Das Beste aus der Onkologie 2023

Barbara Kiesewetter-Wiederkehr

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Offenlegung Interessenskonflikte

1. **Anstellungsverhältnis oder Führungsposition**
   Nein

2. **Beratungs- bzw. Gutachtertätigkeit**
   Nein

3. **Besitz von Geschäftsanteilen, Aktien oder Fonds**
   Nein

4. **Patent, Urheberrecht, Verkaufslizenz**
   Nein

5. **Honorare**
   AAA, Boehringer Ingelheim, Daichii, Ipsen, Novartis, MSD, Eli Lilly, Roche.

6. **Finanzierung wissenschaftlicher Untersuchungen**
   Nein

7. **Andere finanzielle Beziehungen**
   Nein

8. **Immaterielle Interessenkonflikte**
   Nein

Andrés Cervantes
(Valencia, Spanien)

DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE
ÖGHO
SSMO SSOM SGMO
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Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie

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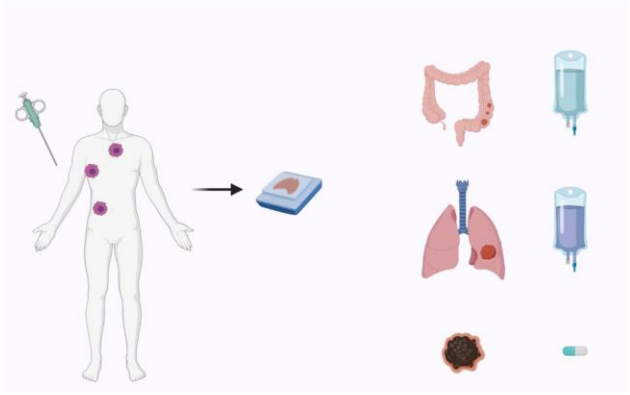
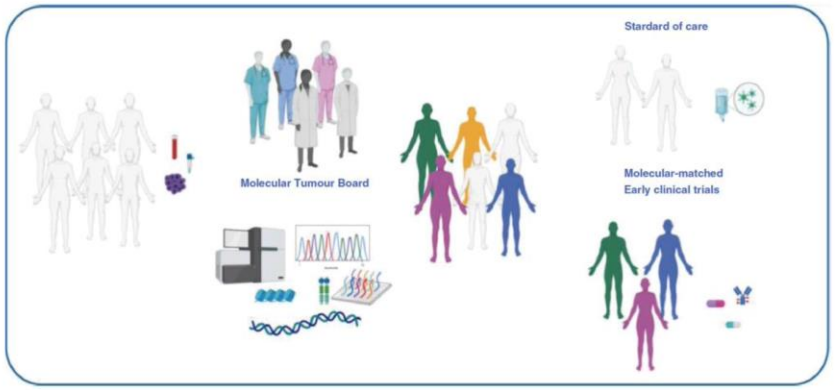
2022 WIEN

7.–10. OKTOBER

Pathology to drive treatment choice as a conventional strategy



Molecular matched approach



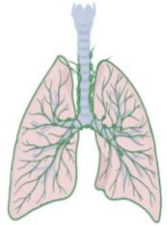
Gambardella V, et al. Br J Cancer 2021; 125: 1261-1269.

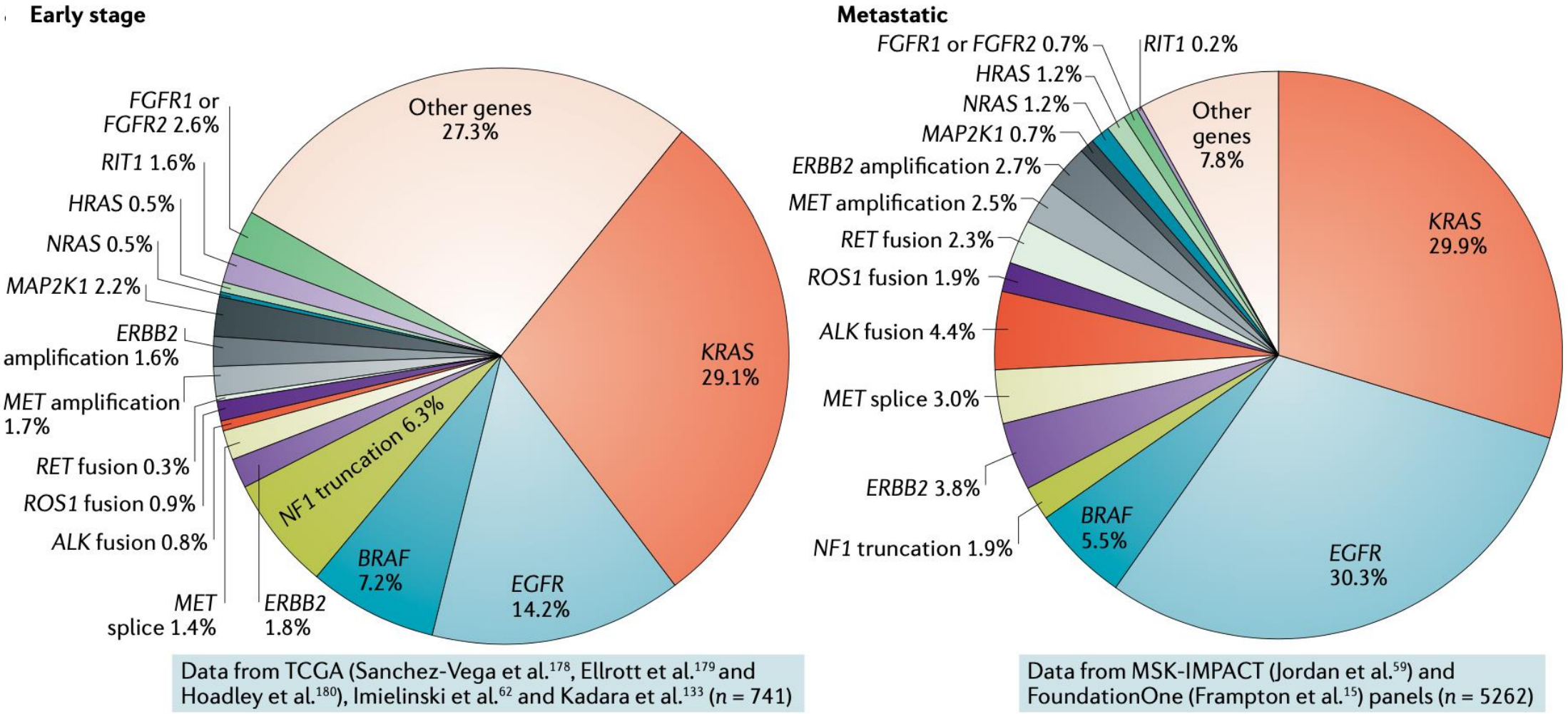
Pathology-driven

Treatment concept of the past decades

Molecular-driven

Organ-based vs Tumor-agnostic





Skoulidis F et al; Nature Reviews Cancer 2019;19:495-509

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

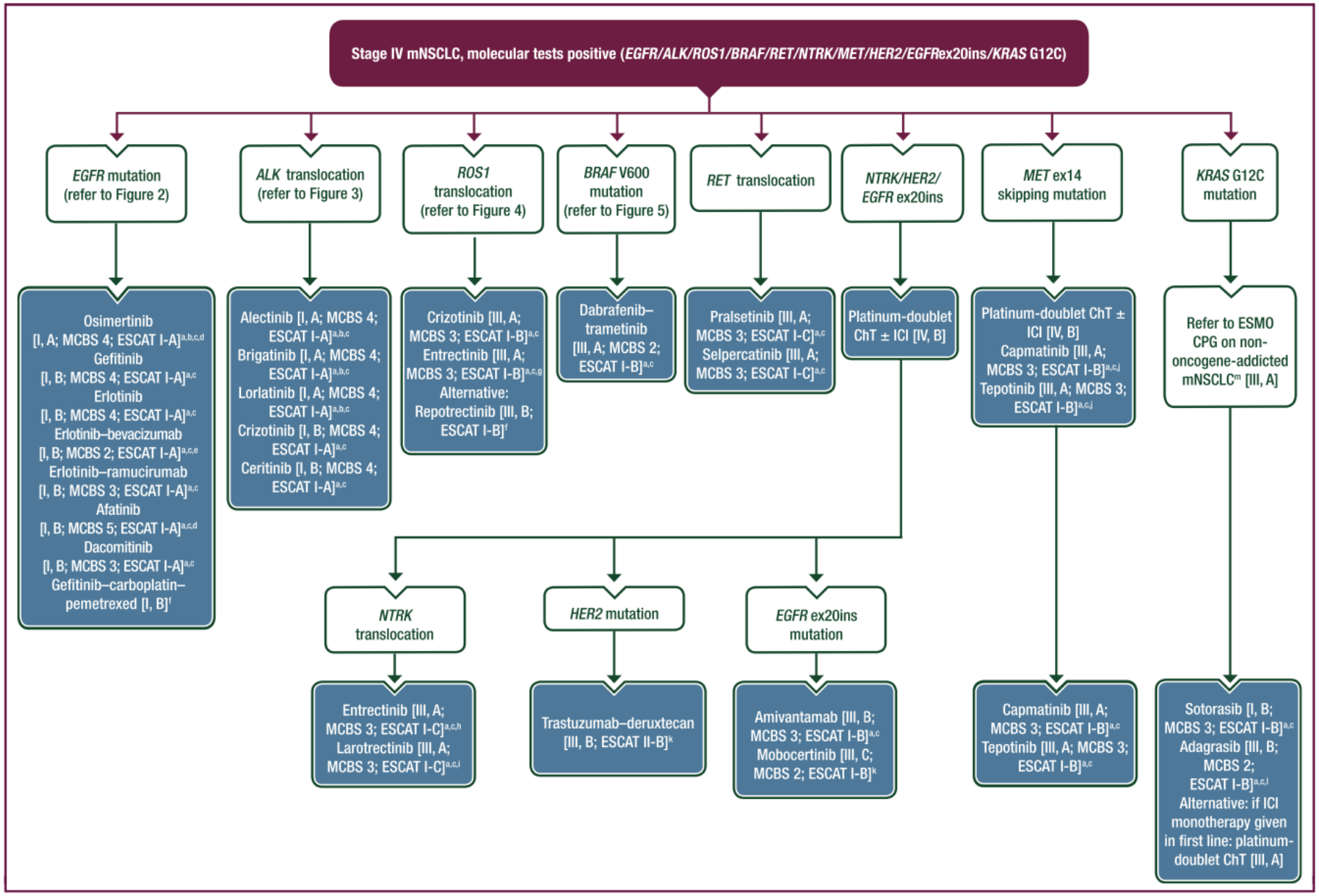
SPECIAL ARTICLE

Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

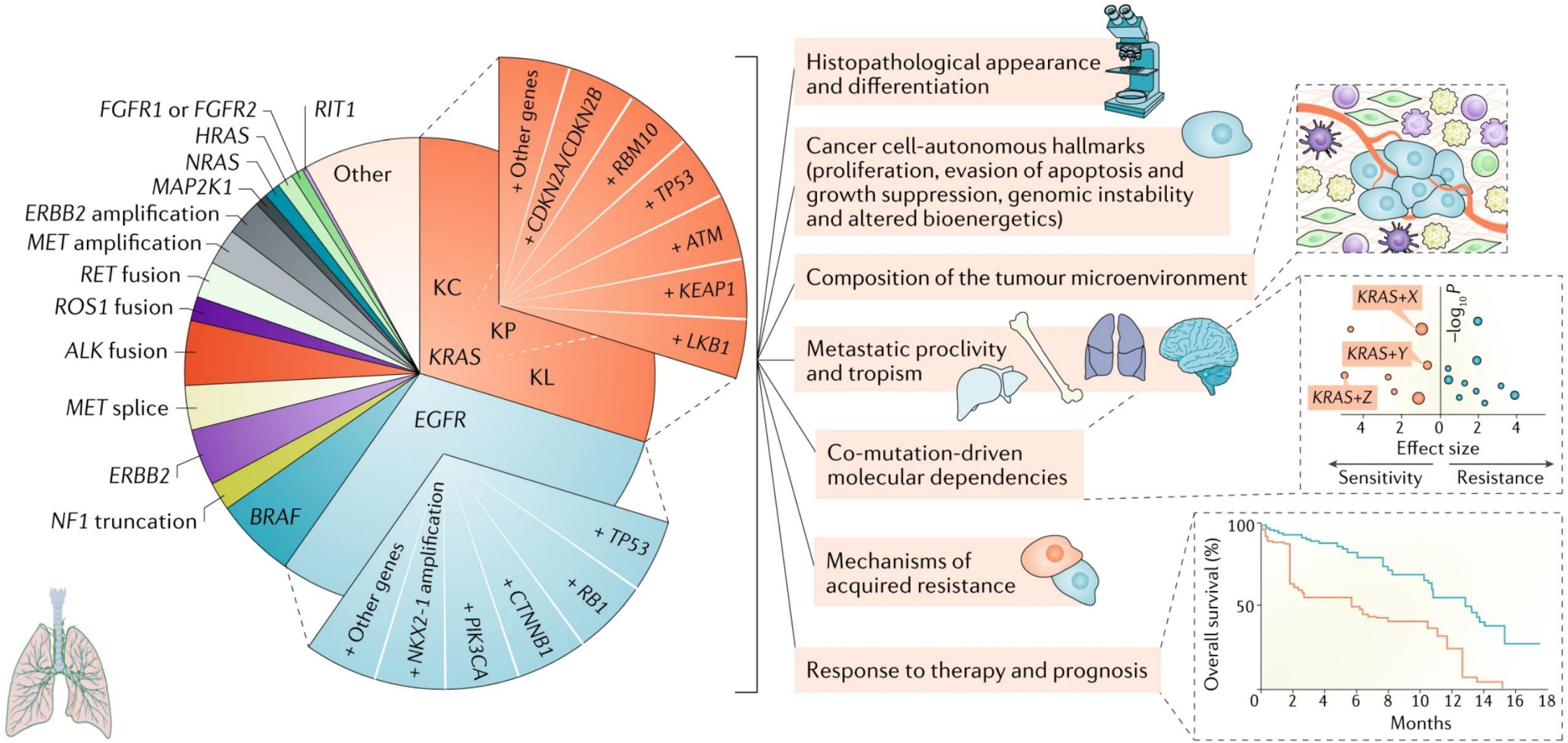
L. E. Hendriks[1], K. M. Kerr[2], J. Menis[3], T. S. Mok[4], U. Nestle[5,6], A. Passaro[7], S. Peters[8], D. Planchard[9], E. F. Smit[10,11], B. J. Solomon[12], G. Veronesi[13,14] & M. Reck[15], on behalf of the ESMO Guidelines Committee*

Das Beste aus der Onkologie

Available online 23 January 2023


Stage IV mNSCLC, molecular tests positive (*EGFR/ALK/ROS1/BRAF/RET/NTRK/MET/HER2/EGFR*ex20ins/*KRAS* G12C)
EGFR mutation (refer to Figure 2)
ALK translocation (refer to Figure 3)
ROS1 translocation (refer to Figure 4)
BRAF V600 mutation (refer to Figure 5)
RET translocation
NTRK/HER2/ EGFR ex20ins
MET ex14 skipping mutation
KRAS G12C mutation
Osimertinib [I, A; MCBS 4; ESCAT I-A][a,b,c,d]
Gefitinib [I, B; MCBS 4; ESCAT I-A][a,c]
Erlotinib [I, B; MCBS 4; ESCAT I-A][a,c]
Erlotinib–bevacizumab [I, B; MCBS 2; ESCAT I-A][a,c,e]
Erlotinib–ramucirumab [I, B; MCBS 3; ESCAT I-A][a,c]
Afatinib [I, B; MCBS 5; ESCAT I-A][a,c,d]
Dacomitinib [I, B; MCBS 3; ESCAT I-A][a,c]
Gefitinib–carboplatin–pemetrexed [I, B][f]
Alectinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Brigatinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Lorlatinib [I, A; MCBS 4; ESCAT I-A][a,b,c]
Crizotinib [I, B; MCBS 4; ESCAT I-A][a,c]
Ceritinib [I, B; MCBS 4; ESCAT I-A][a,c]
Crizotinib [III, A; MCBS 3; ESCAT I-B][a,c]
Entrectinib [III, A; MCBS 3; ESCAT I-B][a,c,g]
Alternative: Repotrectinib [III, B; ESCAT I-B][f]
Dabrafenib–trametinib [III, A; MCBS 2; ESCAT I-B][a,c]
Pralsetinib [III, A; MCBS 3; ESCAT I-C][a,c]
Selpercatinib [III, A; MCBS 3; ESCAT I-C][a,c]
Platinum-doublet ChT ± ICI [IV, B]
Platinum-doublet ChT ± ICI [IV, B]
Capmatinib [III, A; MCBS 3; ESCAT I-B][a,c,j]
Tepotinib [III, A; MCBS 3; ESCAT I-B][a,c,j]
Refer to ESMO CPG on non-oncogene-addicted mNSCLC[m] [III, A]
NTRK translocation
HER2 mutation
EGFR ex20ins mutation
Entrectinib [III, A; MCBS 3; ESCAT I-C][a,c,h]
Larotrectinib [III, A; MCBS 3; ESCAT I-C][a,c,i]
Trastuzumab–deruxtecan [III, B; ESCAT II-B][k]
Amivantamab [III, B; MCBS 3; ESCAT I-B][a,c]
Mobocertinib [III, C; MCBS 2; ESCAT I-B][k]
Capmatinib [III, A; MCBS 3; ESCAT I-B][a,c]
Tepotinib [III, A; MCBS 3; ESCAT I-B][a,c]
Sotorasib [I, B; MCBS 3; ESCAT I-B][a,c]
Adagrasib [III, B; MCBS 2; ESCAT I-B][a,c,l]
Alternative: if ICI monotherapy given in first line: platinum-doublet ChT [III, A]

Molecular driven – Understanding the Impact of Co-Mutations



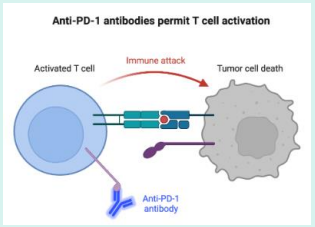
Skoulidis F et al; Nature Reviews Cancer 2019;19:495-509

Antibody Drug Conjugates

Monoclonal Antibodies

Novel Targets

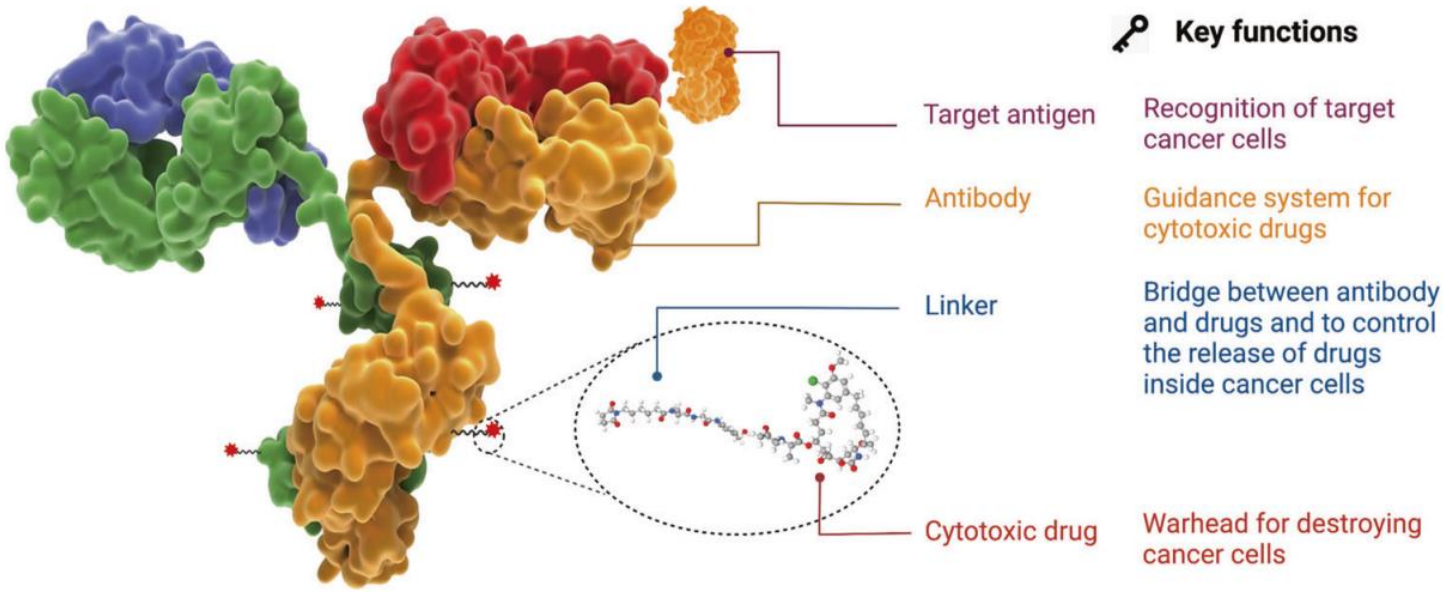
Immunotherapy

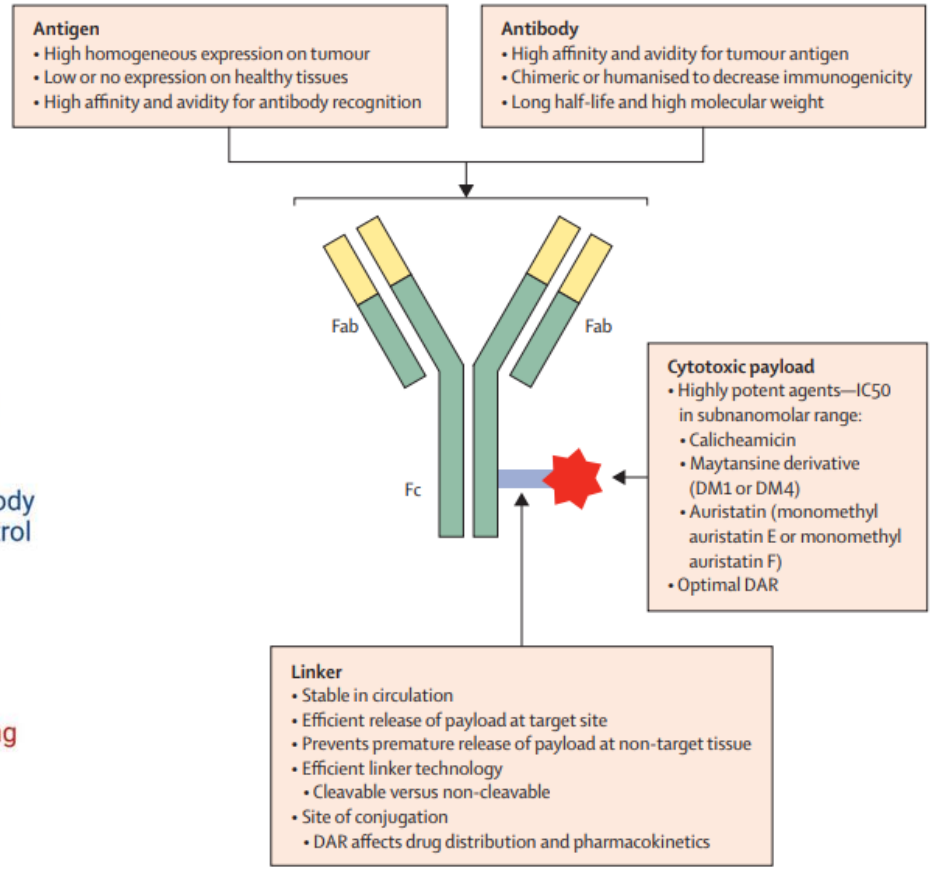


Perioperative Treatment

Tumor-Agnostic Drugs

Antibody drug conjugate: the “biological missile” for targeted cancer therapy





Fu Z et al, Signal Transduct Target Ther 2022;7:93
Chau et al, Lancet 2019;394:793-804

