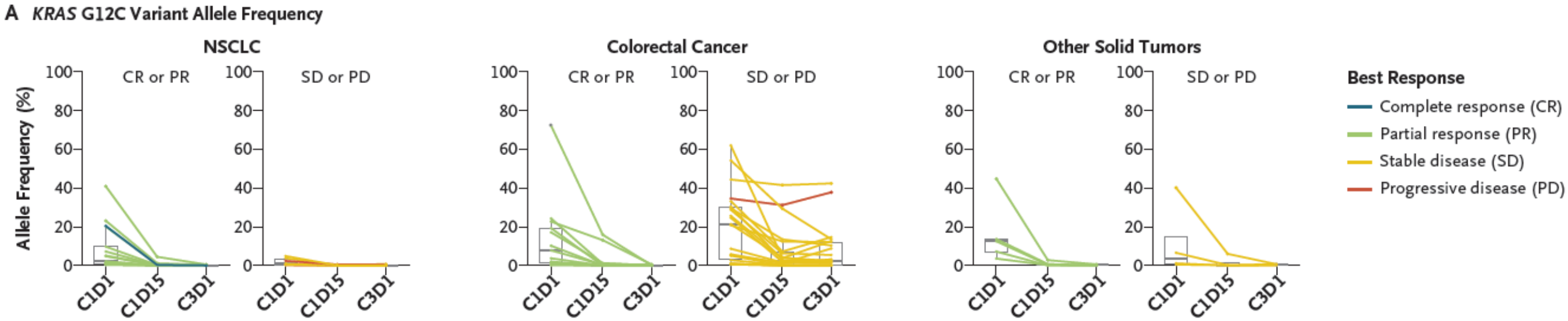
Sacher, LoRusso, Patel et al. NEJM. 2023.

Divarasib Antitumor Activity in Patients with Colorectal Cancer



Sacher, LoRusso, Patel et al. NEJM. 2023.

Divarasib: Biomarkers of Response and Resistance



Sacher, LoRusso, Patel et al. NEJM. 2023.

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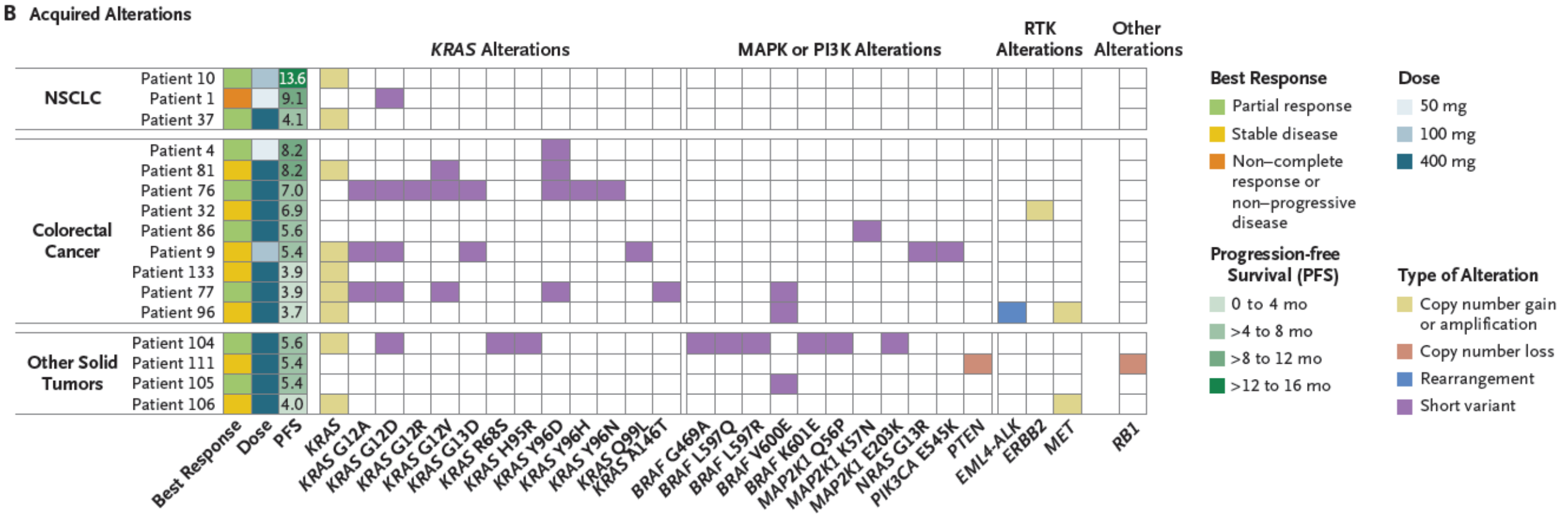
Divarasib: Biomarkers of Response and Resistance



Sacher, LoRusso, Patel et al. NEJM. 2023.