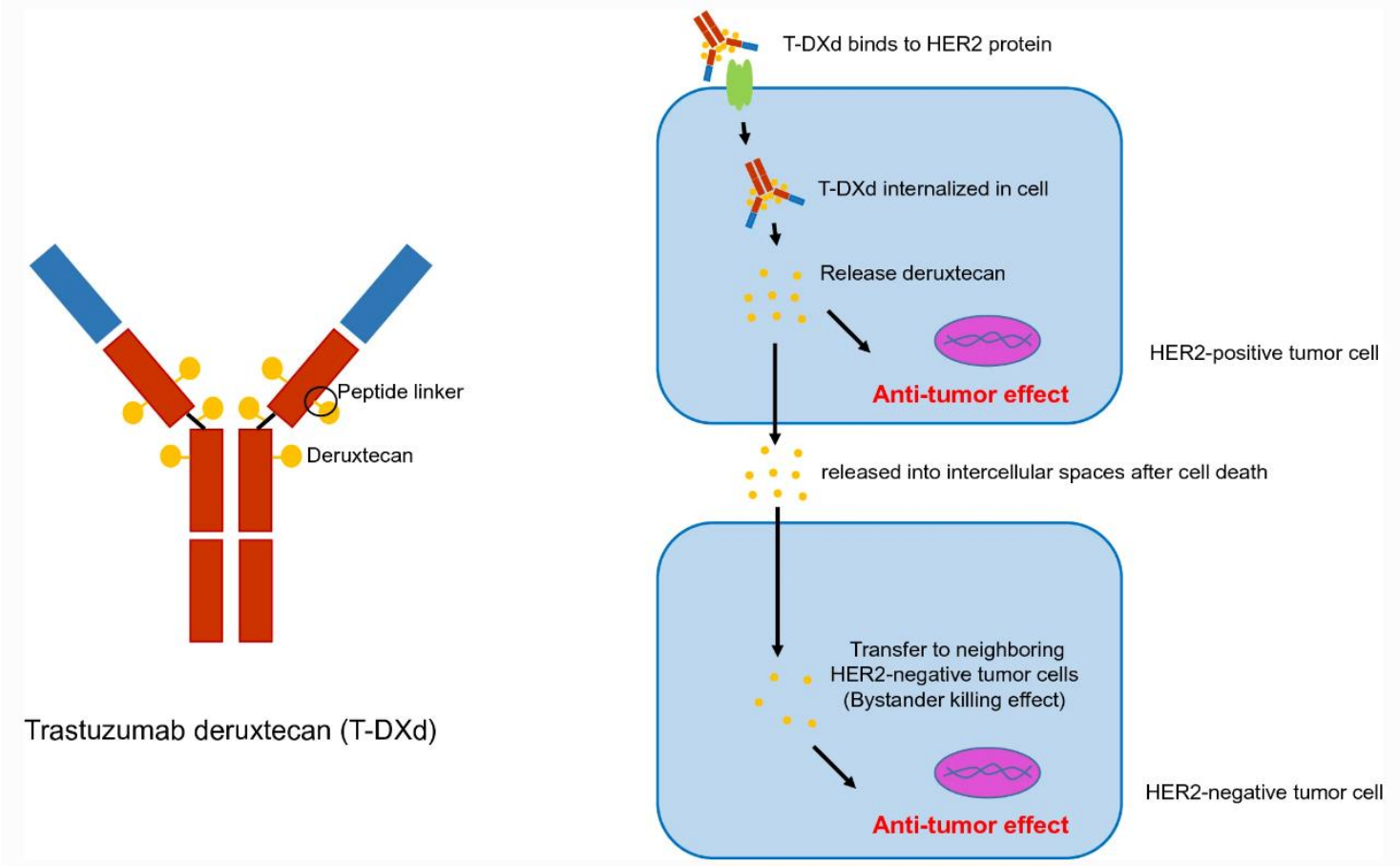
Antibody drug conjugate: the "biological missile" for targeted cancer therapy

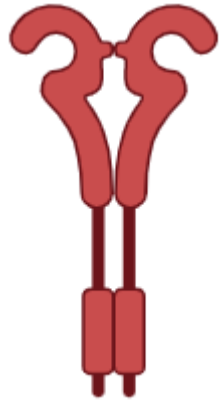
Table 3. The evolution of the ADC drug development

	First-generation ADC	Second-generation ADC	Third-generation ADC
Antibodies	Mouse-original or chimeric humanized antibodies	Humanized antibodies	Fully humanized antibodies or Fabs
Linkers	Unstable	Improved stability: cleavable and non-cleavable linkers;	Stable in circulation; precise control drugs release into tumor sites
Payloads	Low potency, including calicheamicin, duocarmycin and doxorubicin	Potency, such as auristatins and mytansinoids	High potency, such as PBDs, and tubulysin, and novel payloads like immunomodulators
Conjugation methods	Random lysines	Random lysines and reduced interchain cysteines	Site-specific conjugation
DAR	Uncontrollable (0–8)	4–8	2–4
Representative drugs	Gemtuzumab ozogamicin and inotuzumab ozogamicin 2000	Brentuximab vedotin and ado-trastuzumab emtansine	Polatuzumab vedotin, enfortumab vedotin, and fam-trastuzumab deruxtecan
Advantages	• Specific targeting • Increase therapeutic window to some extent	• Improved targeting ability • More potent payloads • Lower immunogenicity	• Higher efficacy though in cancer cells with low antigen; • Improved DAR along with improved stability and PK/PD; • More potent payloads; • Less off-target toxicity
Disadvantages	• Heterogeneity; • Lack of efficacy; • Narrow therapeutic index; • Off-target toxicity as premature drug loss; • High immunogenicity	• Heterogeneity; • Fast clearance for high DARs; • Off-target toxicity as premature drug loss; • Drug resistance	• Possible toxicity due to highly potent payloads; • Catabolism may be different across species • Drug resistance

Fu Z et al, Signal Transduct Target Ther 2022;7:93

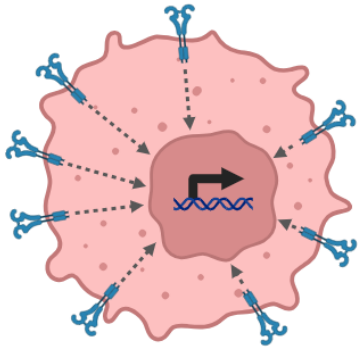
Trastuzumab deruxtecan





ERBB2

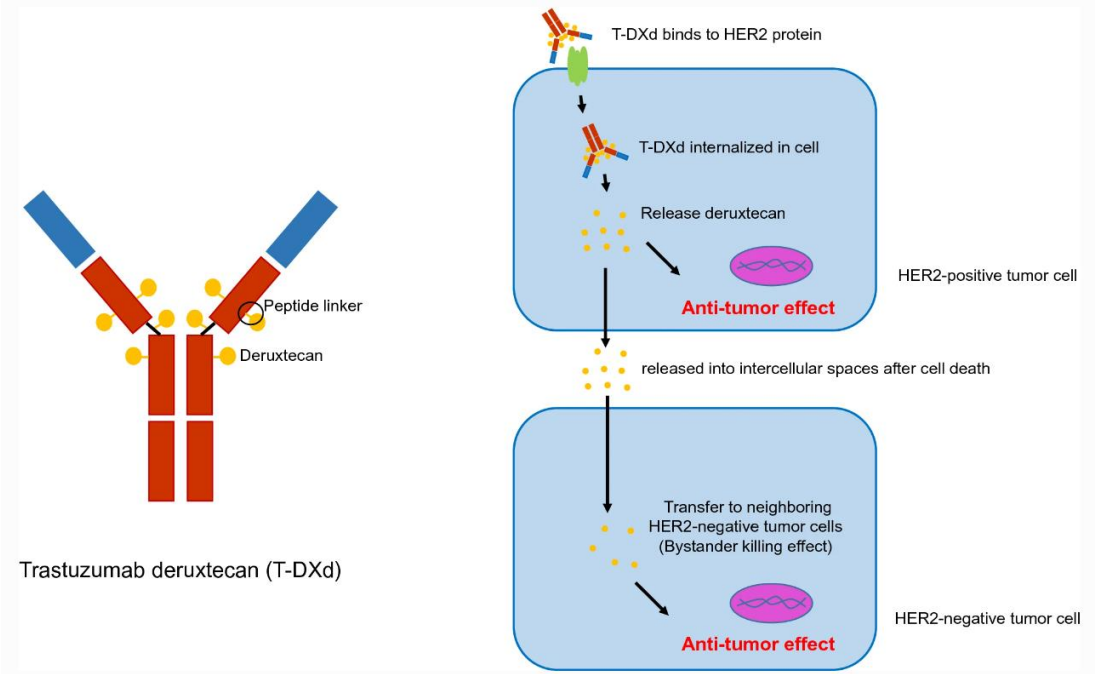
Abnormal HER2+ breast cancer cell



Too many HER2 receptors send more signals, causing cells to grow too quickly

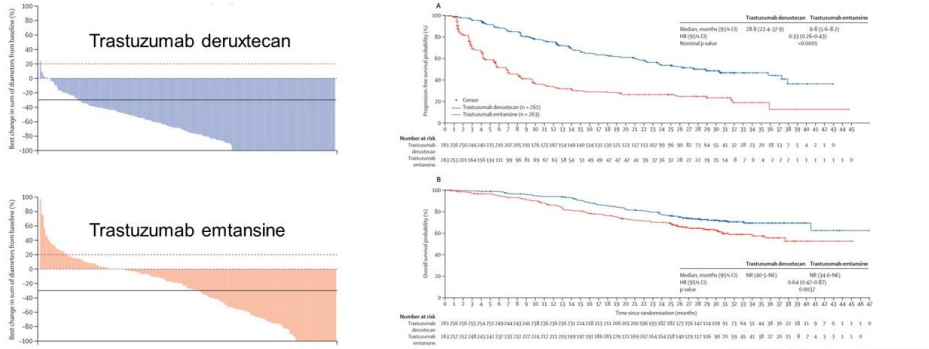
Aoki et al, Gastric Cancer 2021;24:567-576

Trastuzumab deruxtecan



FDA approved HER2 pos BC, HER2 low BC, HER2 mut NSCLC, HER2 pos gastric cancer

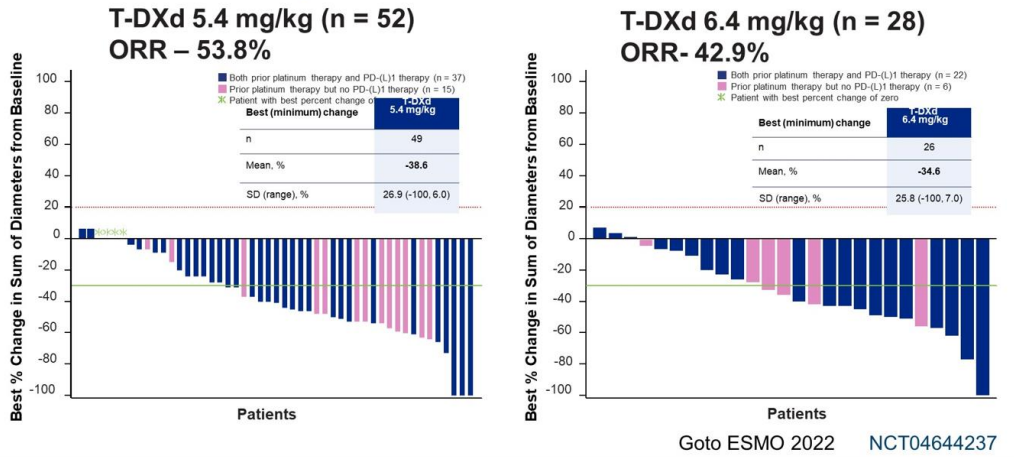
Trastuzumab deruxtecan vs Traztuzumab emtansine in previously treated HER2-positive metastatic breast cancer: DESTINY-Breast03



Hurvitz The Lancet 2022

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Benjamin J. Solomon MBBS, PhD

DESTINY-Lung02



Goto ESMO 2022 NCT04644237

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Aoki et al, Gastric Cancer 2021;24:567-576

2023 ASCO ANNUAL MEETING

DESTINY-PanTumor02

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

Funda Meric-Bernstam

The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 5, 2023

First tumor-agnostic ADC

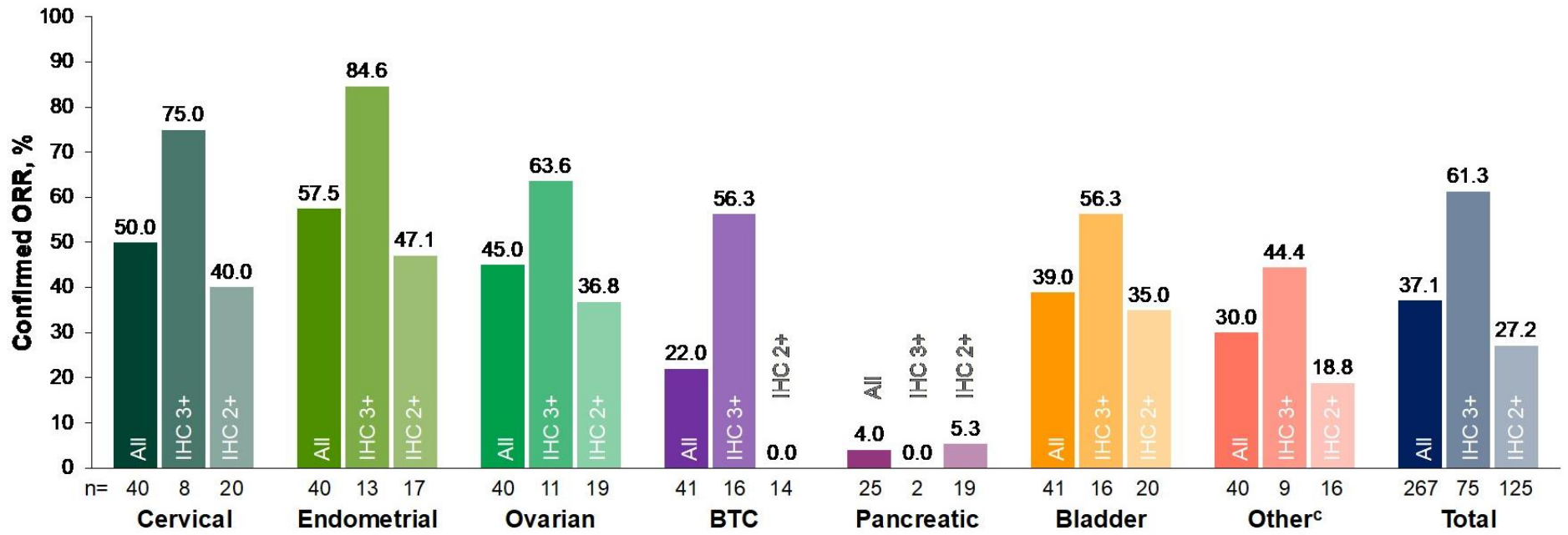
DESTINY PanTumor02 – Baseline Characteristics

Characteristic			All patients (N=267)
Age, median (range), years			62 (23–85)
Female, n (%)			178 (66.7)
Race, n (%)	White		163 (61.0)
	Asian		87 (32.6)
	Other		6 (2.25)
	Not reported		5 (1.9)
Prior lines of therapy	Median (range)		2 (0–13)
	n (%)	0	3 (1.1)
		1	70 (26.2)
		2	84 (31.5)
		≥3	107 (40.1)
		Unknown	3 (1.1)
Prior HER2 therapy, n (%)	Monoclonal antibody		34 (12.7)
	Tyrosine kinase inhibitor		1 (0.4)
ECOG PS, n (%)	0		127 (47.6)
	1		139 (52.1)
	2		1 (0.4)

		All patients (N=267)
HER2 testing for eligibility, n (%)[a]	Local	205 (76.8)
	Central	61 (22.8)
	Unknown[b]	1 (0.4)
HER2-expression for eligibility, n (%)[a]	IHC 3+	108 (40.4)
	IHC 2+	153 (57.3)
	IHC 1+[c]	5 (1.9)
	Unknown[b]	1 (0.4)
Centrally confirmed HER2 status for efficacy evaluation, n (%)	IHC 3+	75 (28.1)
	IHC 2+	125 (46.8)
	IHC 1+	25 (9.4)
	IHC 0	30 (11.2)
	Unknown[d]	12 (4.5)

[a]HER2 expression for eligibility was based on local assessment, based on any HER2 test, where available. [b]Patient had missing IHC status (pancreatic cancer cohort) at data cut-off but was confirmed IHC3+ by local testing post-data cut-off. [c]In the cervical cohort, 5 patients with IHC 1+ status were included per protocol. [d]Includes patients whose samples were not evaluable and may have included patients who did not provide a sample for central testing.
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

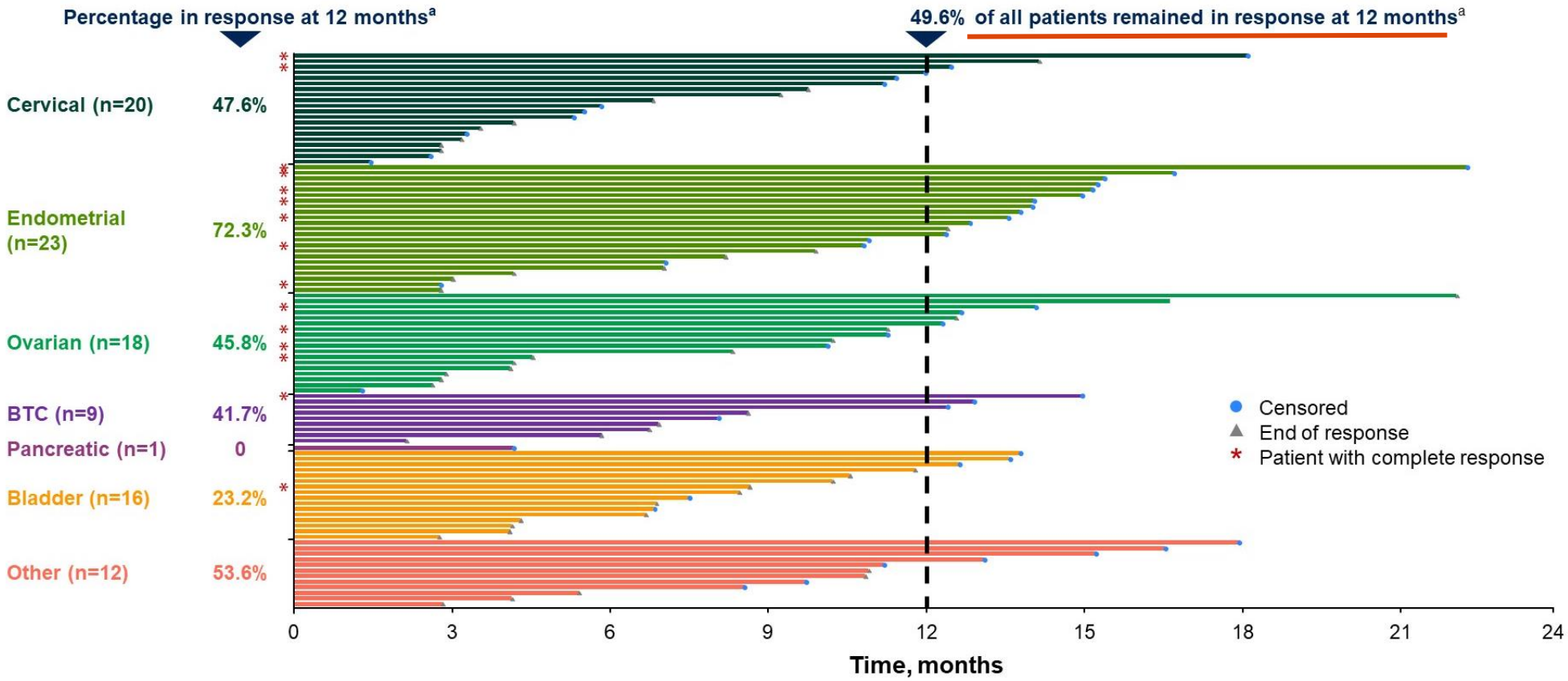
DESTINY PanTumor02 – Response Rate by HER2 status



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

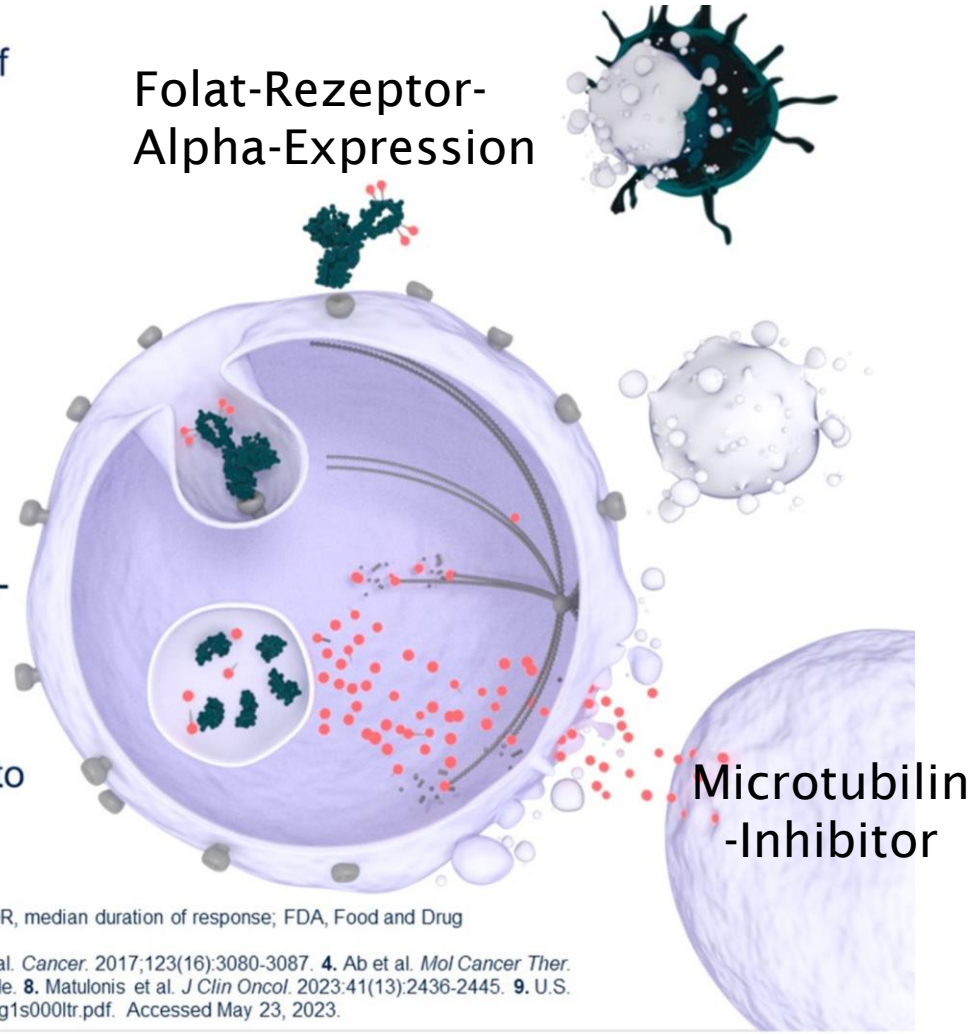
Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

DESTINY PanTumor02 – Duration of response



MIRASOL Phase III Study – Mirvetuximab Soravtansine

- No randomized phase 3 trial has shown an overall survival (OS) benefit of a novel therapy in platinum-resistant ovarian cancer (PROC)[1, 2]
- Mirvetuximab soravtansine (MIRV) is an ADC comprising a FRα-binding antibody, cleavable linker, and maytansinoid DM4, a potent tubulin-targeting agent[3,4]
- FRα is expressed in ~90% of ovarian carcinomas,[5, 6] with 35-40%[7] of PROC tumors exhibiting high FRα expression (≥75% of tumor cells positive with ≥2+ intensity)[8]
- MIRV demonstrated an ORR of 32% and mDOR 6.9 months in the single-arm study SORAYA[8] of BEV pre-treated PROC to support accelerated approval by the FDA[9]
- MIRASOL is the confirmatory, randomized, global phase 3 trial designed to support approval worldwide

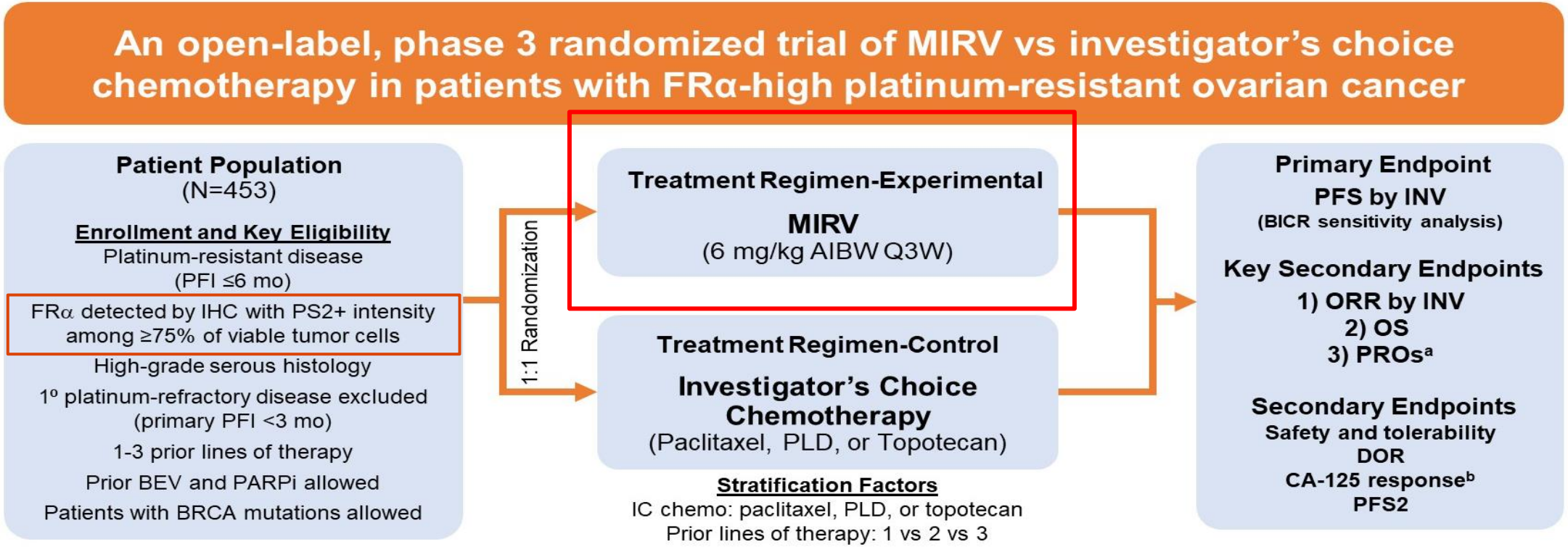


PFS, progression-free survival; OS, overall survival; FRα, folate receptor alpha; ORR, objective response rate; ADC, antibody-drug conjugate; mDOR, median duration of response; FDA, Food and Drug Administration; BEV, bevacizumab; US, United States; EU, Europe.

1. Pujade-Lauraine et al. *J Clin Oncol*. 2014;32(13):1302-1308. **2.** Richardson et al. *JAMA Oncol*. 2023;10.1001/jamaoncol.2023.0197. **3.** Moore et al. *Cancer*. 2017;123(16):3080-3087. **4.** Ab et al. *Mol Cancer Ther*. 2015;14(7):1605-1613. **5.** Markert et al. *Anticancer Res*. 2008;28(6A):3567-3572. **6.** Martin et al. *Gynecol Oncol*. 2017;147(2):402-407. 7. Data on file. **8.** Matulonis et al. *J Clin Oncol*. 2023:41(13):2436-2445. **9.** U.S. FOOD & DRUG ADMINISTRATION. BLA ACCELERATED APPROVAL. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761310Orig1s000ltr.pdf. Accessed May 23, 2023.

MIRASOL Phase III Study Design

N=435

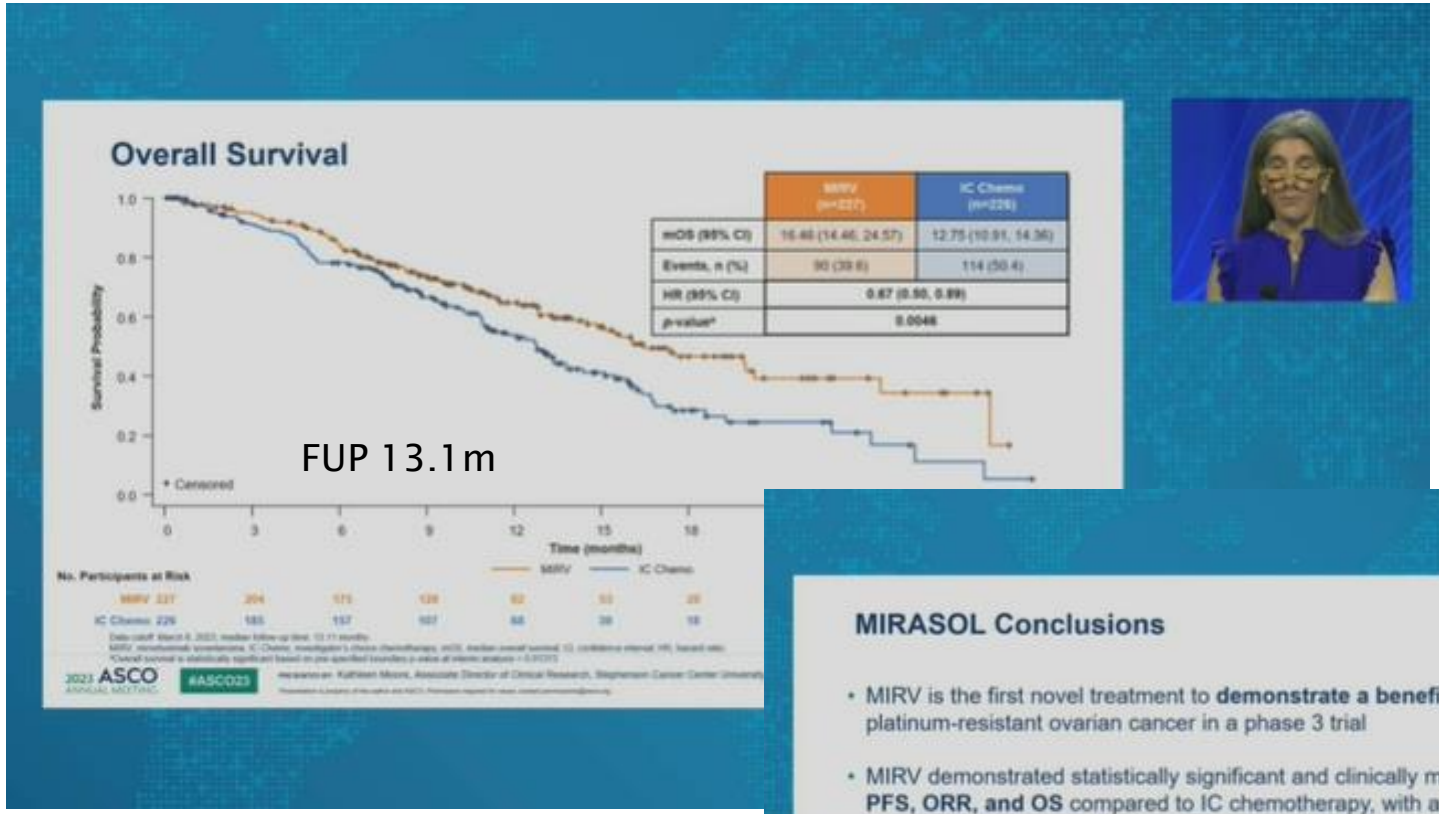


AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.
[b]Gynecological Cancer InterGroup (GCIG) criteria.

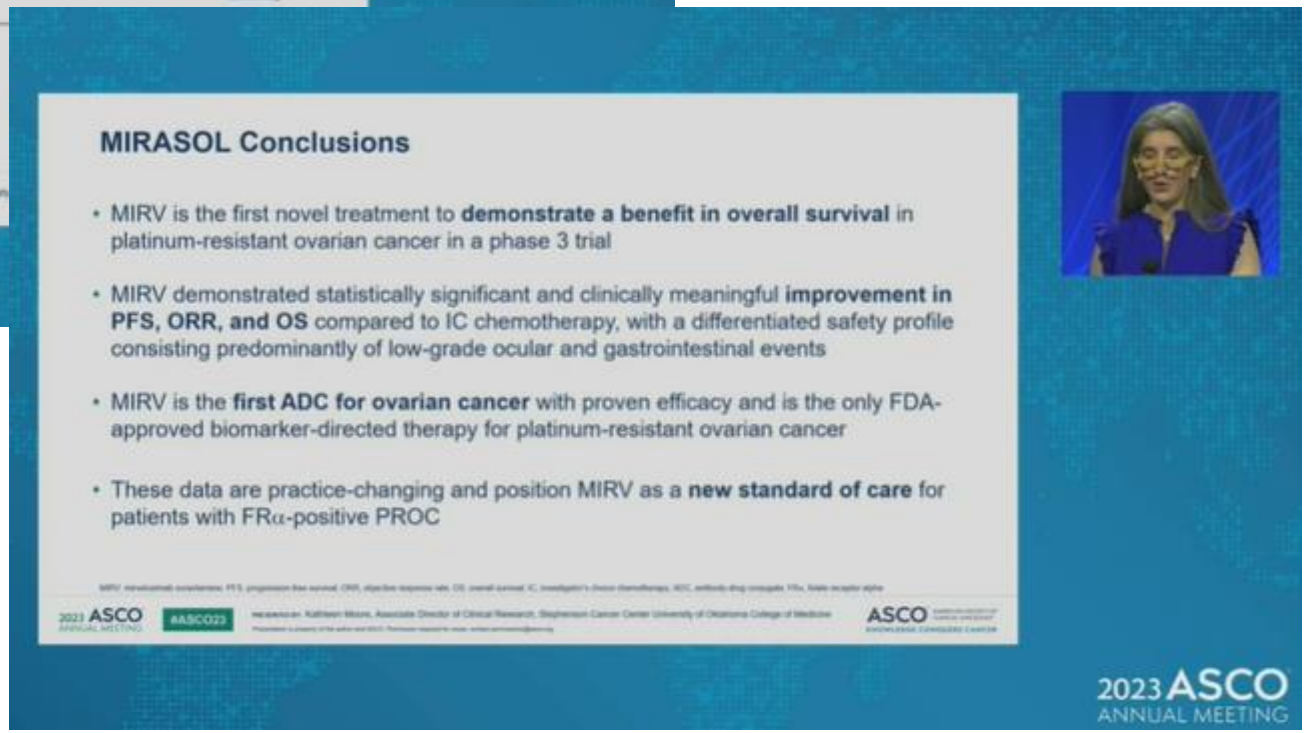
1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

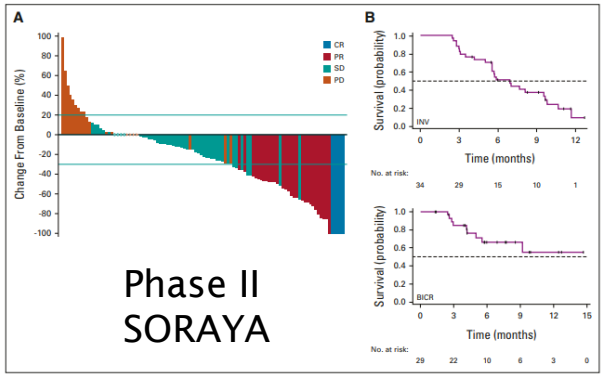
PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

„Clinical Practice Changing“



„First targeted approval agent since beva 2014“



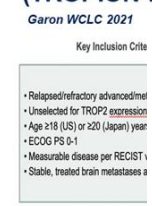


Phase II
SORAYA

Moore NK, ASCO 2023
Matulonis UA et al, J Clin Oncol 2023;41:2436-2445

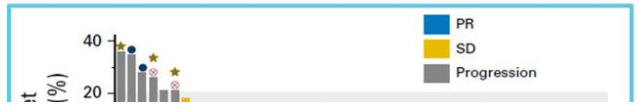
Datopotamab deruxtecan in previously treated metastatic NSCLC (TROPION-PanTumor01 phase I, NSCLC cohort)

Garon WCLC 2021



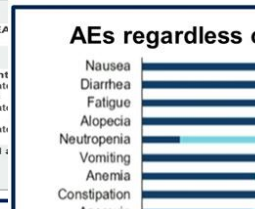
Sacituzumab govitecan in previously treated metastatic NSCLC

Heist JCO 2017



TROP2

- mPFS: 5.2 month
- mOS: 9.5 months



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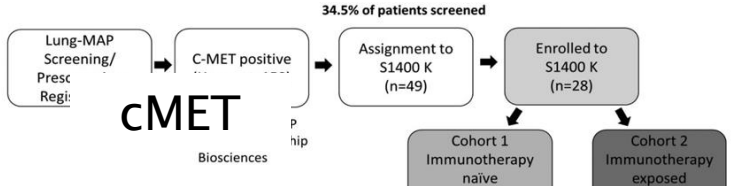
Telisotuzumab vedotin, a phase II study in patients with c-MET+ stage IV or recurrent squamous cell lung cancer (LUNG-MAP sub-study S1400K, NCT03574753)

Waqar Clin Can Res 2021



cMET

Biosciences

- There were 3 G5 events (2 pneumonitis in cohort 2 and 1 bronchopulmonary hemorrhage in cohort 1)
- Telisotuzumab vedotin

2023 ASCO ANNUAL MEETING #ASCO23

TABLE 5. Most Common (≥ 10%) TRAEs in the Safety Population

TRAEs	All Grades, No. (%)	Grades 3-4, No. (%)
Patients with any event	91 (86)	31 (29)
Blurred vision	43 (41)	6 (6)
Keratopathy[a]	31 (29)	9 (9)
Nausea	31 (29)	0 (0)
Dry eye	26 (25)	2 (2)
Fatigue	25 (24)	1 (1)
Diarrhea	23 (22)	2 (2)
Asthenia	16 (15)	1 (1)
Photophobia	14 (13)	0 (0)

Trastuzumab-deruxtecan - pneumonitis

16:30 – 16:45 GMT-5

PRESENTATION 1

The Evolution of ADC Development

Sarat Chandarlapaty, MD, PhD
Memorial Sloan Kettering Cancer Center

16:45 – 17:00 GMT-5

PRESENTATION 2

Managing Antibody Drug Conjugate Toxicities

Thomas Powles, MD
Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St. Bartholomew's Hospital

17:00 – 17:15 GMT-5

PRESENTATION 3

The Next Frontier: Resistance to ADCs and Combination Strategies

Erika P. Hamilton, MD
Sarah Cannon Research Institute, Tennessee Oncology

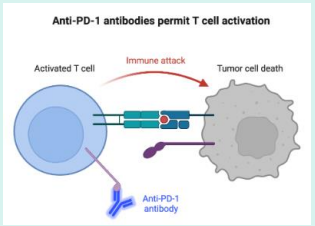
Moore NK, ASCO 2023
Matulonis UA et al, J Clin Oncol 2023;41:2436-2445

Antibody Drug Conjugates

Monoclonal Antibodies

Novel Targets

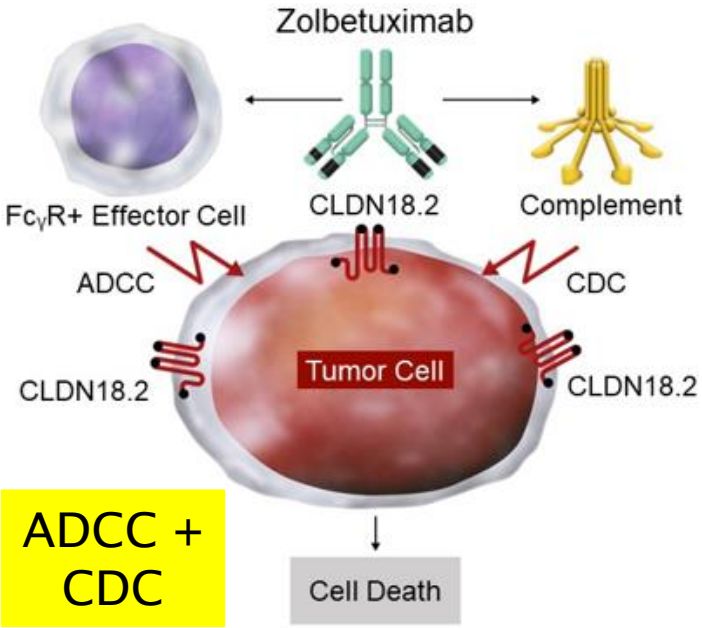
Immunotherapy



Perioperative Treatment

Tumor-Agnostic Drugs

Introduction: Zolbetuximab as Treatment for Patients With LA Unresectable or mG/GEJ Adenocarcinoma



- Treatment for patients with advanced G/GEJ adenocarcinoma is a high and ongoing unmet medical need[1]
  - Overall survival is ~1 year with chemotherapy alone; combining targeted therapy (eg, trastuzumab, nivolumab) with chemotherapy has improved survival in some patients[1–11]
- Zolbetuximab is a first-in-class chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC[8,12–15]

CLDN18.2 is a tight junction protein exclusively expressed in normal gastric mucosa cells and is retained in most G/GEJ adenocarcinomas[14,19,20,21,22,23,24]. In normal gastric mucosa, CLDN18.2 is typically buried within tight junctions[19]. During malignant transformation, loss of gastric mucosa cell polarity may result in CLDN18.2 becoming more exposed and, thus, accessible to therapeutic antibodies[15,20,21,22,23,24,25].

1. Van Cutsem et al. Lancet. 2016; 388(10060):2654-2664; 2. Lordick F et al. A
NEJM. 2021; 384(13):1191-1203; 6. NHCPRC. Chin J Cancer Res. 2022; 34(3):207-237; 7. Bang Y-J et al. Lancet. 2010; 376(9742):687-97; 8. Pellino et al. J Pers Med. 2021 Oct 26;11(11):1095; 9. Shah MA et al. J Clin Oncol. 2023 Mar 1;41(7):1470-1491; 10. Janjigian YY et al. Lancet. 2021; 398(10294):27-40; 11. Shitara K et al. Nature. 2022; 603(7903):942-948; 12. Sahin U et al. Eur J Cancer. 2018;100:17–26; 13. Rhode C et al. Jpn J Clin Oncol. 2019;49:870–6; 14. Türeci Ö et al. Ann Oncol. 2019;30:1487-95; 15. Sahin U et al. Ann Oncol. 2021;32:609–19; 16. Shitara et al. Lancet. 2023; S0140-6736(23)00620-7.

Xu RH, ASCO 2023
Shah MA et al, Nat Med 2023;29:2133-2141

ASCO Gastrointestinal Cancers Symposium

Zolbetuximab + mFOLFOX6 as 1L treatment for patients with CLDN18.2+/ HER2− locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: Primary phase 3 results from SPOTLIGHT

Kohei Shitara, Florian Lordick, Yung-Jue Bang, Peter Enzinger, David Ilson, Manish A. Shah, Eric Van Cutsem, Rui-Hua Xu, Giuseppe Aprile, Jianming Xu, Joseph Chao, Roberto Pazo-Cid, Yoon-Koo Kang, Jianning Yang, Diarmuid Moran, Pranob Bhattacharya, Ahsan Arozullah, Jung Wook Park, Jaffer A. Ajani

Presented at ASCO-GI, January 19–21, 2023
In Person: Moscone West, San Francisco, CA
Virtual: #GI23
Abstract: LBA292

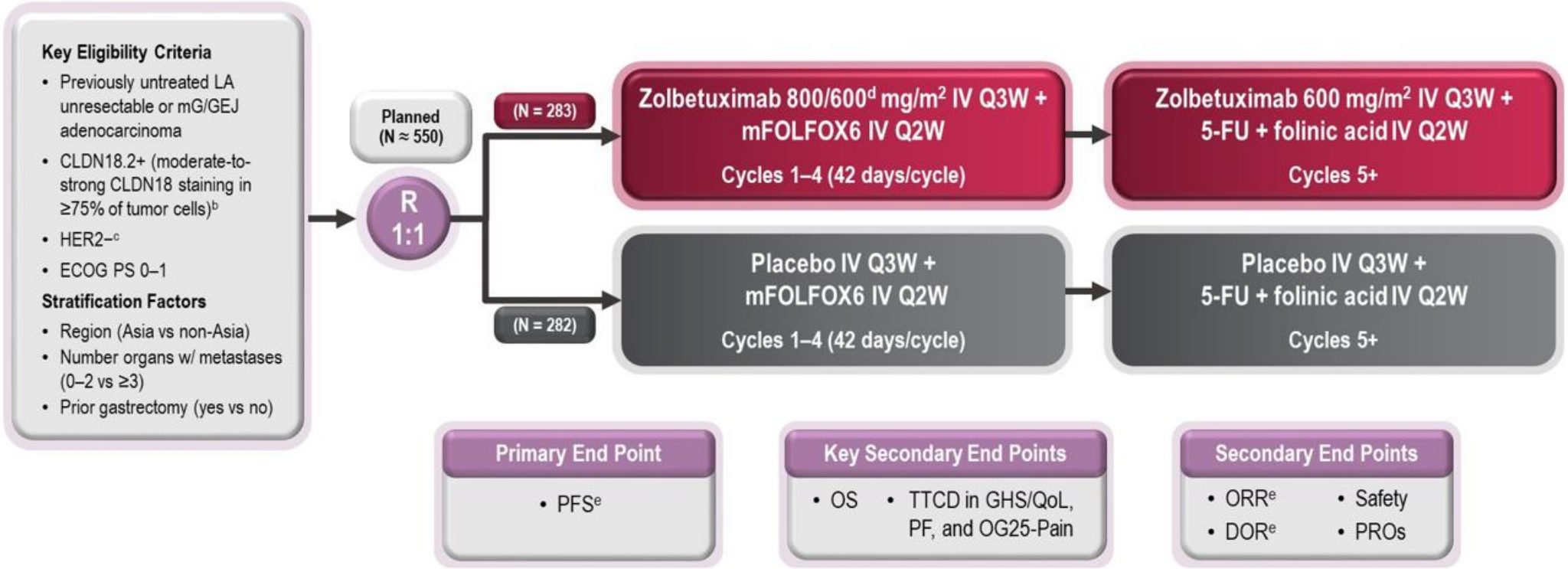
2023 ASCO ANNUAL MEETING

Updates on Abstract 405736 Zolbetuximab + CAPOX in 1L Claudin-18.2+ (CLDN18.2+)/HER2− Locally Advanced (LA) or Metastatic Gastric or Gastroesophageal Junction (mG/GEJ) Adenocarcinoma: Primary Phase 3 Results From GLOW

Rui-Hua Xu, Kohei Shitara, Jaffer A. Ajani, Yung-Jue Bang, Peter Enzinger, David Ilson, Florian Lordick, Eric Van Cutsem, Javier Gallego Plazas, Jing Huang, Lin Shen, Sang Cheul Oh, Patrapim Sunpaweravong, Hwoei Fen Soo Hoo, Haci Mehmet Turk, Jung Wook Park, Diarmuid Moran, Pranob Bhattacharya, Ahsan Arozullah, Manish A. Shah

Presented at the 2023 ASCO Annual Meeting, June 3, 2023, 12:30–1:45 PM (CT)
Virtual: #ASCO2023
Abstract: 405736

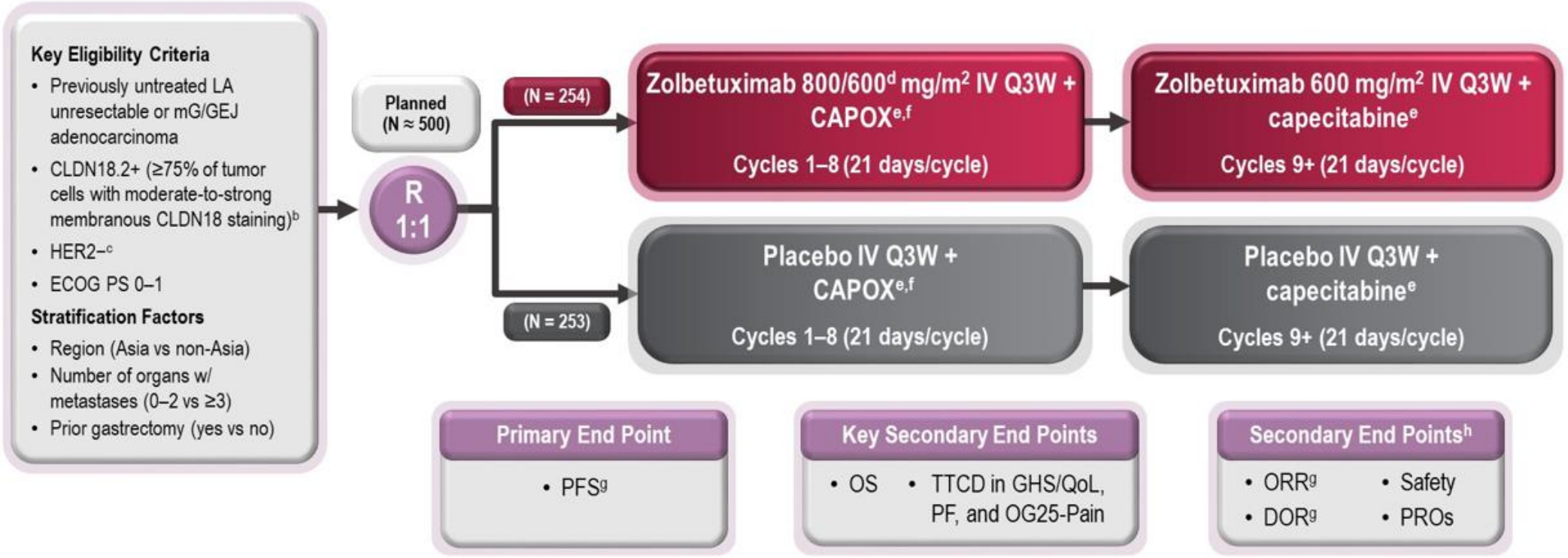
SPOTLIGHT: double blind randomized phase III upfront mG/GEJ



CLDN18.2 assessment: CLDN18.2-positive (defined as ≥75% of tumour cells showing moderate-to-strong membranous CLDN18 staining, determined by central immunohistochemistry using the investigational VENTANA CLDN18 [43-14A] RxDx Assay [Roche Diagnostic Solutions; Tucson, AZ, USA]), HER2-negative

Shitara K, ASCO 2023
Shitara K et al, Lancet 2023;401:1655-68

GLOW: double blind randomized phase III upfront mG/GEJ



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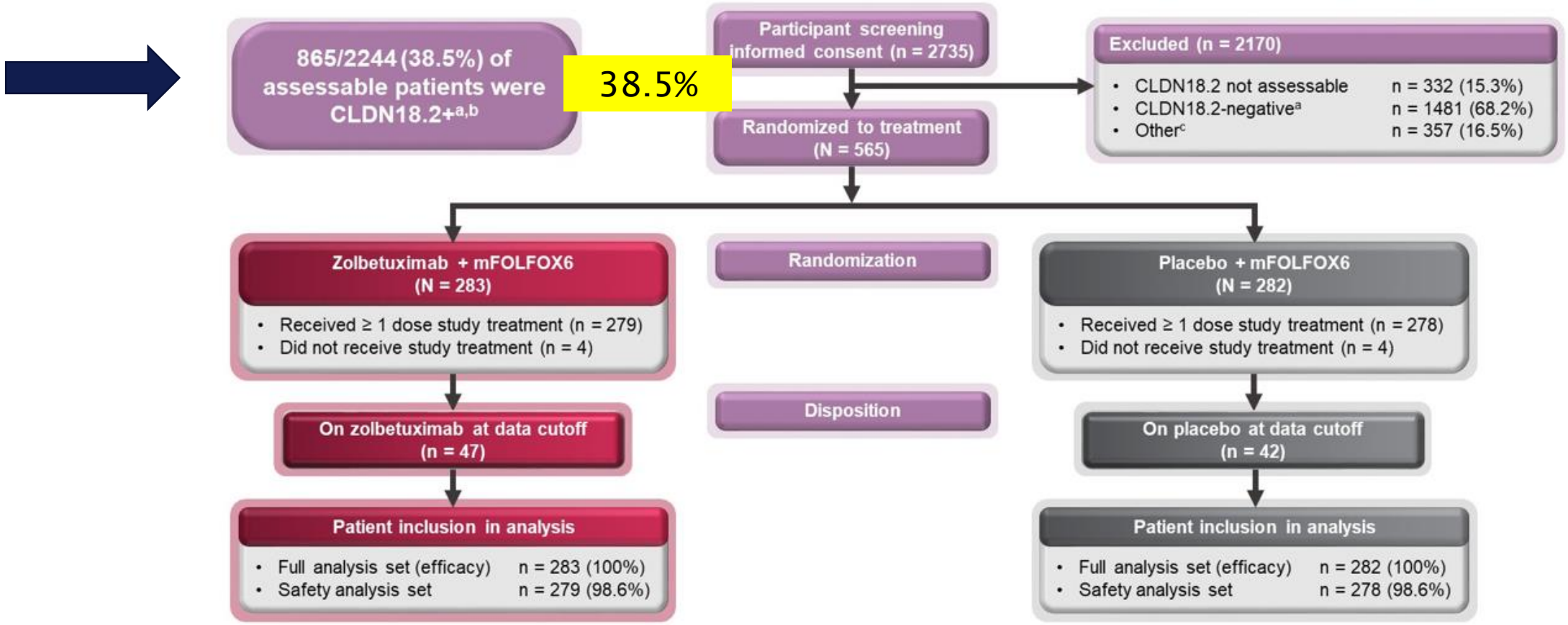
Xu RH, ASCO 2023
Shah MA et al, Nat Med 2023;29:2133-2141