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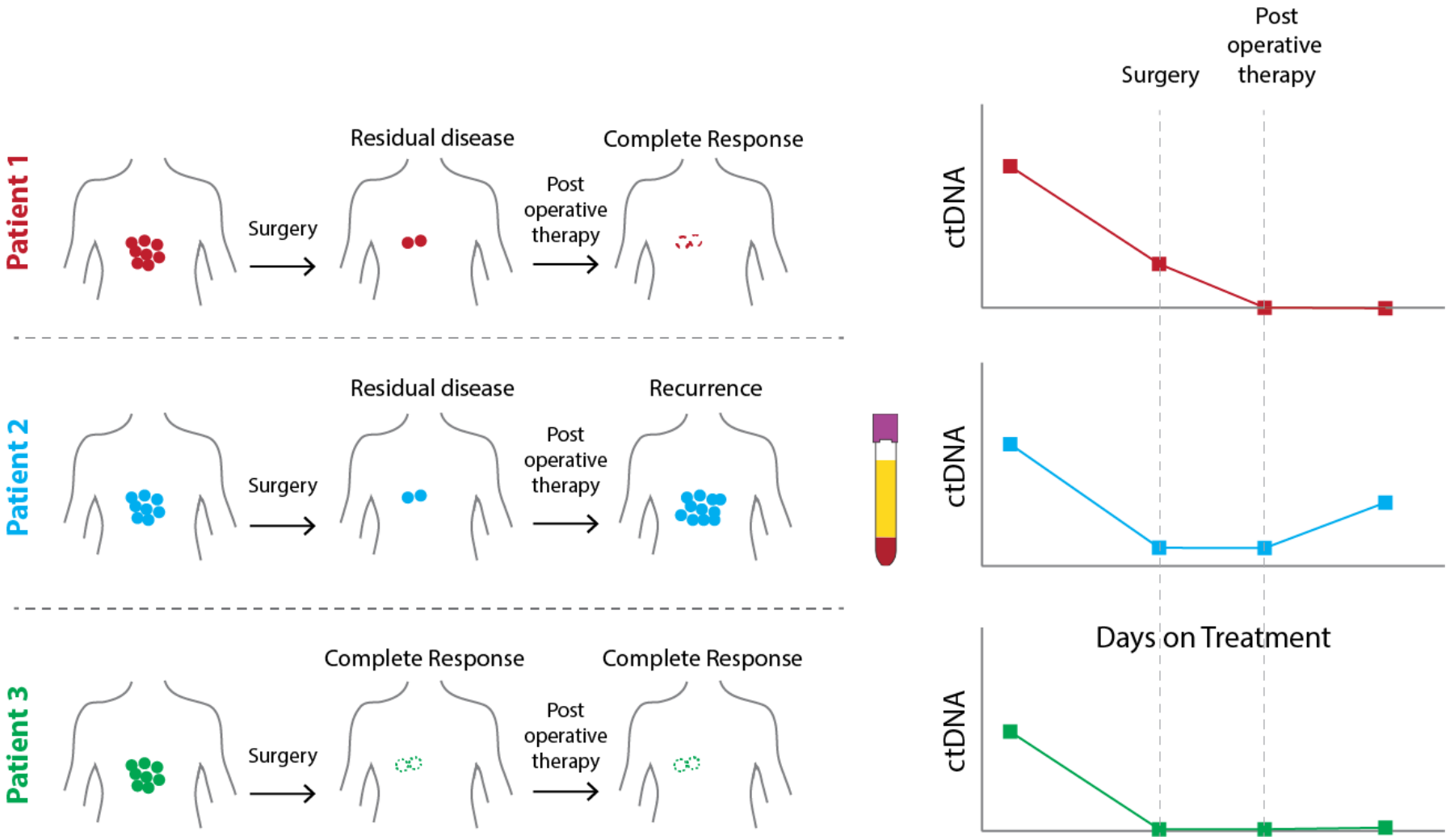
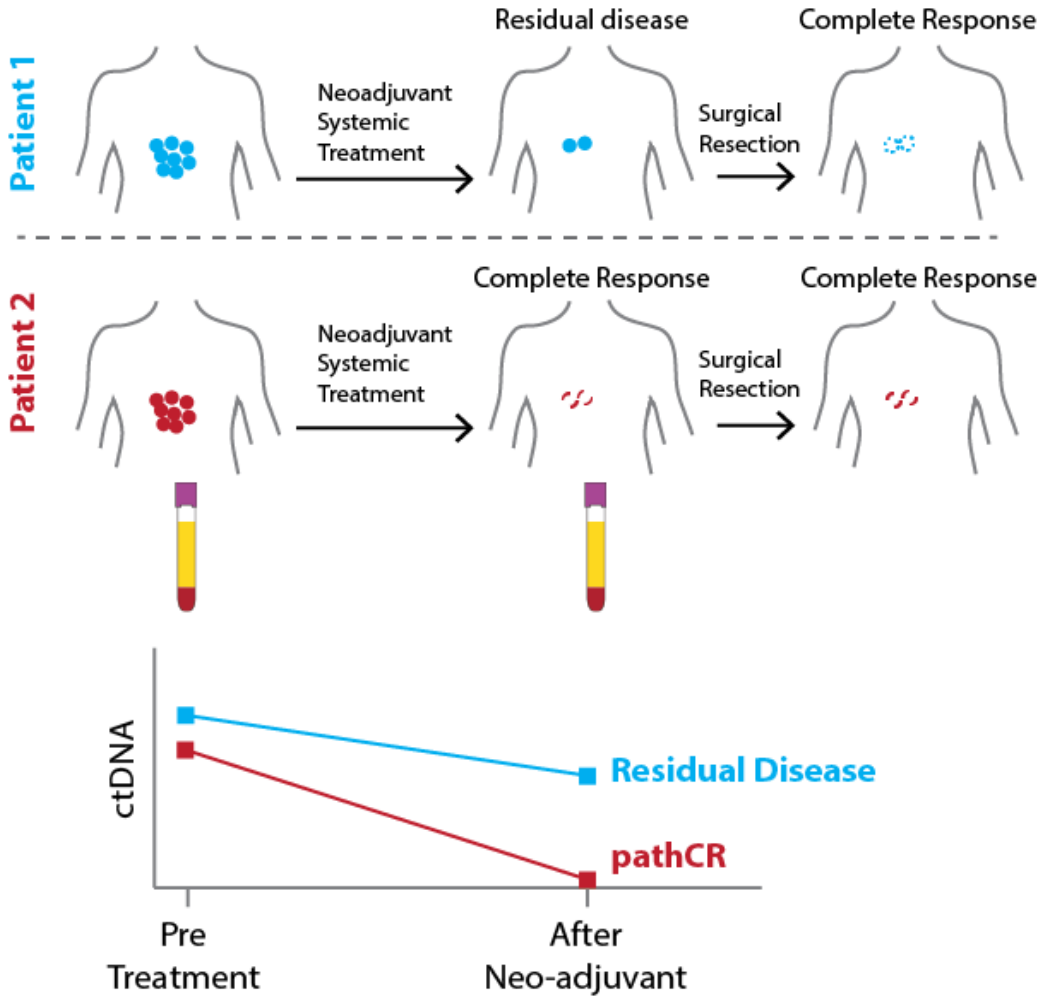