SPOTLIGHT: double blind randomized phase III upfront mG/GEJ

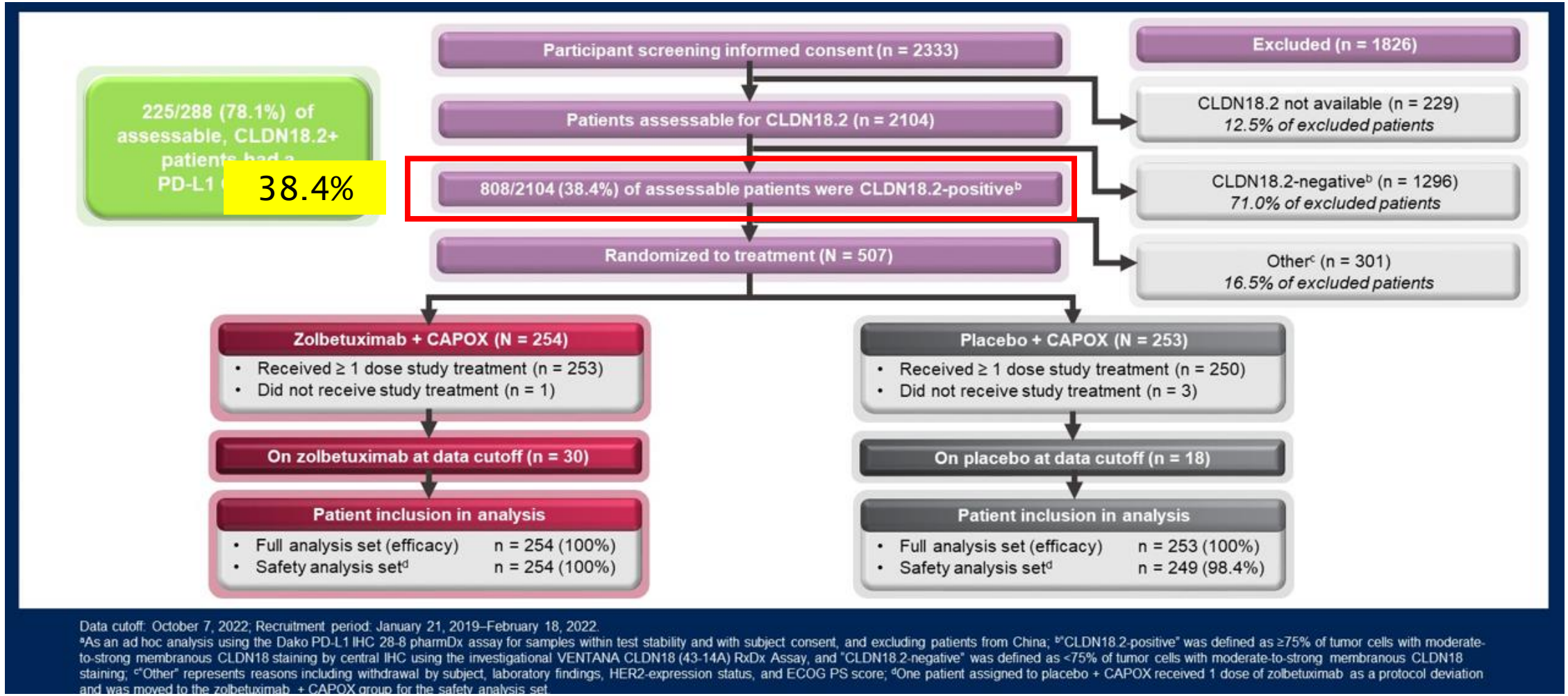


Data cutoff: September 9, 2022; Recruitment period: June 21, 2018–April 1, 2022.

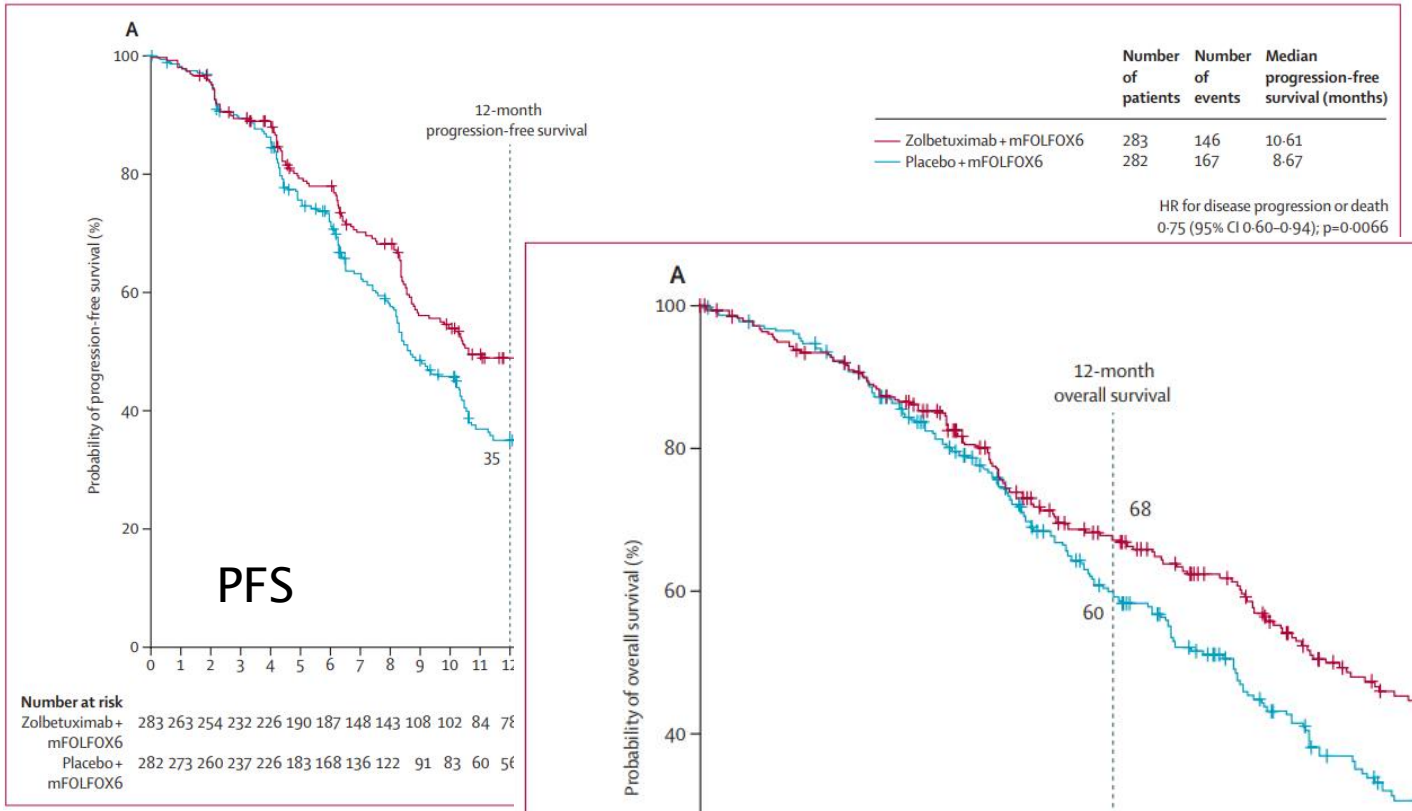
[a]CLDN18.2+ was defined as moderate-to-strong CLDN18 staining in ≥75% of tumor cells by central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay. [b]These data exclude Chinese patients. [c]"Other" represents reasons including withdrawal by subject, laboratory findings, HER2-expression status, and ECOG PS score.

Shitara K, ASCO 2023
Shitara K et al, Lancet 2023;401:1655-68

GLOW: double blind randomized phase III upfront mG/GEJ

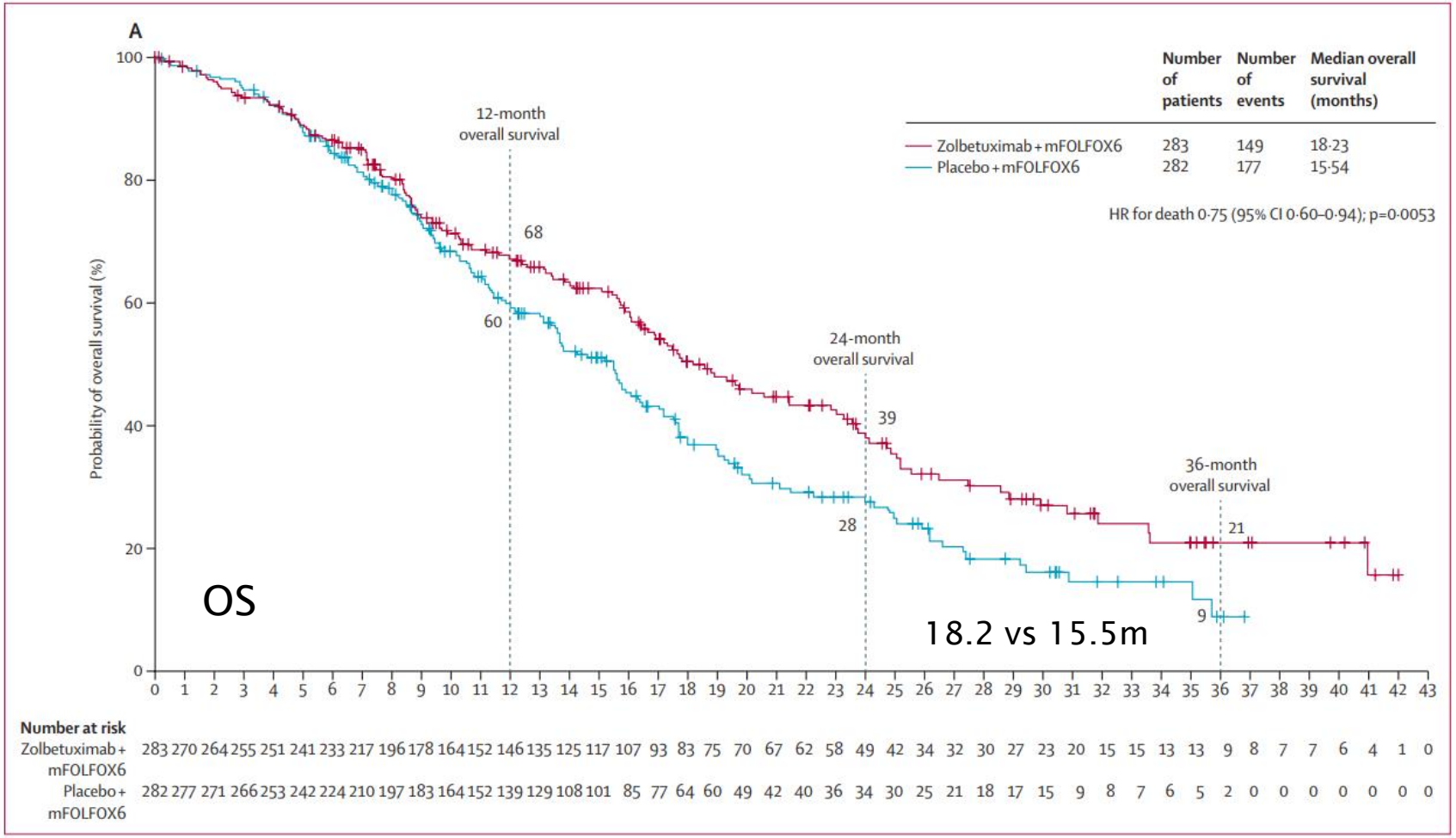


Xu RH, ASCO 2023
Shah MA et al, Nat Med 2023;29:2133-2141



	Number of patients	Number of events	Median progression-free survival (months)
Zolbetuximab + mFOLFOX6	283	146	10·61
Placebo + mFOLFOX6	282	167	8·67

HR for disease progression or death 0·75 (95% CI 0·60–0·94); p=0·0066



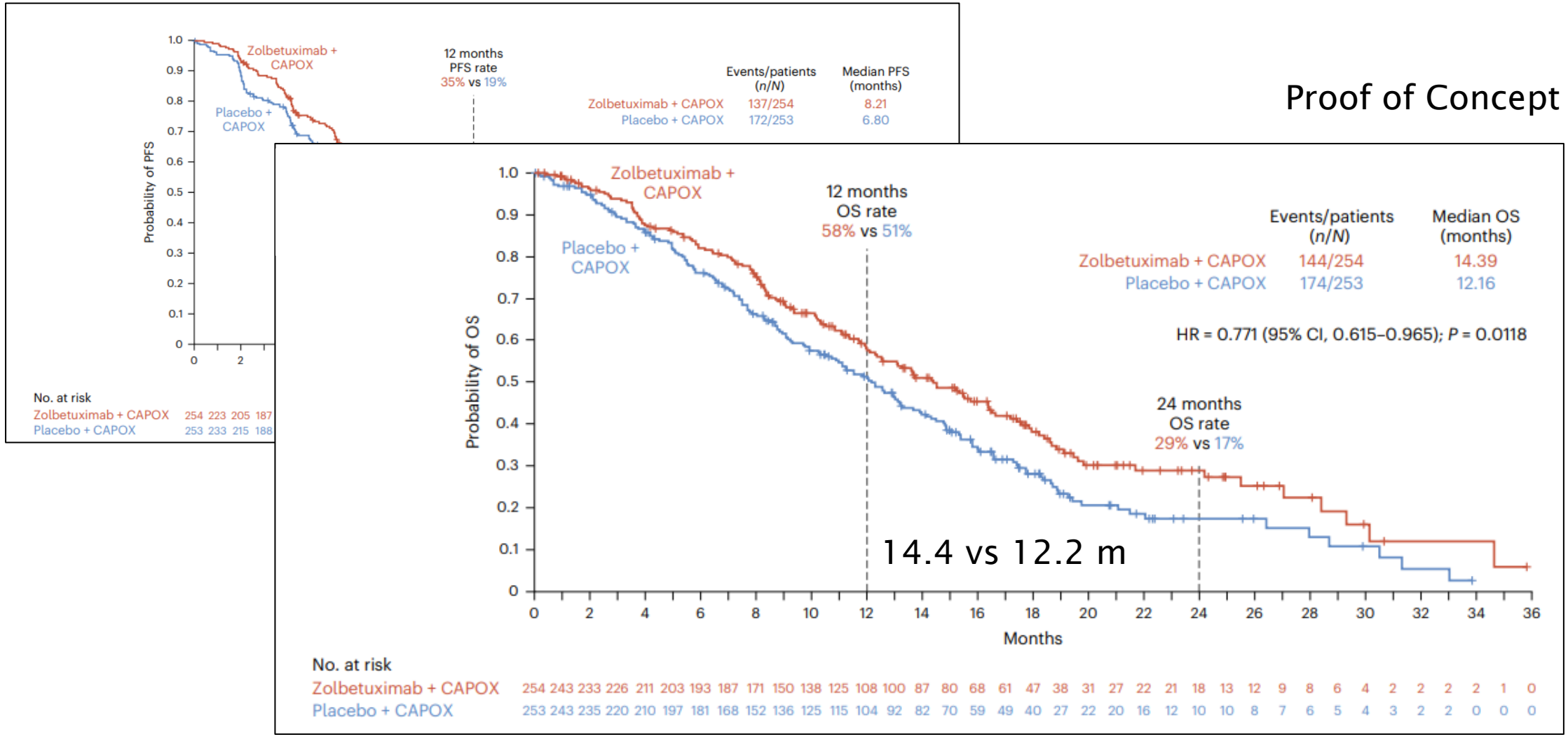
	Number of patients	Number of events	Median overall survival (months)
Zolbetuximab + mFOLFOX6	283	149	18·23
Placebo + mFOLFOX6	282	177	15·54

HR for death 0·75 (95% CI 0·60–0·94); p=0·0053

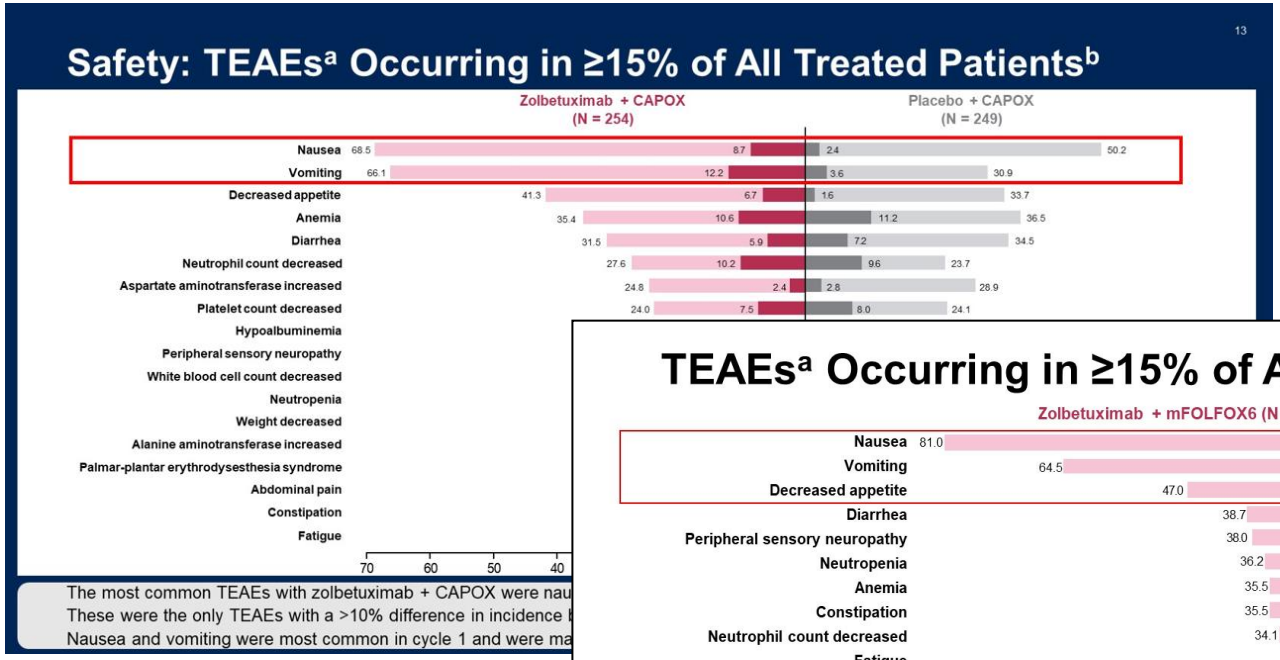
Shitara K, ASCO 2023
Shitara K et al, Lancet 2023;401:1655-68

GLOW: double blind randomized phase III upfront mG/GEJ -OS

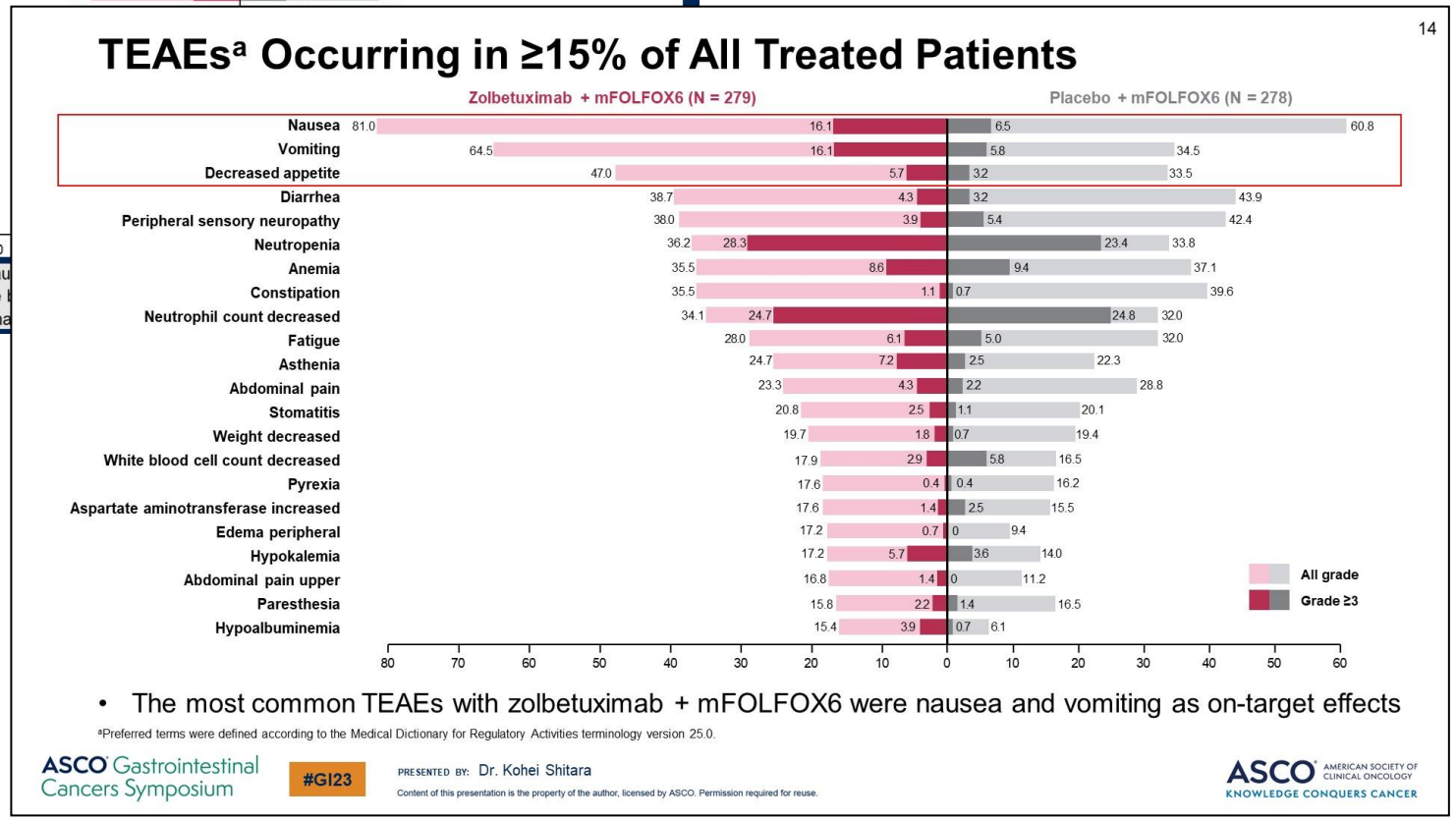
Proof of Concept



Xu RH, ASCO 2023
Shah MA et al, Nat Med 2023;29:2133-2141



>30% increase in vomiting
>20% increase in nausea
„on-target“ effect



More toxicity
RRs similiar

15

Conclusions

- **Zolbetuximab + CAPOX showed a statistically significant and clinically meaningful survival benefit**
  - PFS and OS benefits were sustained at 24 months, and patients continue to be followed for survival
- **Zolbetuximab + CAPOX demonstrated a tolerable and manageable safety profile**
  - Nausea and vomiting were the most frequent TEAEs and initial onset occurred mostly in the first zolbetuximab cycle
  - In the zolbetuximab arm, nausea and vomiting were more common in patients without prior gastrectomy
- **Efficacy and safety results were consistent with those observed in SPOTLIGHT (zolbetuximab + mFOLFOX6)**
- **GLOW confirms zolbetuximab + chemotherapy is a new potential standard-of-care treatment for patients with CLDN18.2+/HER2− LA unresectable or mG/GEJ adenocarcinoma**

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Rui-Hua Xu

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Conclusions

Zolbetuximab + mFOLFOX6 showed a statistically and clinically significant improvement of both PFS and OS

- One of the longest mOS in patients with LA unresectable or mG/GEJ adenocarcinoma in phase 3 trials
- Survival benefits were also observed across most subgroups

Zolbetuximab + mFOLFOX6 demonstrated a tolerable and manageable safety profile

- Safety profile was consistent with prior studies of zolbetuximab and mFOLFOX6
- Nausea and vomiting were the most frequent TEAEs and first occurred mostly in the first zolbetuximab cycle

Zolbetuximab + mFOLFOX6 is a new potential standard-of-care treatment for a biomarker-based subgroup of patients with CLDN18.2+/HER2− LA unresectable or mG/GEJ adenocarcinoma

ASCO Gastrointestinal Cancers Symposium #GI23 PRESENTED BY: Dr. Kohei Shitara

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

SPOTLIGHT- und GLOW-Studien waren definitiv die Highlights des Jahres! In diesen beiden Studien wurde der Anti-Claudin-18.2-Antikörper Zolbetuximab entweder mit FOLFOX bzw. CAPOX bei Patienten mit CLDN 18.2-positivem Magen-/Ösophagus-Adenokarzinom im Stadium IV getestet. Sowohl PFS als auch OS wurden in beiden Phase-III-Studien verlängert, daher wird dies der neue Standard sein. Dies ist die erste zielgerichtete Therapiestudie in Frontline Setting von Stadium IV Magen/Öso Adenos seit 13 Jahren (vor 13 Jahren TOGA-Studie mit Trastuzumab).