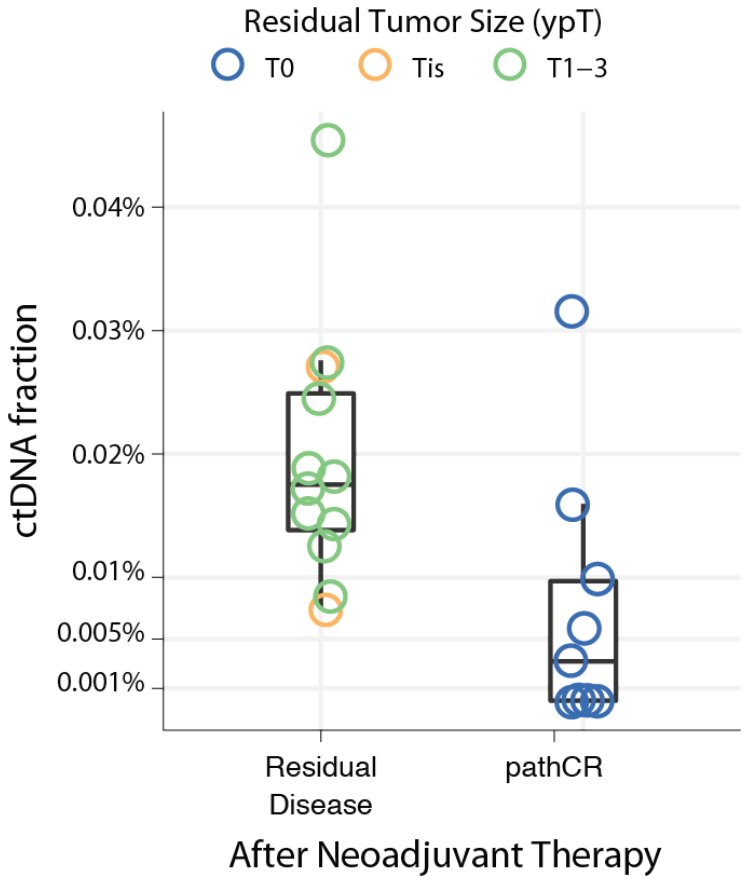
Can ctDNA analysis help individualize treatment of early-stage cancers by detecting minimal residual disease (MRD)?



After neoadjuvant therapy, ctDNA levels were significantly lower in patients with breast cancer who achieved pathCR

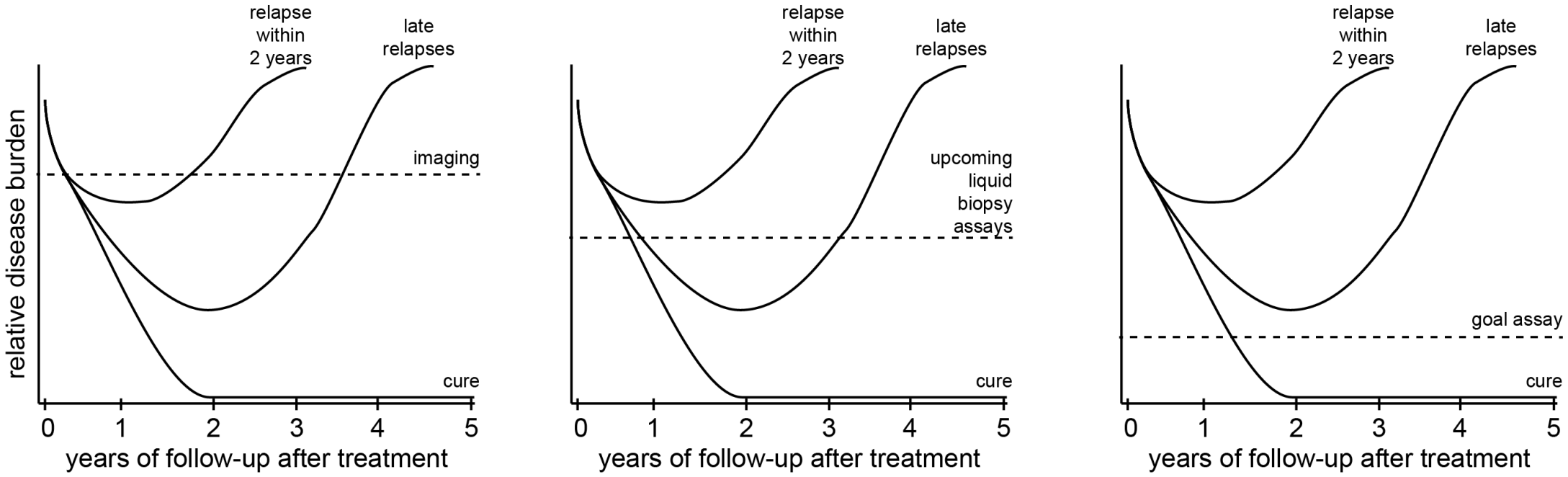




McDonald et al. Science Translational Medicine 2019 – Murtaza Lab

How sensitive do we need to get for treatment de-escalation studies?