Prof. Ilhan-Mutlu

2023 ASCO® ANNUAL MEETING

INDIGO: a Phase 3 global, randomized, double-blinded study of vorasidenib versus placebo in patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation

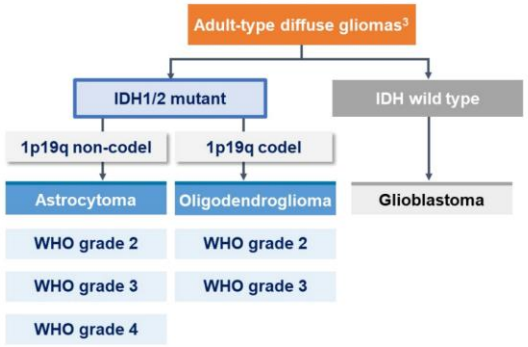
Ingo K. Mellinghoff,[1] Martin J. van den Bent,[2] Deborah T. Blumenthal,[3] Mehdi Touat,[4] Katherine B. Peters,[5] Jennifer Clarke,[6] Joe Mendez,[7] Liam Welsh,[8] Warren P. Mason,[9] Andreas F. Hottinger,[10] Juan M. Sepulveda,[11] Wolfgang Wick,[12] Riccardo Soffietti,[13] Steven Schoenfeld,[14] Dan Zhao,[14] Susan Pandya,[14] Lori Steelman,[14] Islam Hassan,[14] Patrick Y. Wen,[15]* Timothy F. Cloughesy[16]*

*[1]Memorial Sloan-Kettering Cancer Center, New York City, NY, USA; [2]Erasmus Medical Center, Rotterdam, Netherlands; [3]Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel; [4]Pitié Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP) Sorbonne Université, Paris, France, [5]Duke University Medical Center, Durham, NC, USA; [6]University of California, San Francisco; [7]Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA; [8]The Royal Marsden Hospital, London, UK; [9]Toronto General Hospital, Toronto, M5G2C4, Canada; [10]University Hospital of Lausanne, Lausanne, Switzerland; [11]Hospital Universitario 12 de Octubre, Madrid, Spain; [12]Universitatsklinikum Heidelberg, Heidelberg, Germany; [13]University of Turin, Torino, Italy; [14]Servier Pharmaceuticals, Boston, MA, USA; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]University of California, Los Angeles, CA, USA. *These authors contributed equally*

ClinicalTrials.gov identifier: NCT04164901. This study was sponsored by Servier

IDH1/2-mutant diffuse gliomas

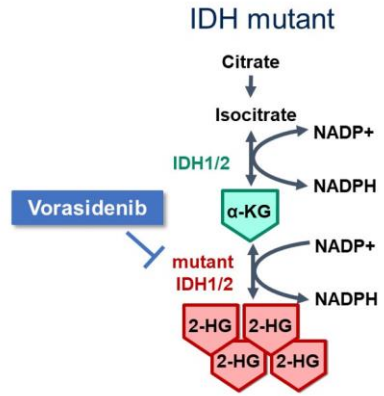
- IDH1/2 mutations occur in most low-grade diffuse gliomas[1,2]
- Characteristic molecular and clinical features[3]
- Distinct disease entity in revised WHO classification (2021)[3]
- Median age ~40 years[4]



1. Yan H *et al. N Engl J Med* 2009;360:765–73; 2. Hartmann C *et al. Acta Neuropathol* 2009;118:469–74; 3. Louis DN *et al. Neuro Oncol* 2021;23:1231–51; 4. Ostrom QT *et al. Neuro Oncol* 2022;24:v1–v95.
codel, codeletion.

Vorasidenib

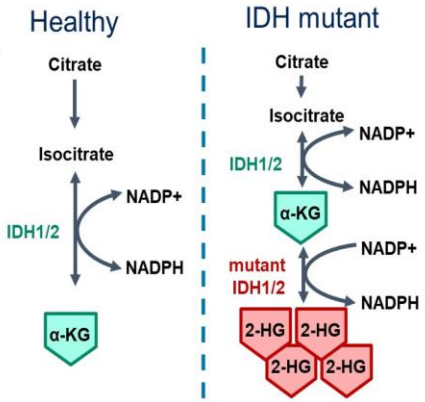
- Oral inhibitor of mutant IDH1 and IDH2[1]
- Specifically designed for brain penetrance[1]
- Reduced tumor 2-HG by >90% in resected grade 2/3 non-enhancing diffuse glioma[1]
- 2-HG reduction associated with:[2]
  - Lower tumor cell proliferation
  - Reversal of IDH1/2 mutation-associated gene expression programs
  - Increased DNA 5-hydroxy-methylcytosine
  - Increased tumor infiltrating lymphocytes



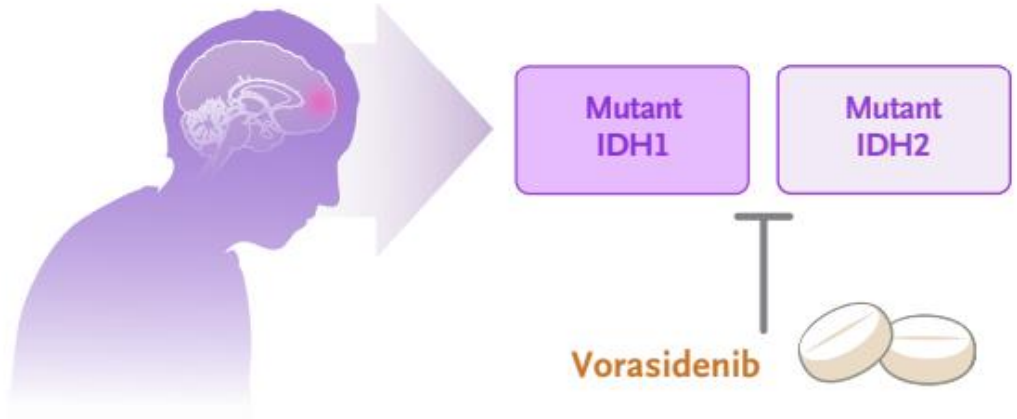
Competitive inhibition of α-KG-dependent enzymes

Isocitrate dehydrogenase

- IDH1/2 hotspot mutations occur in various cancers, including diffuse gliomas[1]
- IDH1/2 mutations result in:[2]
  - Overproduction of R-2-hydroxyglutarate
  - Epigenetic dysregulation
  - Impaired cellular differentiation
  - Immunosuppressive tumor microenvironment



Competitive inhibition of α-KG-dependent enzymes



Mellinghoff IK, ASCO 2023
Mellinghoff IK et al, NEJM 2023;389:589-601

INvestigating vorasiDenIb in GliOma (NCT04164901)

Key eligibility criteria

- ≥12 years of age
- IDH1/2-mutated* grade 2 oligodendroglioma or astrocytoma per WHO 2016 guidelines
- Prior surgery only
- Measurable non-enhancing disease (≥1 target lesion measuring ≥1 cm × ≥1 cm), confirmed by blinded review
- Not in need of immediate chemotherapy or radiotherapy per investigator assessment

1:1 double-blind randomization (N=331)

Stratified by 1p19q status and baseline tumor size

Vorasidenib 40 mg (N=168)

Orally, once daily, 28-day cycles

Centrally confirmed progressive disease permitted unblinding and crossover†

Placebo (N=163)

IDMC regularly reviewed safety and other clinical data, as well as the efficacy data following prespecified interim analyses

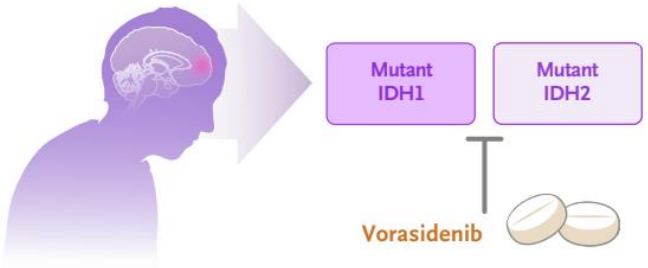
*Centrally confirmed using an investigational clinical trial assay, based on the Oncomine Dx Target Test and developed in partnership with Thermo Fisher Scientific Inc.;
†Real-time single BIRC reader.
IDMC, independent data monitoring committee.

1 Primary endpoint

PFS: time from randomization to the first imaging-based disease progression as assessed by BIRC or death because of any cause
- MRI every 3 months for 3 years, then every 6 months

2 Key secondary endpoint

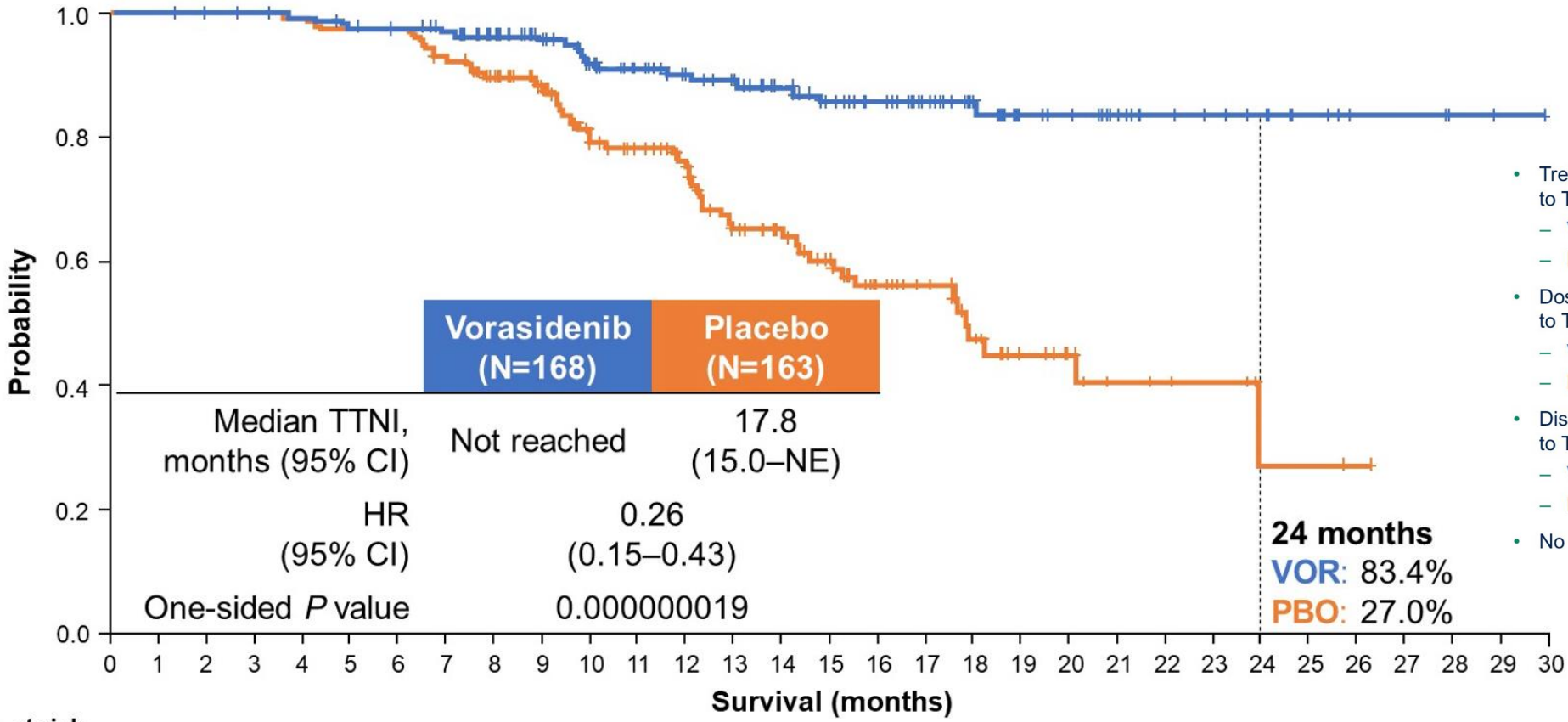
TTNI: time from randomization to the initiation of first subsequent anticancer therapy or death because of any cause



2 years of recriutment, >70 centers in 10 countries

Mellinghoff IK, ASCO 2023
Mellinghoff IK et al, NEJM 2023;389:589-601

Key secondary endpoint: Time to next treatment initiation



- Treatment interruption due to TEAE
  - **Vorasidenib** 29.9% (n=50)
  - **Placebo** 22.7% (n=37)
- Dose reduction due to TEAE
  - **Vorasidenib** 10.8% (n=18)
  - **Placebo** 3.1% (n=5)
- Discontinuation due to TEAE
  - **Vorasidenib** 3.6% (n=6)
  - **Placebo** 1.2% (n=2)
- No fatal TEAE

No. at risk

VOR	168	168	167	167	165	161	160	156	146	130	117	105	95	86	75	65	57	48	38	27	25	18	15	13	11	7	4	4	2	1	0
PBO	163	163	162	161	159	156	155	146	134	119	97	88	77	60	54	45	35	30	21	14	11	7	6	5	2	2	1	0			

+ Censored.
P value is from one-sided stratified log-rank test.

Mellinghoff IK, ASCO 2023
Mellinghoff IK et al, NEJM 2023;389:589-601

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

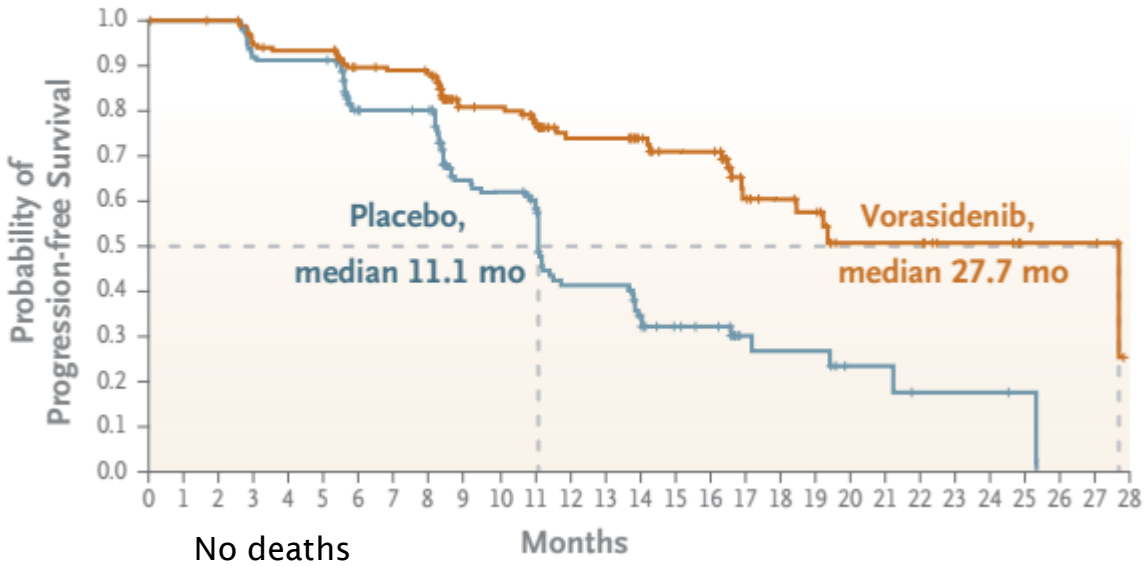
Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

Mellinghoff IK et al. DOI: 10.1056/NEJMoa2304194

N = 331 Patienten
Age 16-71 Jahre

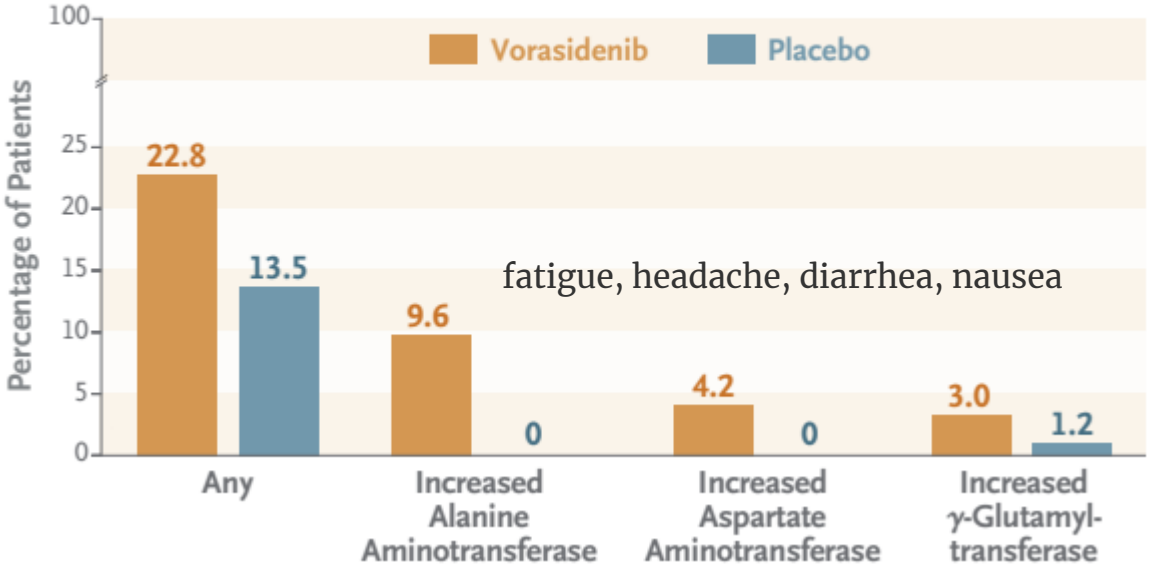
Progression-free Survival

HR for disease progression or death, 0.39 (95% CI, 0.27–0.56); P<0.001



No deaths

Adverse Events of Grade ≥3



fatigue, headache, diarrhea, nausea

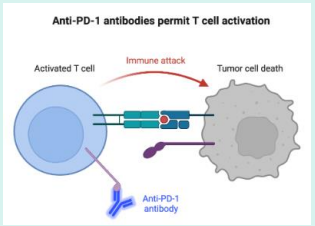
Significant improvement of imaging-based PFS and TTNI with a manageable safte profile in patients who were not in need of immediate chemotherapy or radiotherapy

Antibody Drug Conjugates

Monoclonal Antibodies

Novel Targets

Immunotherapy

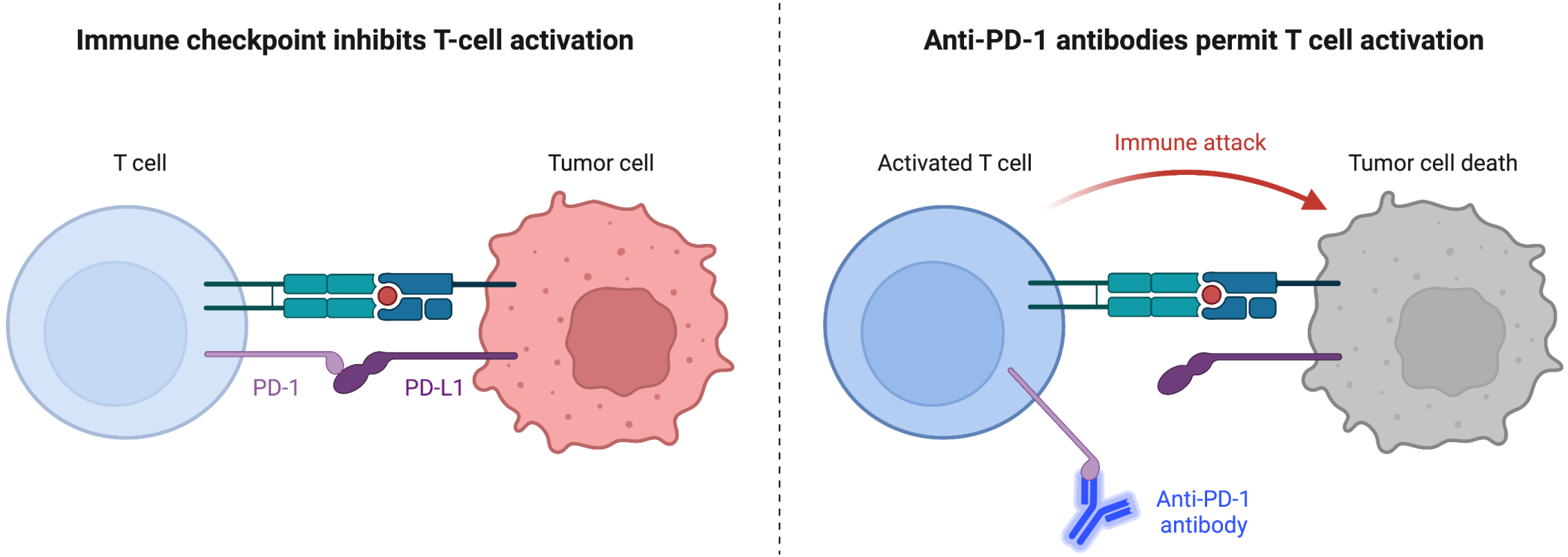


Perioperative Treatment

Tumor-Agnostic Drugs

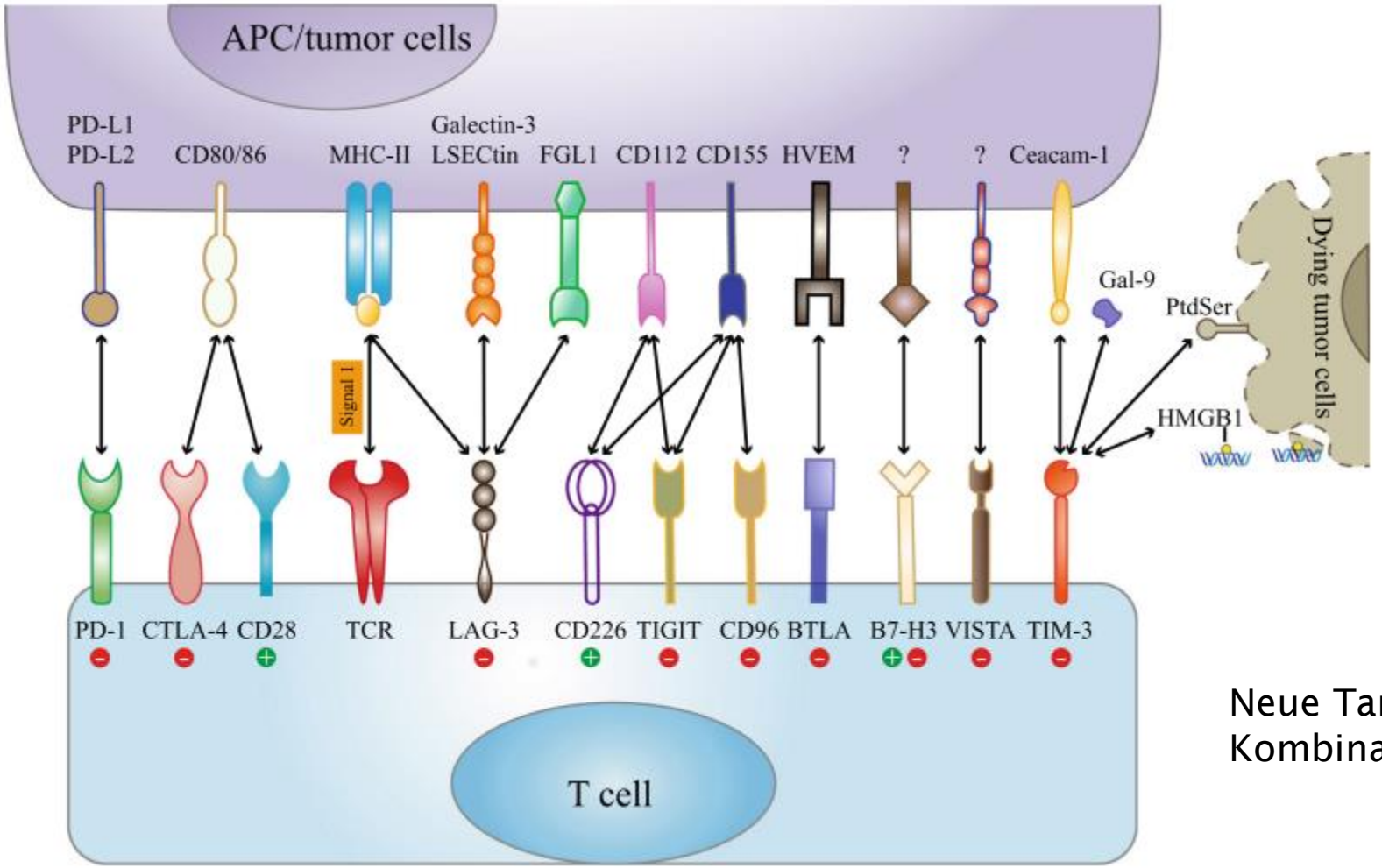
2023

“A decade of immune checkpoint-inhibitors in cancer therapy“



Immunotherapy using immune-checkpoint modulators revolutionizes the oncology field far beyond their remarkable clinical efficacy in some patients. It creates radical changes in the evaluation of treatment efficacy and toxicity with a more holistic vision of the patient with cancer.

Immunotherapy in 2023 – is there still anything to learn?



Microbiome?

Neue Targets?
Kombinationspartner?