Improving limit of detection



Current clinical practice

Treatment escalation trials
High Positive Predictive Value

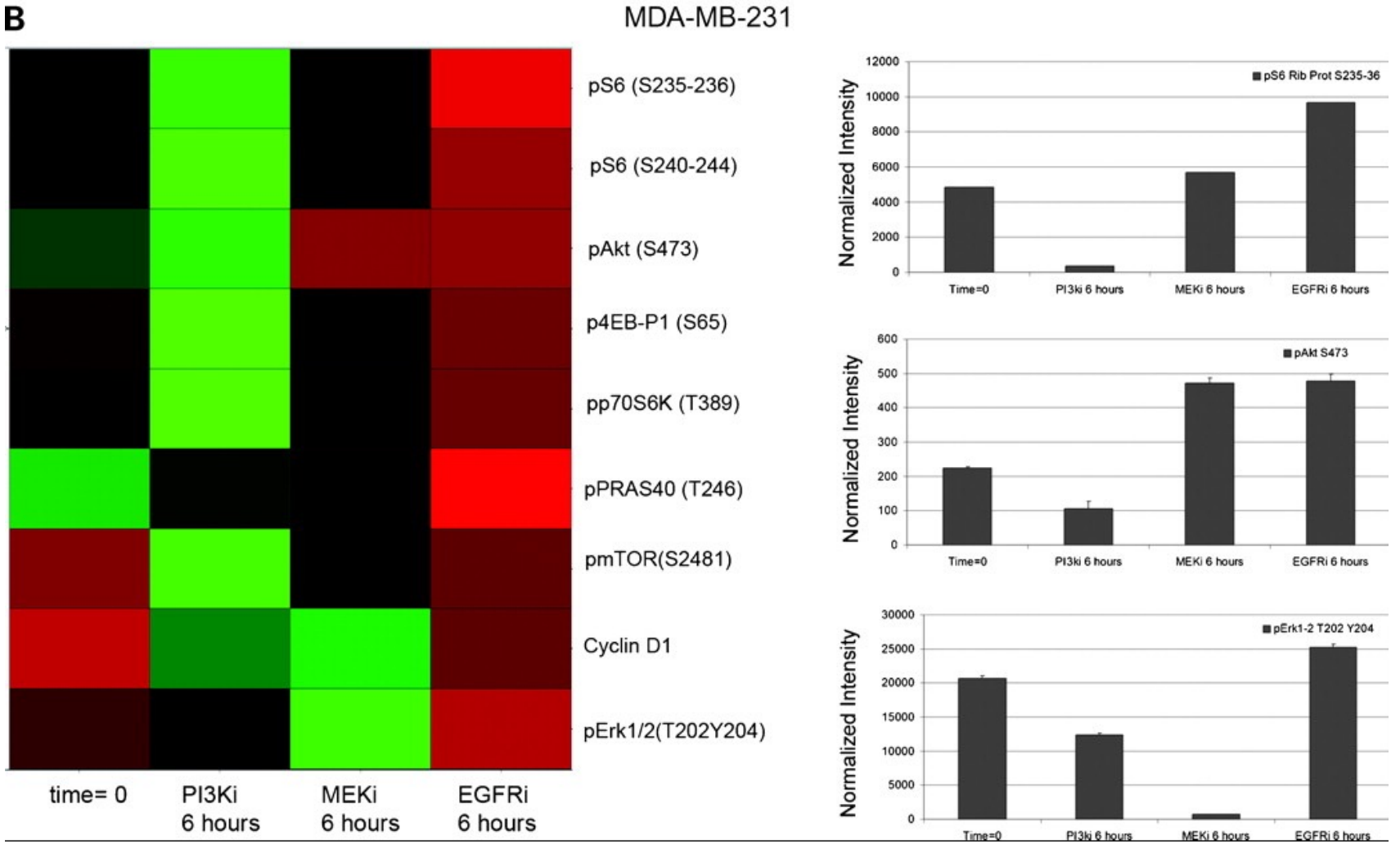
Treatment de-escalation trials
Need to achieve high Negative Preditive Value

Adapted from van Dongen et al. Blood 2015

PhosphoProteomics

Pharmacodynamic modulation of signaling pathways by targeted kinase inhibitors

Low phosph levels
High phosph levels



Boyd et al. *Mol Cancer Ther*. 2008;7(12):3695-3706.

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Poster ID: HER2 -17

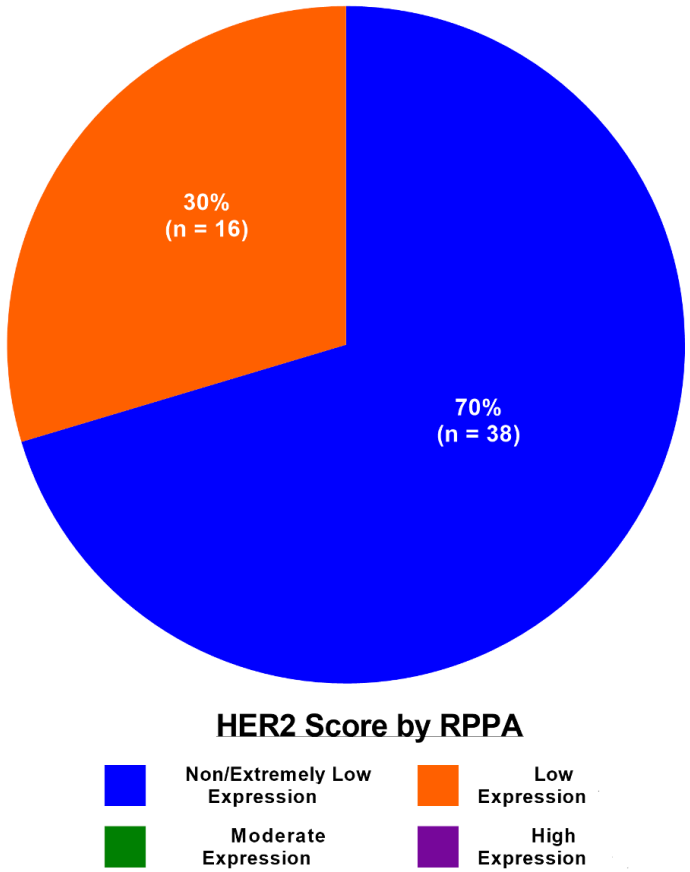
Novel Quantitative HER2 Assay for Determining Dynamic HER2 Expression in the HER2 IHC 0 "Ultra-Low" Setting: Implications for Precision Therapy in HER2- Breast Cancer

Brian Corgiat[1], Joyce O'Shaughnessy,[2] Patricia LoRusso[3], Kris Weinberg[1], Justin Davis[1], Chelsea Gawryletz[3], Emanuel F Petricoin III[4]

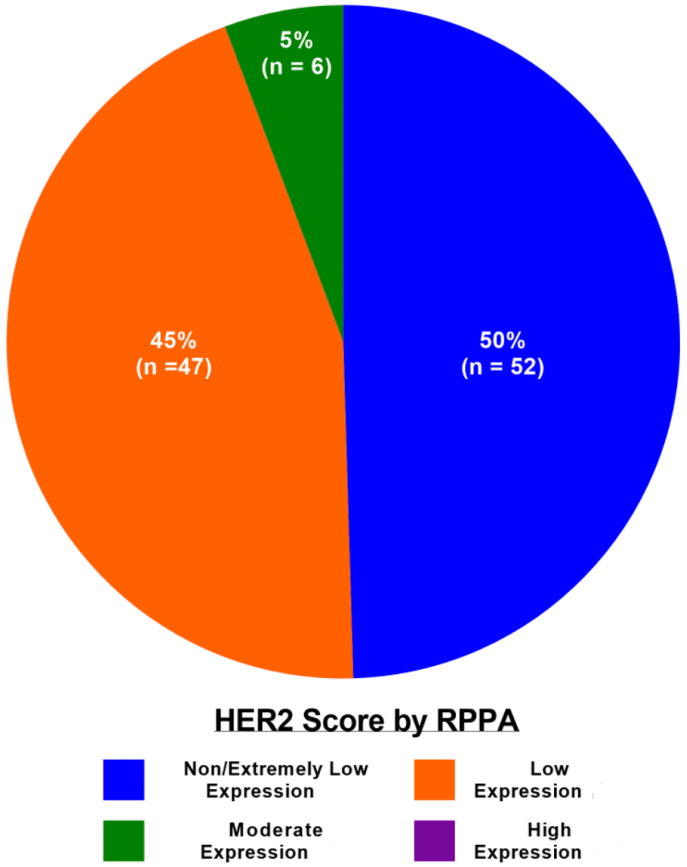
Contact: Emanuel Petricoin epetrico@gmu.edu

[1]Theralink Technologies, Inc.; [2] Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, [3]Yale Cancer Center, [4] UCHealth- Cancer Care and Hematology, [5] George Mason University

ER- Cohort (n = 54)



ER+ Cohort (n = 105)



RESULTS:

When evaluated by a quantitative HER2 assay, cases that were defined as HER2 LOW (1+ by IHC or 2+ by IHC and FISH-) actually had very little to no actual HER2 expression in 70% (ER-, N=38) to 50% (ER+, N=52) of time.