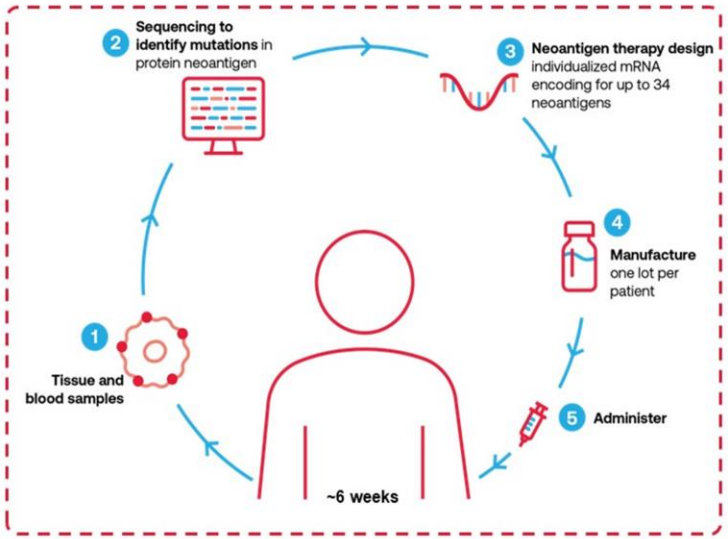
Quin et al, Molecular Cancer:2019;18:155

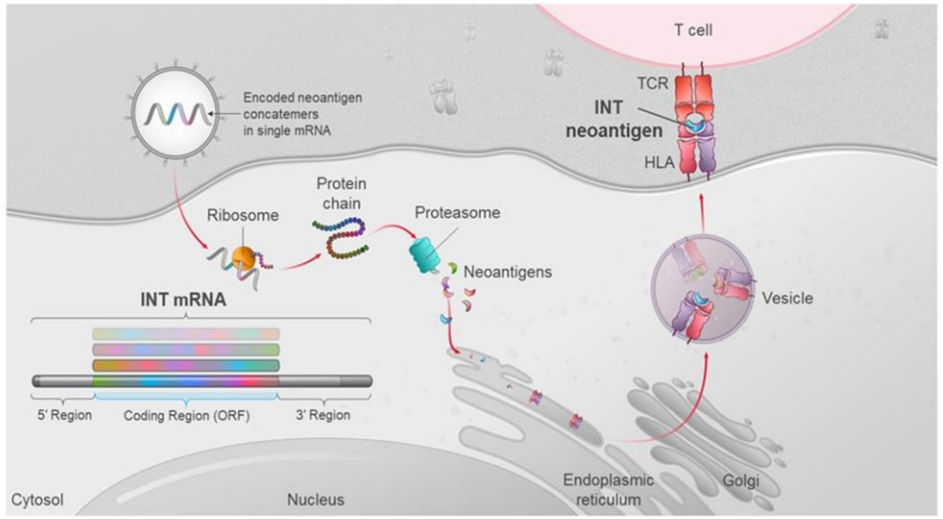
Personalized mRNA-Based Cancer Vaccine Plus Pembrolizumab for High-Risk Melanoma

KN942

mRNA-4157 (V940) Mechanism of Action

- mRNA-4157 (V940) is **an individualized neoantigen therapy** designed to target an individual patient's unique tumor mutations and encodes up to 34 neoantigens[1,2]
- Therapies targeting neoantigens can increase endogenous **neoantigen T-cell responses and induce epitope spreading** to novel antigens with the ability **to drive antitumor responses** and **maintain memory** with cytolytic properties, potentially **producing long-term disease control** for patients[3-7]

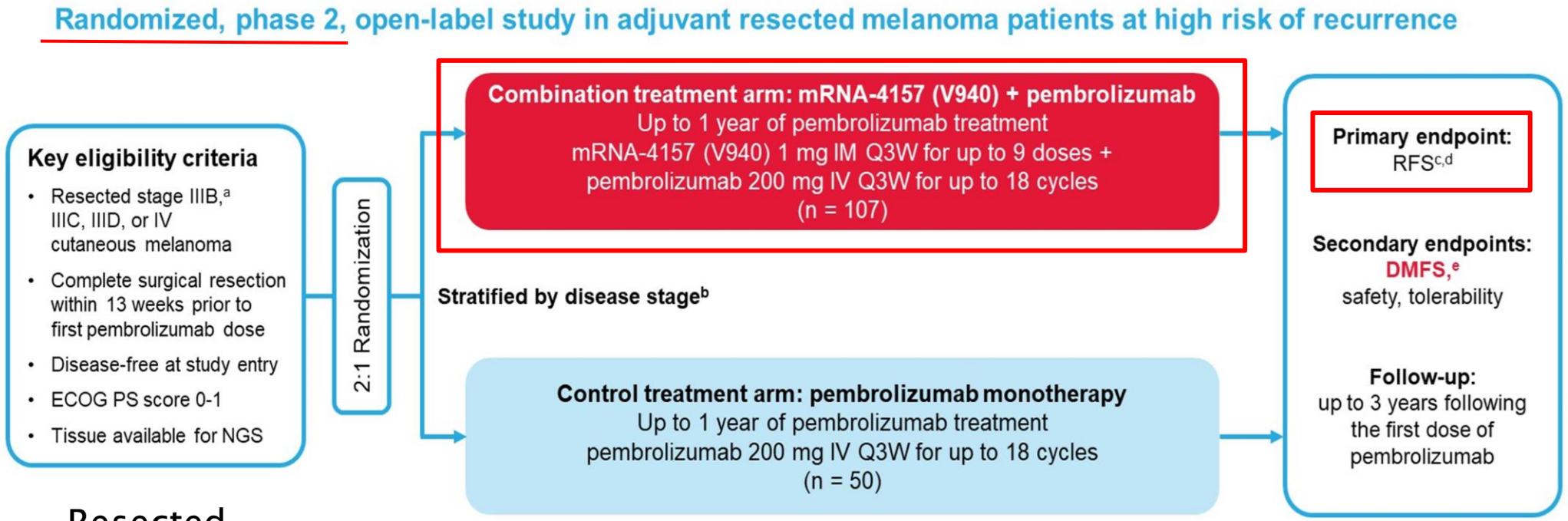




Based on the technology developed for CovidVaccs…

Khattak et, ASCO 2023

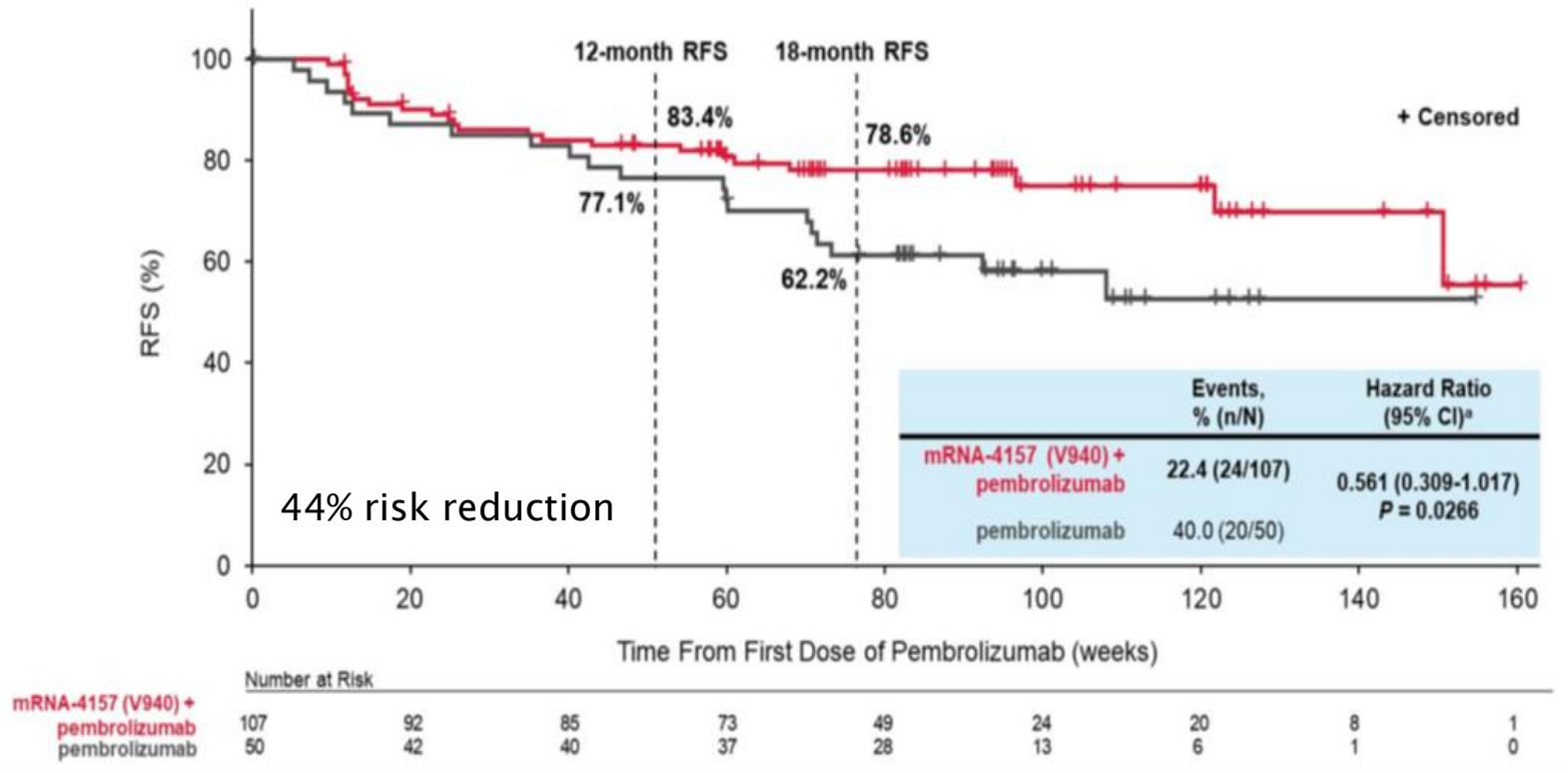
mRNA-4157-P201/Keynote-942 Study Design



Resected melanoma

[a]Patients with stage IIIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent. [b]According to the 8th edition of the American Joint Committee on Cancer Staging Manual. [c]The primary endpoint was investigator-assessed RFS (defined as the time from first dose of pembrolizumab until the date of first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause) in the intention-to-treat population. [d]The primary analysis for RFS was specified to occur after all patients completed ≥12 months on study and ≥40 RFS events were observed. Descriptive analysis was specified to occur when ≥51 RFS events were observed. [e]Investigator-assessed DMFS was defined as the time from first dose of pembrolizumab until the date of first distant recurrence or death from any cause. [f]The stratified log-rank test was used for comparison. [g]Time of database cutoff was November 14, 2022.

Keynote-942 Trial: Primary Endpoint RFS

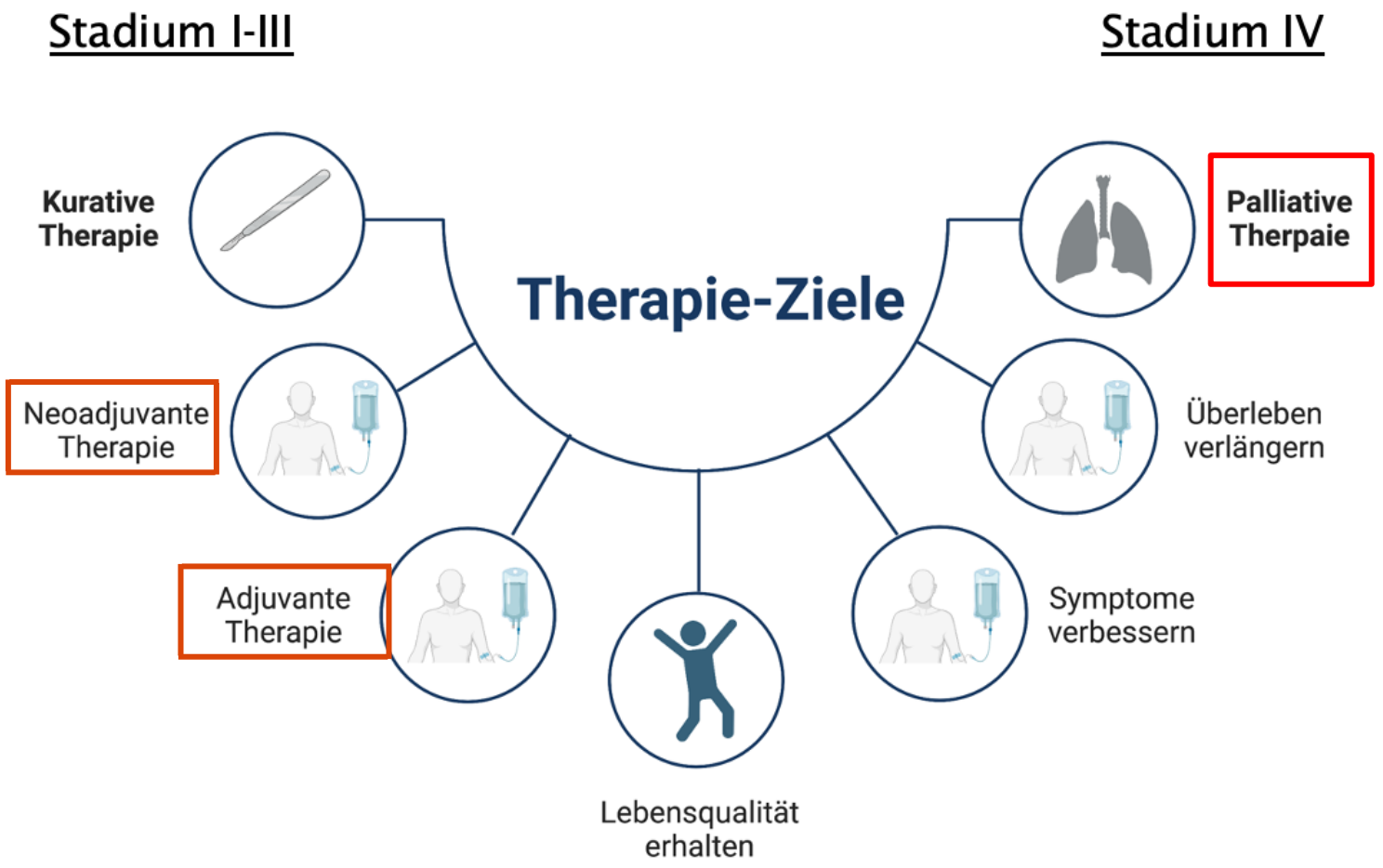


- Proof of concept
- Phase II only
- Short FUP time
- Tissue based
- Time factor

TMB independent effect

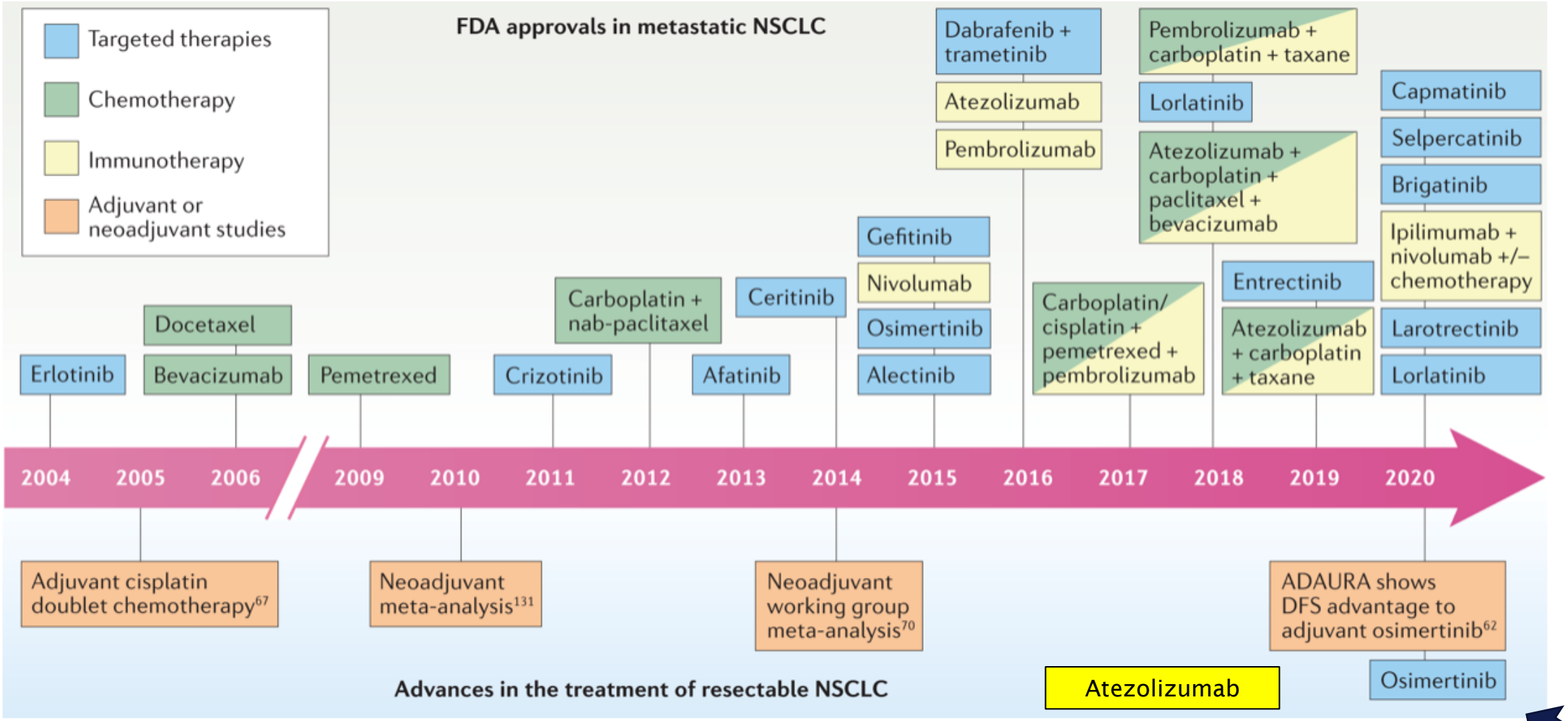
From new Targets to Evolvement of…

The earlier the better? Immunotherapy in early lung cancer



Overall survival
Disease-free survival
Langzeit Tox

Perioperative Therapie beim NSCLC



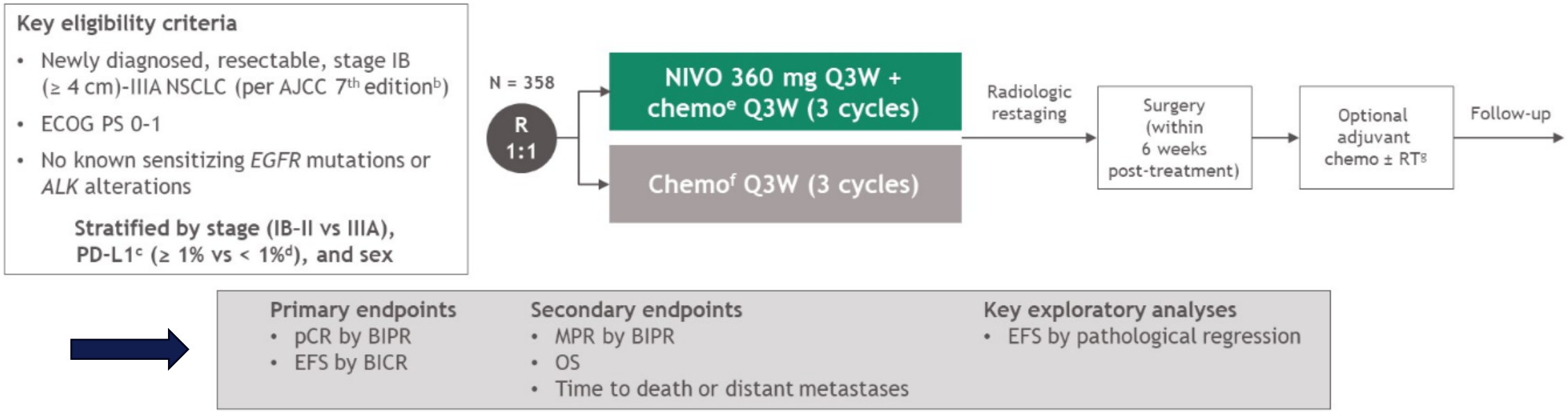
Atezolizumab

Pembrolizumab

Chaft JE et al, Nature Reviews Clin Oncol 2021;18:547-57

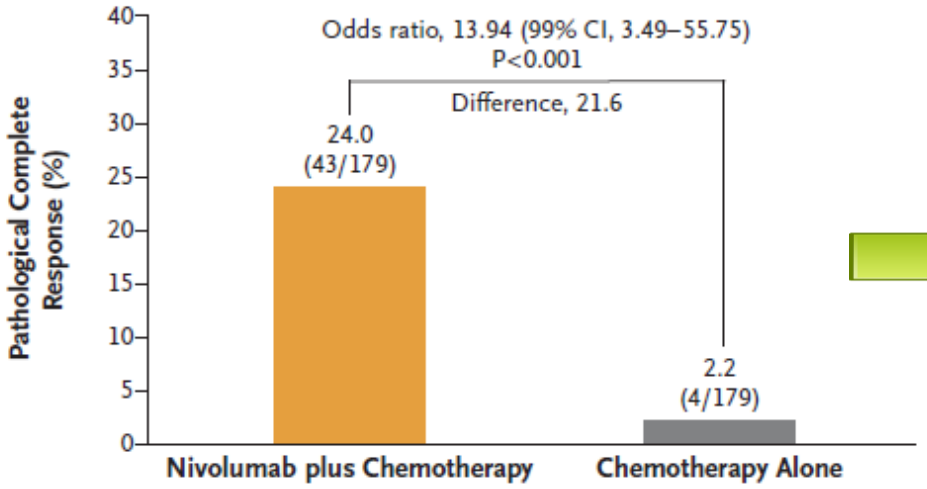
CheckMate 816 Study Design

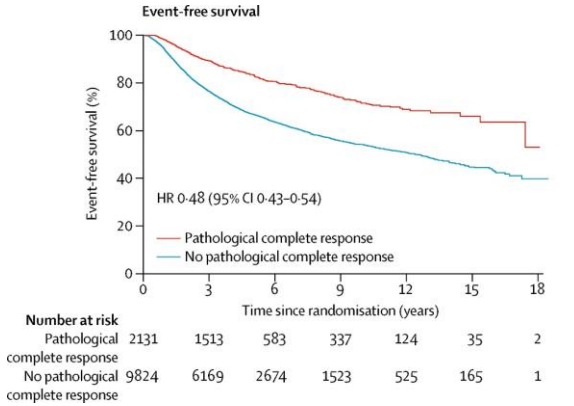
- In CheckMate 816,[a] neoadjuvant NIVO + chemo significantly improved the primary endpoints of EFS and pCR vs chemo in patients with resectable NSCLC[1]
  - NIVO + chemo is now indicated in the United States as neoadjuvant treatment for adult patients with resectable (tumors ≥ 4 cm or node positive) NSCLC[2]
- Here, we present a post hoc analysis evaluating the association between pathological regression and EFS from CheckMate 816

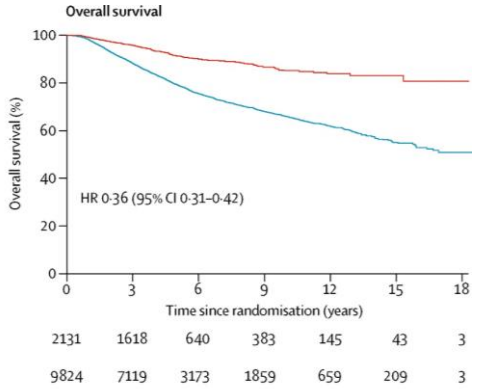


Database lock: September 16, 2020 (final analysis of pCR); October 20, 2021 (preplanned interim analysis 1 of EFS); minimum follow-up: 21 months.