Corgiat, O'Shaughnessy, LoRusso, et. al., SABC Dec 2022

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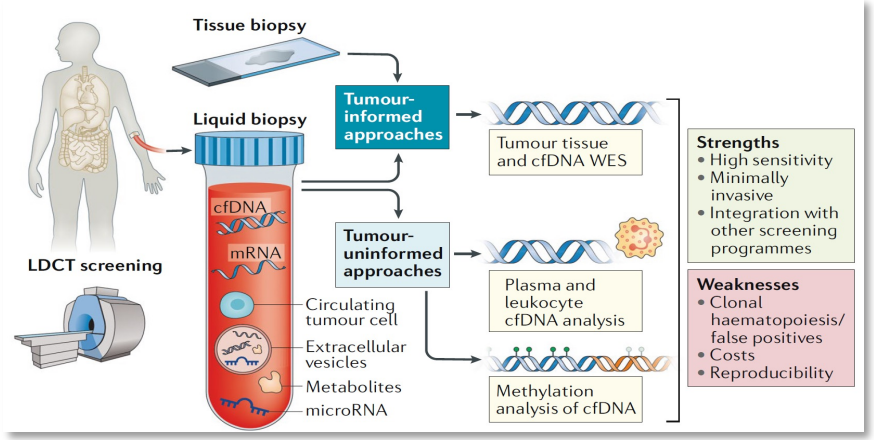
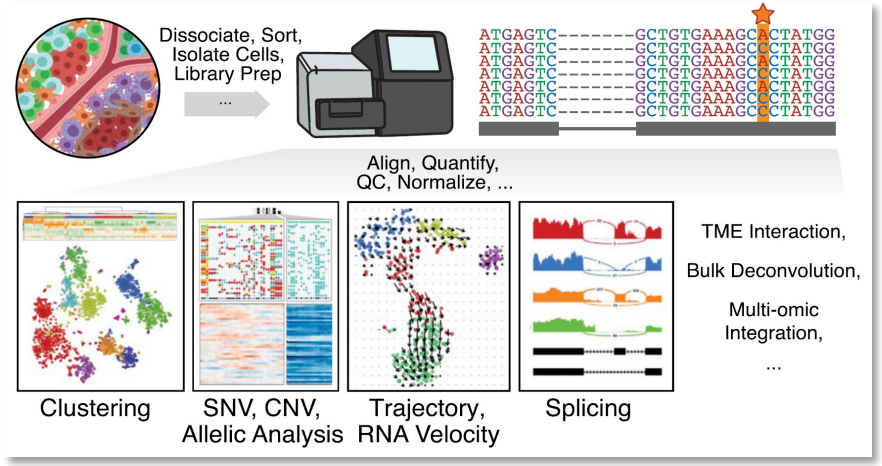
Liquid biopsy



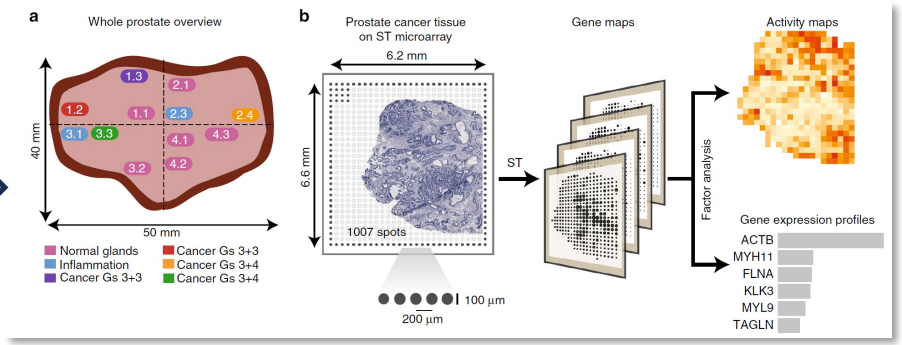
Rolfo and Russo., 2020. Nature Reviews Clinical Oncology

Single-cell transcriptomics



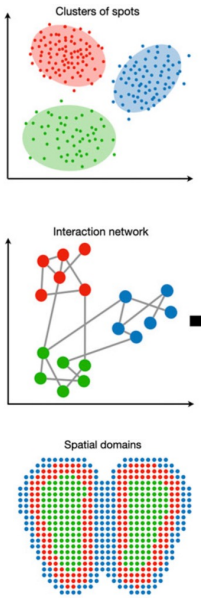
Fan et al., 2020. Experimental & Molecular Medicine volume