CheckMate 816 Primary Endpoint Event-free Survival





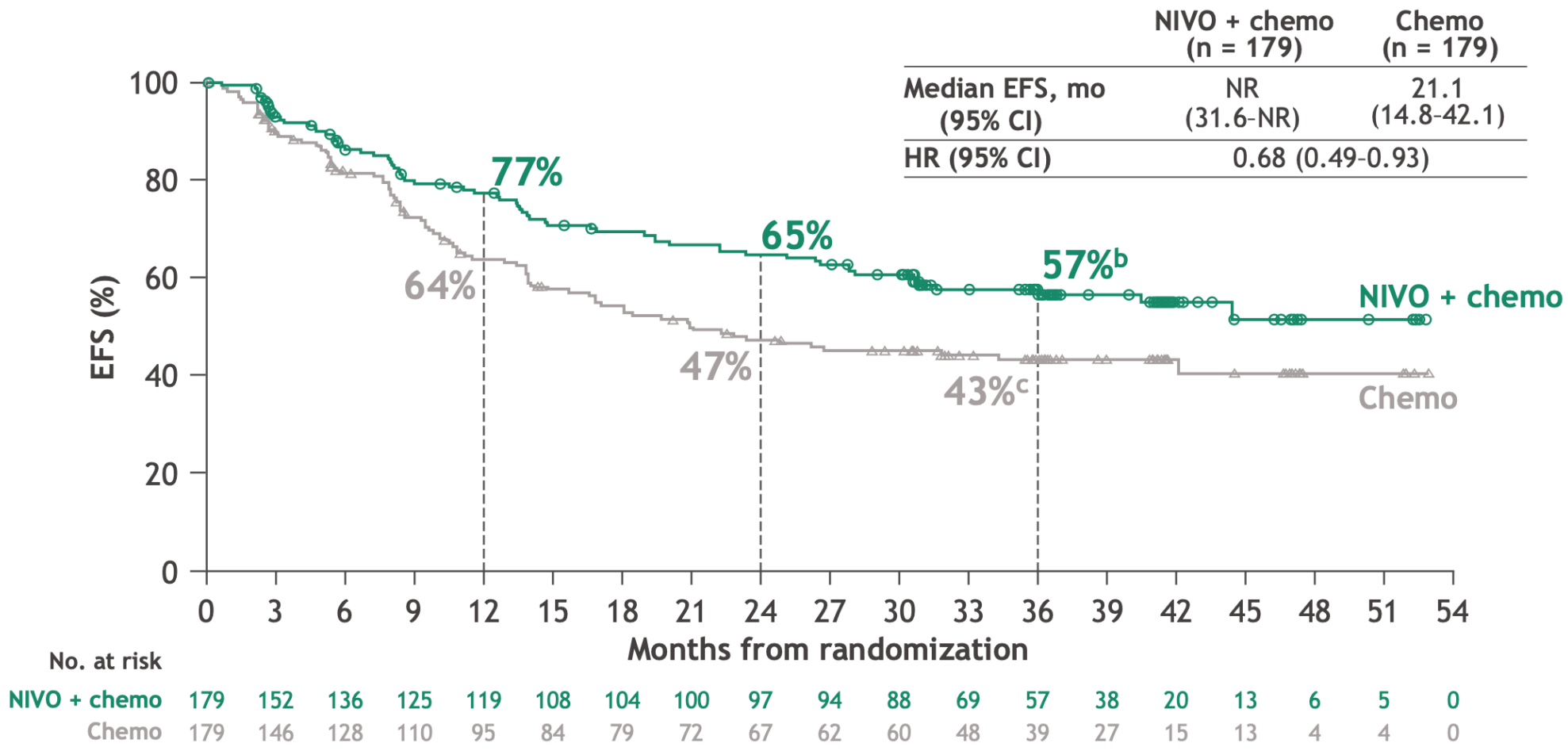


Erhöhung der Rate an CRs um >20%

pCR and long-term outcome in breas cancer

Reck M et al, NEJM 2016;375:1823-33
Cortazar P et al, Lancet 2014;384:164-72

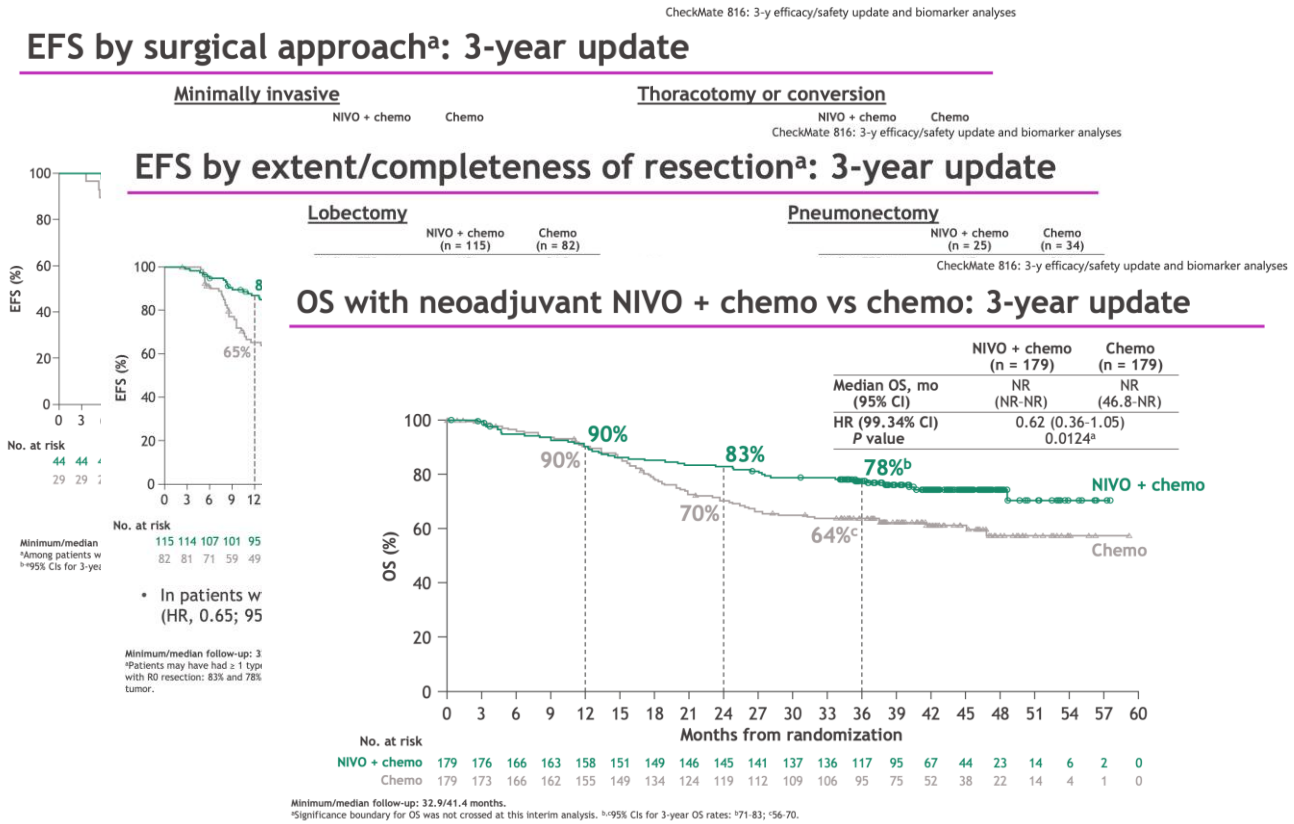
EFS with neoadjuvant NIVO + chemo vs chemo: 3 year update ELCLC 2023



CheckMate 816 Update ELCC 2023

elcc European Lung Cancer Congress 2023

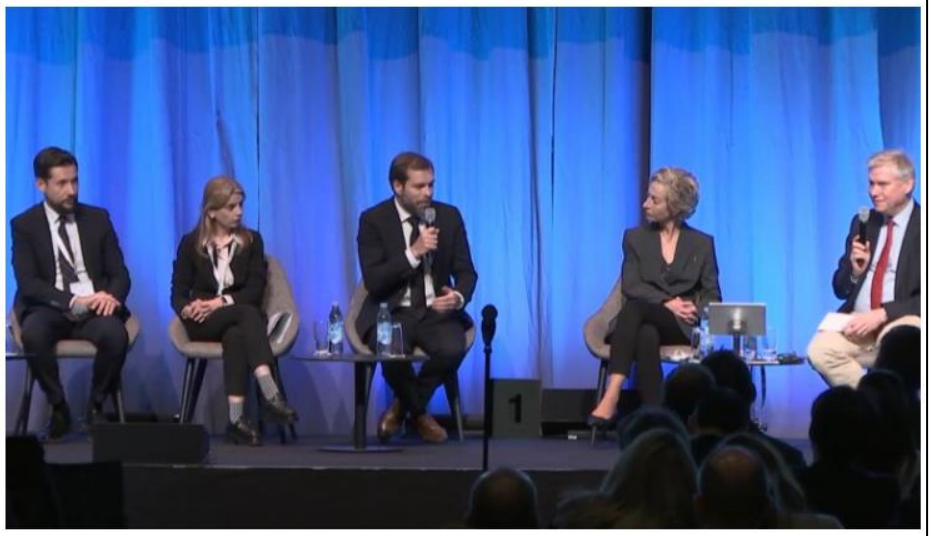
COPENHAGEN DENMARK
29 MARCH - 1 APRIL 2023



Median FUP 41.4m
Minimal invasive versus srugery
Lobectomy Pneumectomy
4 Base-line gene inflammatory signature

Long-term event-free survival benefits of neoadjuvant nivolumab plus chemotherapy for resectable NSCLC

30 Mar 2023 | Immunotherapy | Cytotoxic Therapy | Clinical Research | ELCC 2023



Additional exploratory analyses of the phase III CheckMate 816 trial reveal that event-free survival at 3 years is not influenced by surgical parameters and suggest that tumour inflammation may be a useful predictive biomarker

Perioperative pembrolizumab + platinum-based chemotherapy for resectable locally advanced non-small cell lung cancer: The phase III KEYNOTE-671 study

Stratification by sex, stage (IB vs II vs IIIA), histology, PD-L1 tumor expression per SP142 assay (TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1)

Previously untreated stage locally advanced NSCLC
Able to undergo surgery
Biopsy of suspicious hilar or mediastinal lymph node(s), II-IIIA/B (T3-4 N2)
ECOG PS 0/1
(planned N = 786, R 1:1)

Cisplatin + Gemcitabine/Pemetrexed + Pembrolizumab x4

Cisplatin + Gemcitabine/Pemetrexed + Placebo x4

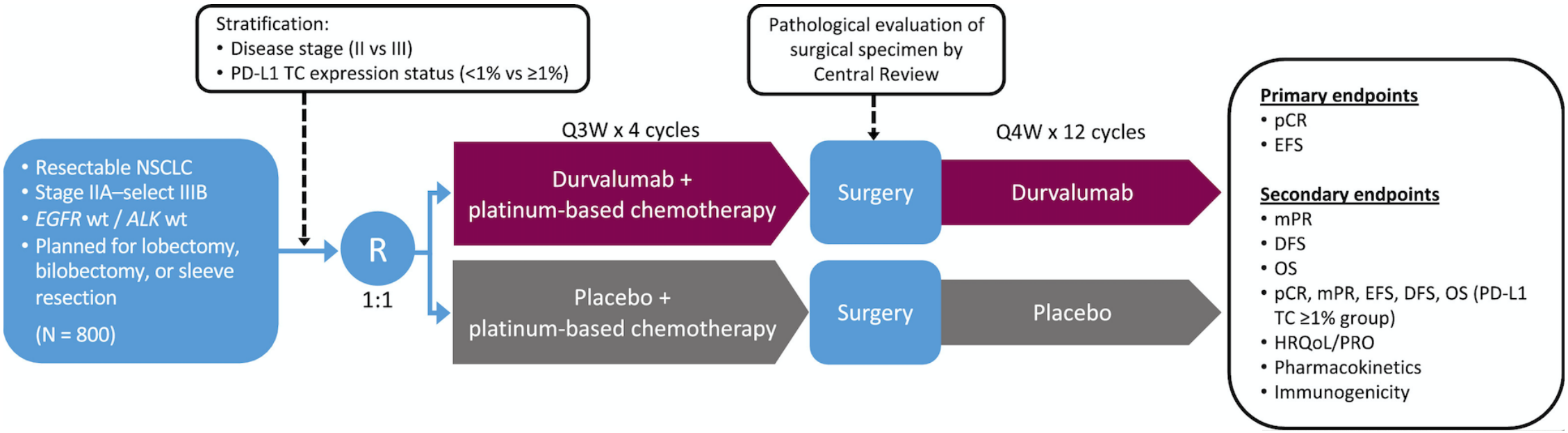
Pembrolizumab
or
Placebo x13

- Primary endpoint dual: Event-free survival and overall survival
- Key secondary endpoints: pCR and mPR (<10% viable tumor cells)

LUNG CANCER—NON-SMALL CELL LOCAL-REGIONAL/SMALL CELL/OTHER THORACIC CANCERS

KEYNOTE-671: Randomized, double-blind, phase 3 study of pembrolizumab or placebo plus platinum-based chemotherapy followed by resection and pembrolizumab or placebo for early stage NSCLC.

Phase III, Double-Blind, Placebo-Controlled Study of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab for the Treatment of Patients With Resectable Stages II and III non-small-cell Lung Cancer: The AEGEAN Trial



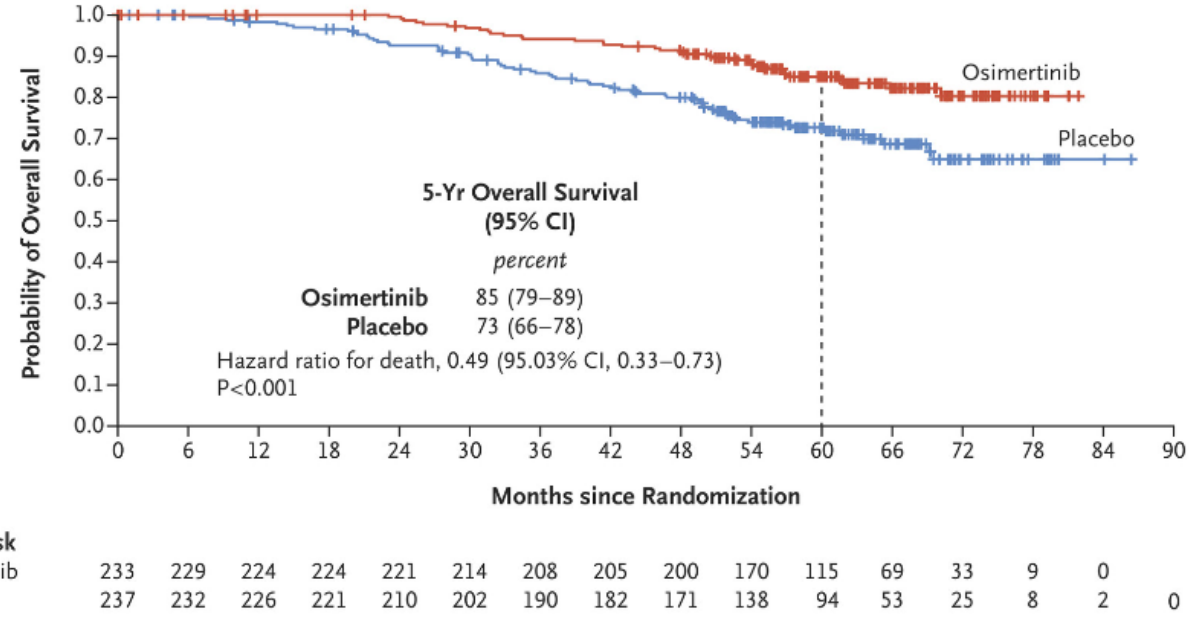
From: Is there a benefit of PD-(L)1 inhibitors?

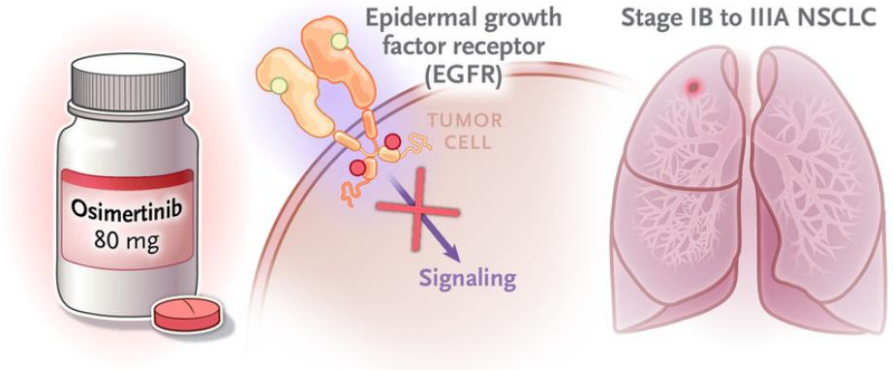
To: Which is the optimal study design & concept?

Heymach JV et al, Clin Lung Cancer 2022;23:e247-e251

Perioperative immunotherapy as standard in NSCLC.

ADAURA Osimertinib adjuvant für EGFR mut





ALINA Trial ESMO Presidential

Tsuboi M et al, NEJM 2023 389:137-147

Ribociclib and endocrine therapy as adjuvant treatment in pa… breast cancer: NATALEE trial

Dennis Slamon,[1] Daniil Stroyakovskiy,[3] Aditya Bardia,[7] Stephen Chia,[8] Seock-Michael Untch,[15] Rebecca Moroose,[16]

[1]David Geffen School of Medicine at UCLA, Los Angele… Research Institute, Tennessee Oncology, Nashville, TN… Hospital Erlangen Comprehensive Cancer Center Erla… Ireland; [7]Massachusetts General Hospital Cancer Cent… Institute, Seoul National University Hospital, Seoul Nat… de Investigación Biomédica en Red de Cáncer, Grupo … Melbourne, VIC, Australia; [12]Department of Medical On… China; [13]University of California, Los Angeles, Jonsson… Brazil; [15]Interdisciplinary Breast Cancer Center, Helios … Washington DC; [18]TRIO - Translational Research in On… University of Texas MD Anderson Cancer Center, Hous…

NATALEE study design[1,2]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥ 20%
      - Oncotype DX Breast Recurrence Score ≥ …
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

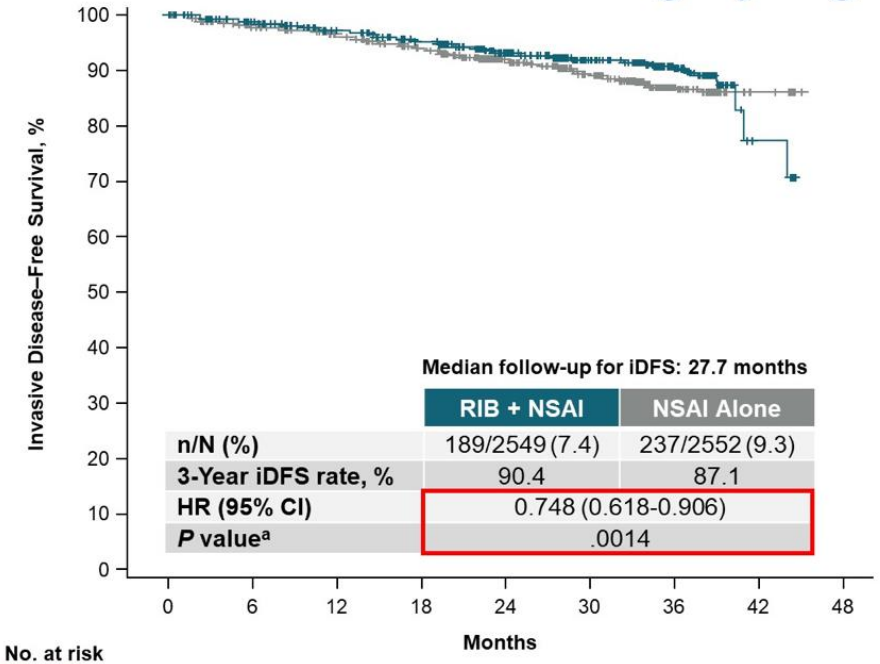
Ribociclib 400 mg/day

Primary End Point

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal wo…
Receipt of prior (neo)adjuvant chemotherapy: …
Geographic location: North America/Western Eu…

[a] Enrollment of patients with stage II disease was capped at 40% … CT; chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EB… prediction analysis of microarray 50; PK, pharmacokinetics; PRO… 1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701…

Ribociclib achieved highly significant iDFS benefit



Median follow-up for iDFS: 27.7 months

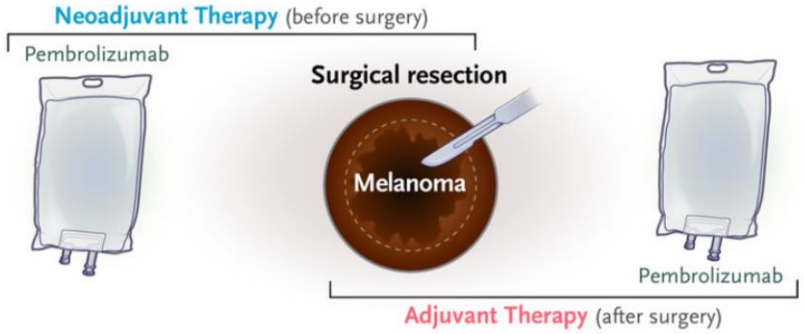
	RIB + NSAI	NSAI Alone
n/N (%)	189/2549 (7.4)	237/2552 (9.3)
3-Year iDFS rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906)	
P value[a]	.0014	

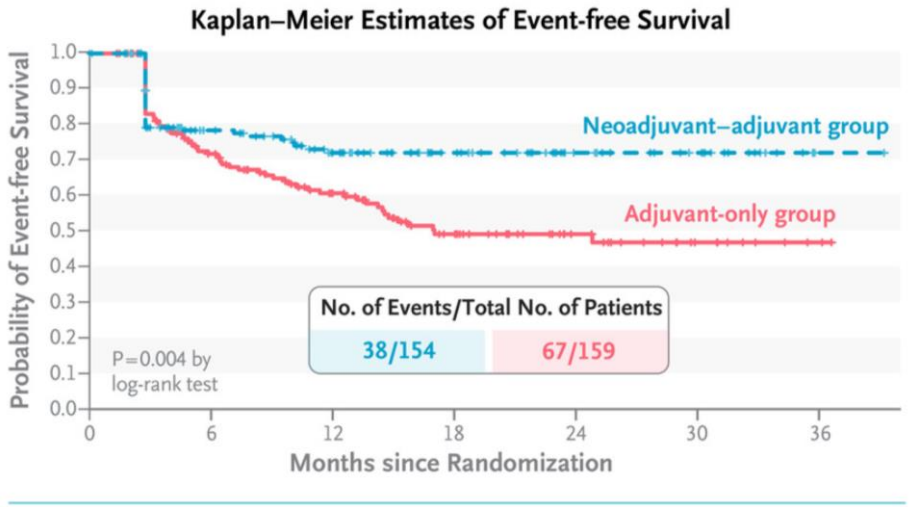
No. at risk									
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

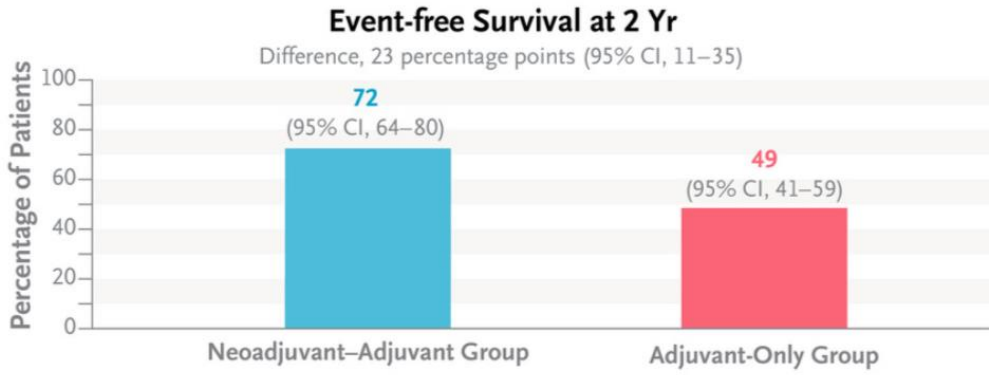
- Based on the *P* value of .0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%
- Risk of invasive disease was reduced by 25.2% with RIB + NSAI vs NSAI alone
- Ongoing patients will remain on treatment and follow-up will continue as prespecified

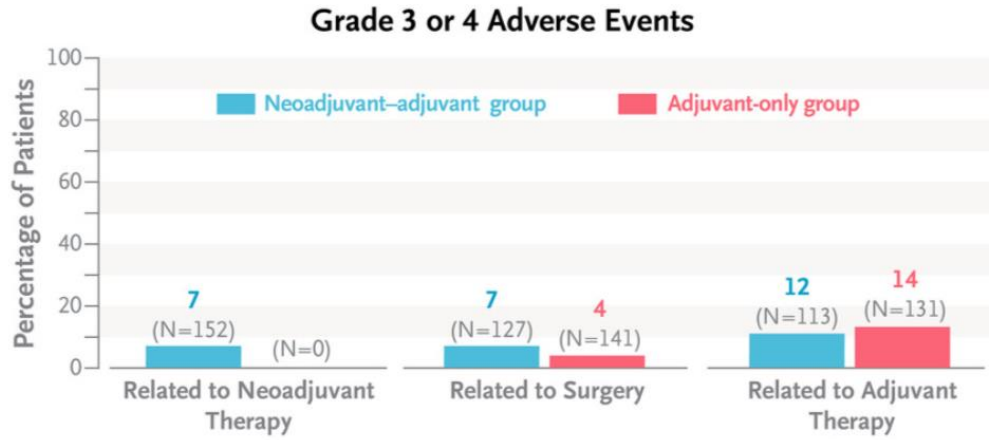
iDFS, invasive disease–free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value.

Challenge – Optimierung der perioperativen Konzepte.









OPTIMALES STUDIENDESIGN?

Patel SP et al, NEJM 2023;399:9

Let‘s take it even further – is systemic therapy enough in localized cancer?

September 12, 2023

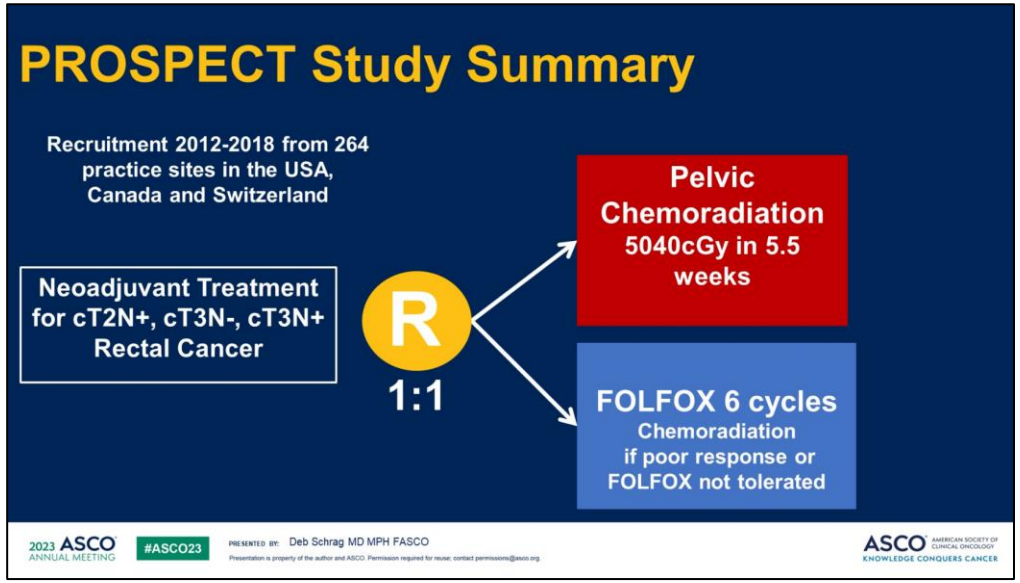
MARS 2: Chemo Alone May Be Superior to Surgery Plus Chemo in Mesothelioma

Bryant Furlow

Follow @BryantFurlow

Chemotherapy alone may produce better outcomes than surgery plus chemotherapy in patients with mesothelioma, according to research presented at the 2023 World Conference on Lung Cancer.

In this phase 3 trial, MARS 2, patients who received chemotherapy and underwent extended pleurectomy decortication had more serious adverse events and worse quality of life than patients who received chemotherapy alone.



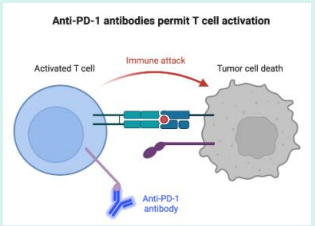
Integration der systemische Therapie ins perioperative Setting als onkologische Herausforderung?