Spatial transcriptomics & proteomics

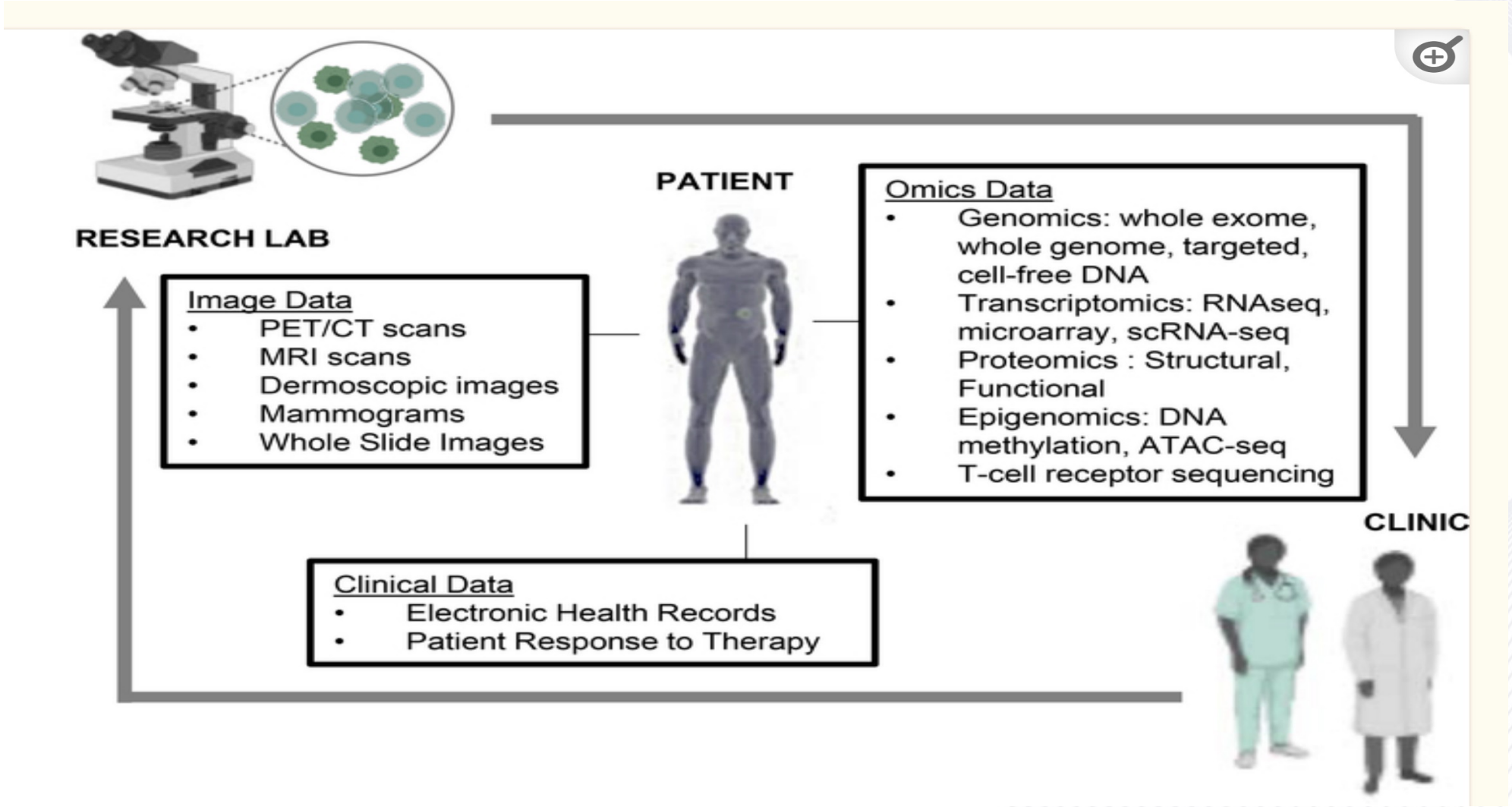


Berglund et al., 2080. Nature Communications

Advanced integrative computational analysis & AI



Patient Derived Dataset AI models for Bench-to-Bedside Cancer Care



Bhinder et al, Cancer Disc 2021

Conclusions

- Drug discovery & development have come a long way since declaring the War on Cancer
- However, we realize more than ever we have a long way to go
- Exciting times integrating novel technologies into the development of new anticancer agents to unfold the mysteries of cancer biology so as to enhance therapeutic outcomes for patients

Thank You!!!