Antibody Drug Conjugates

Monoclonal Antibodies

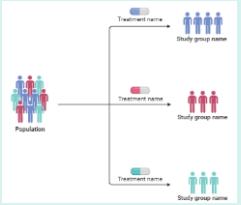
Novel Targets

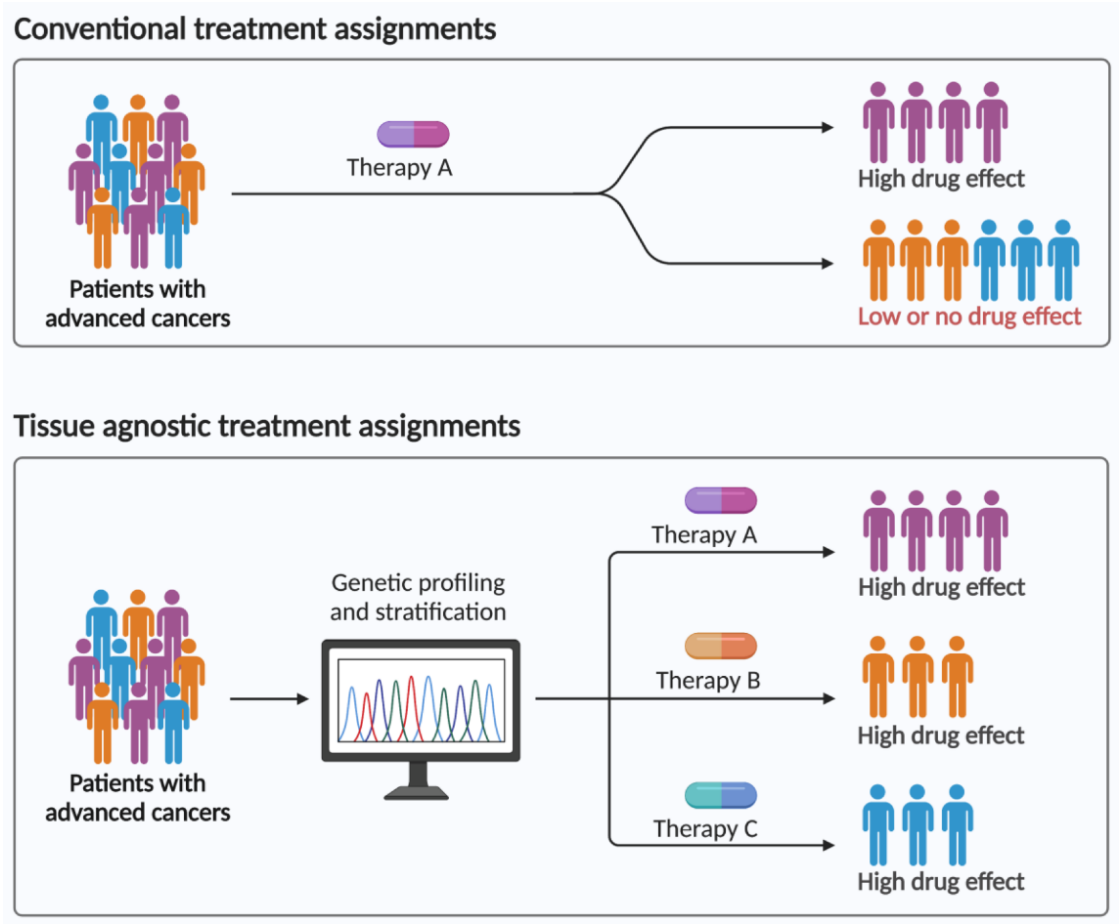
Immunotherapy

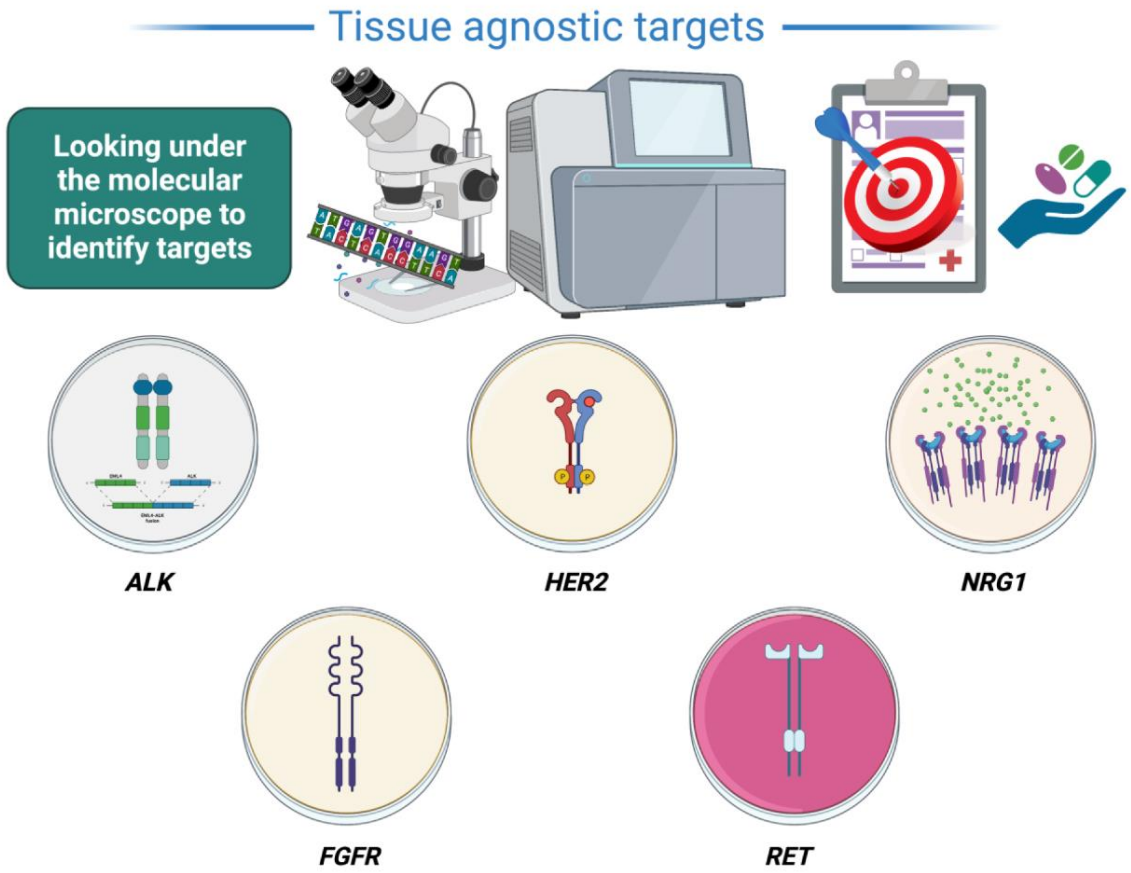


Perioperative Treatment

Tumor-Agnostic Drugs





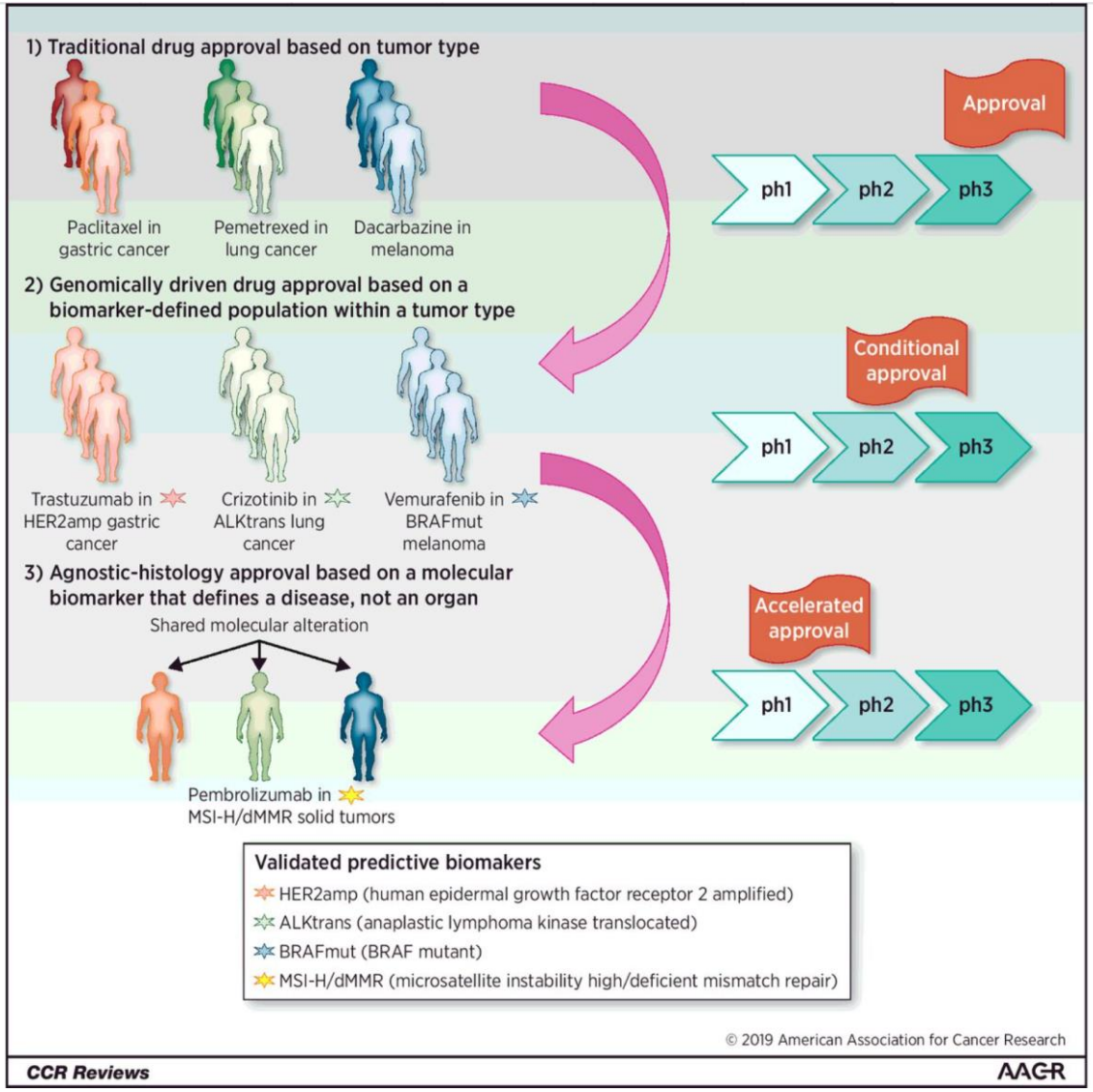


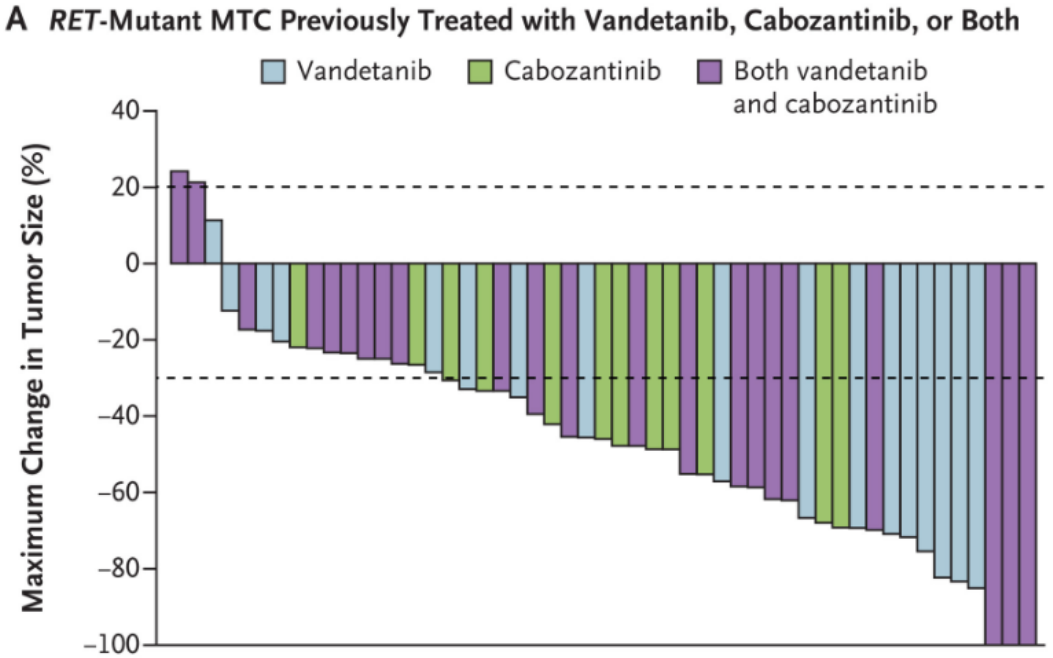
Adagrasib in Treatment of *KRAS* G12C–Mutated Advanced Solid Tumors

ctDNA analysis of NTRK fusion and mechanisms of acquired resistance to TRK inhibitors.

Erdafitinib Achieves Responses Across Multiple Cancer Types With *FGFR* Alterations

Tateo et al, Pharmaceuticals 2023





Proffered Paper session

LBA4 - Randomized Phase 3 Study of First-line Selpercatinib versus Chemotherapy and Pembrolizumab in RET Fusion-positive NSCLC

Presentation Number LBA4
Speakers Herbert Ho Fung Loong (Sha Tin, Hong Kong PRC)
Lecture Time 17:35 - 17:47

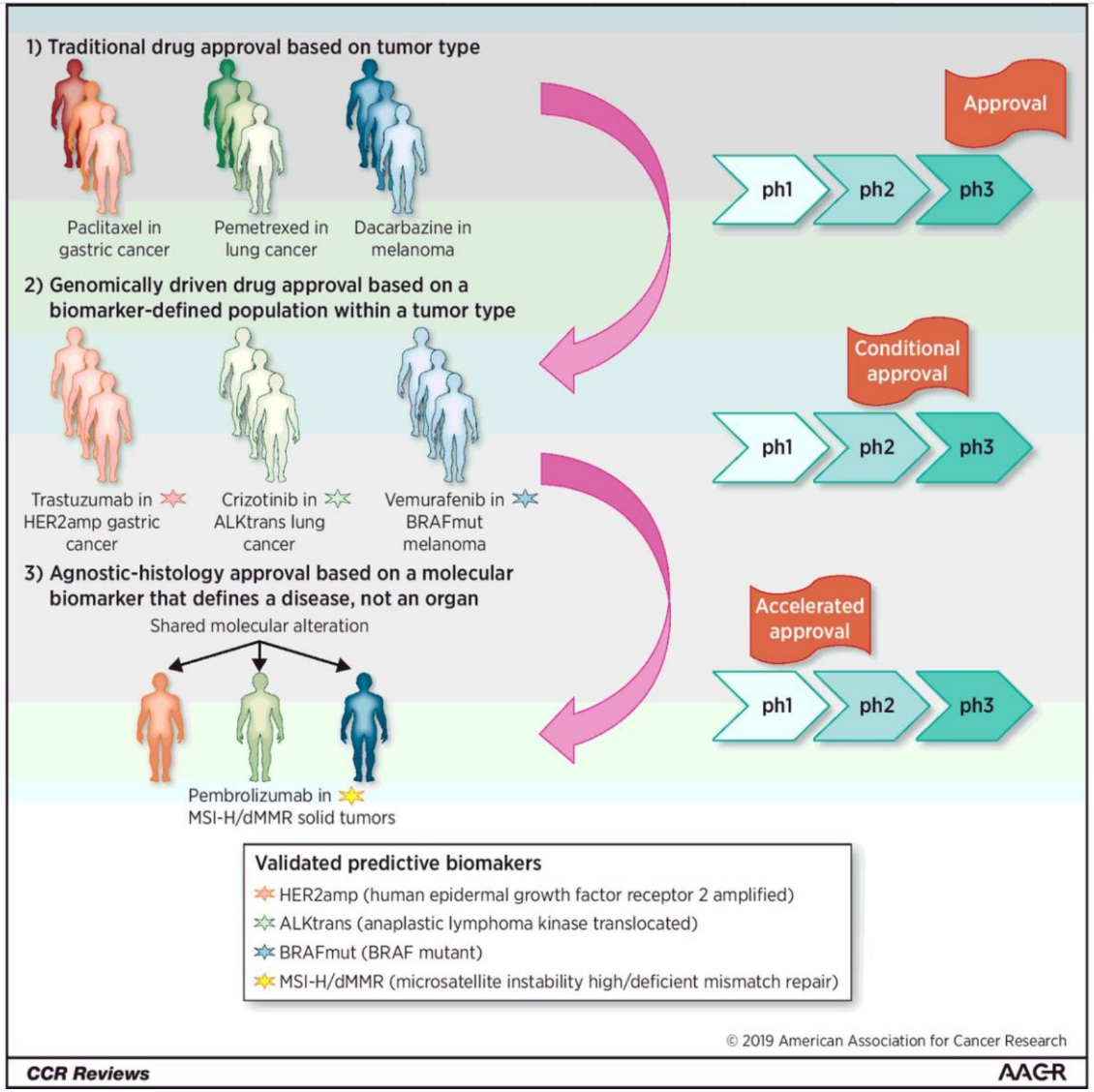
ESMO 2023

Proffered Paper session

LBA3 - Randomized Phase 3 Study of Selpercatinib versus Cabozantinib or Vandetanib in Advanced, Kinase Inhibitor-Naïve, RET-mutant Medullary Thyroid Cancer

Presentation Number LBA3
Speakers Julien Hadoux (Villejuif, Cedex, France)
Lecture Time 17:10 - 17:22

Hierro C et al, Clin Cancer Res 2019;25:3210-19
Wirth LJ NEJM 2020;825-835



› Int J Cancer. 2023 Jun 15;152(12):2474-2484. doi: 10.1002/ijc.34473. Epub 2023 Feb 24.

The evidence base of US Food and Drug Administration approvals of novel cancer therapies from 2000 to 2020

Concerns have been raised that regulatory programs to accelerate approval of cancer drugs in cancer may increase uncertainty about benefits and harms for survival and quality of life (QoL). We analyzed all pivotal clinical trials and all non-pivotal randomized controlled trials (RCTs) for all cancer drugs approved for the first time by the FDA between 2000 and 2020. We report regulatory and trial characteristics. Effects on overall survival (OS), progression-free survival and tumor response were summarized in meta-analyses. Effects on QoL were qualitatively summarized. Between 2000 and 2020, the FDA approved 145 novel cancer drugs for 156 indications based on 190 clinical trials. Half of indications (49%) were approved without RCT evidence; 82% had a single clinical trial only. OS was primary endpoint in 14% of trials and QoL data were available from 25%. The median OS benefit was 2.55 months (IQR, 1.33-4.28) with a mean hazard ratio for OS of 0.75 (95%CI, 0.72-0.79, I^2 ... of 156 indications. Over time, priority review was used increasingly and the mean number of trials per indication decreased from 1.45 to 1.12. More ... 1% in 2016-2020). For 21 years, novel cancer drugs have typically been approved based on one single, often uncontrolled, clinical trial, measuring ... thout solid evidence that novel drugs improve their survival or QoL and there is no indication towards improvement.

82% single arm trial only

OS was the primary endpoint in 14%

Median OS Benefit 2.55 months

QOL benefit proven for 4%

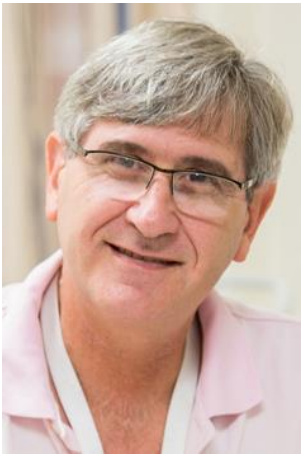
Hierro C et al, Clin Cancer Res 2019;25:3210-19
Gloy V et al, Int J Cancer2023;152:2474-2484

Disclosures

Areas of Expertise
Thoracic Oncology & Endocrine Malignancies

Advisory Board
Members of the Division of Oncology, Medical University of Vienna

ESMO Working Group Member
Magnitude of Clinical Benefit Scale



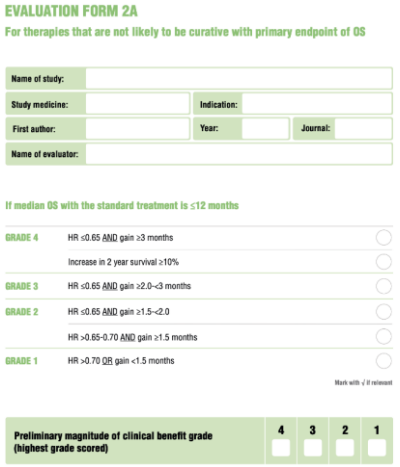
Chair:
Nathan I Cherny

ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS)

"…. a standardized, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anticancer therapies…"

- Easy to use for the qualified clinician
- Corresponding forms online available*
- Considers OS, PFS, QOL and lower end of 95% CI of HR
- Dynamic tool – will be revised on a regular basis

*http://www.esmo.org/Policy/Magnitude-of-Clinical-Benefit-Scale/Scale-Evaluation-Forms



EVALUATION FORM 2A

For therapies that are not likely to be curative with primary endpoint of OS

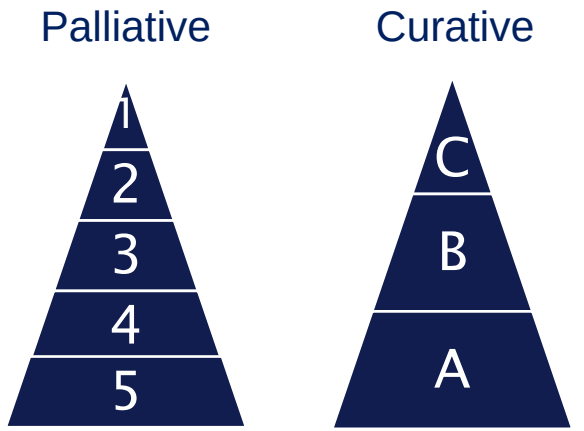
Name of study:					
Study medicine:		Indication:			
First author:		Year:		Journal:	
Name of evaluator:					

If median OS with the standard treatment is ≤12 months

GRADE 4	HR ≤0.65 AND gain ≥3 months	○
	Increase in 2 year survival ≥10%	○
GRADE 3	HR ≤0.65 AND gain ≥2.0-<3 months	○
GRADE 2	HR ≤0.65 AND gain ≥1.5-<2.0	○
	HR >0.65-0.70 AND gain ≥1.5 months	○
GRADE 1	HR >0.70 OR gain <1.5 months	○

Mark with √ if relevant

	4	3	2	1
Preliminary magnitude of clinical benefit grade (highest grade scored)	☐	☐	☐	☐

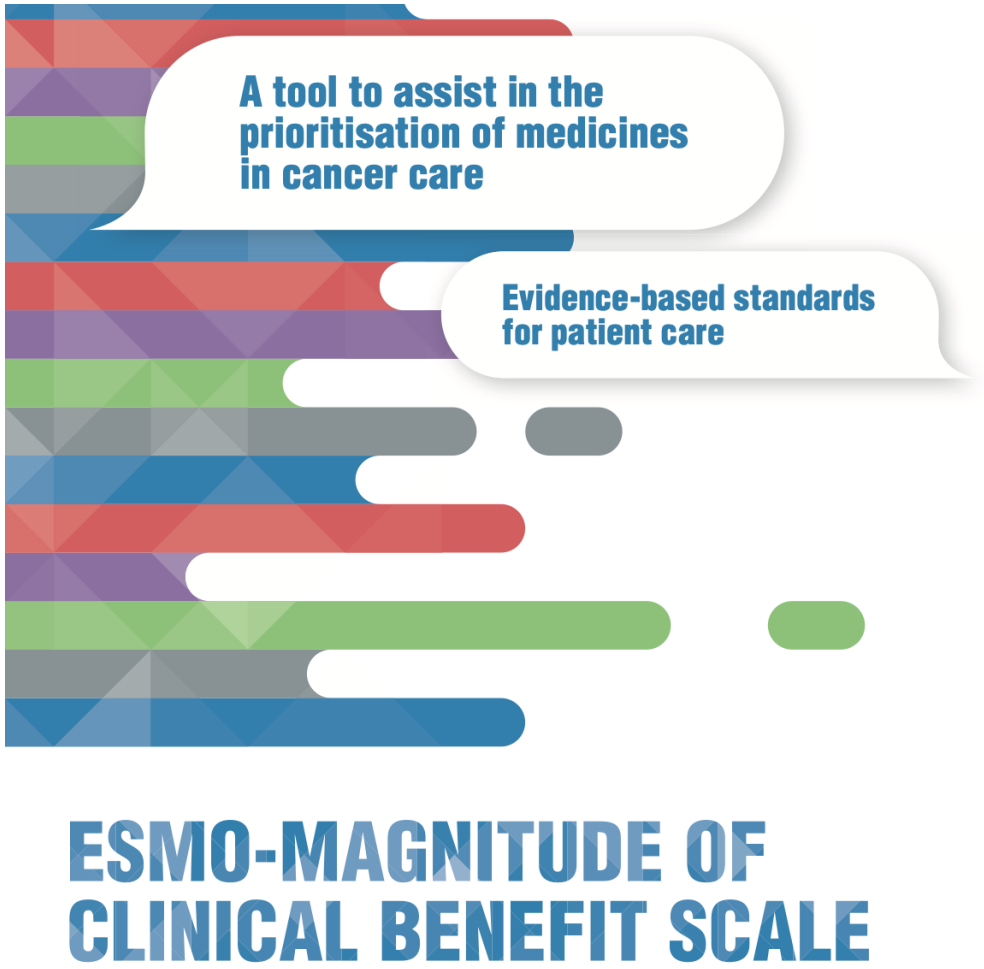


5 / A highest level of clinical benefit

Cherny NI et al, Ann Oncol 2015;26:1547-73

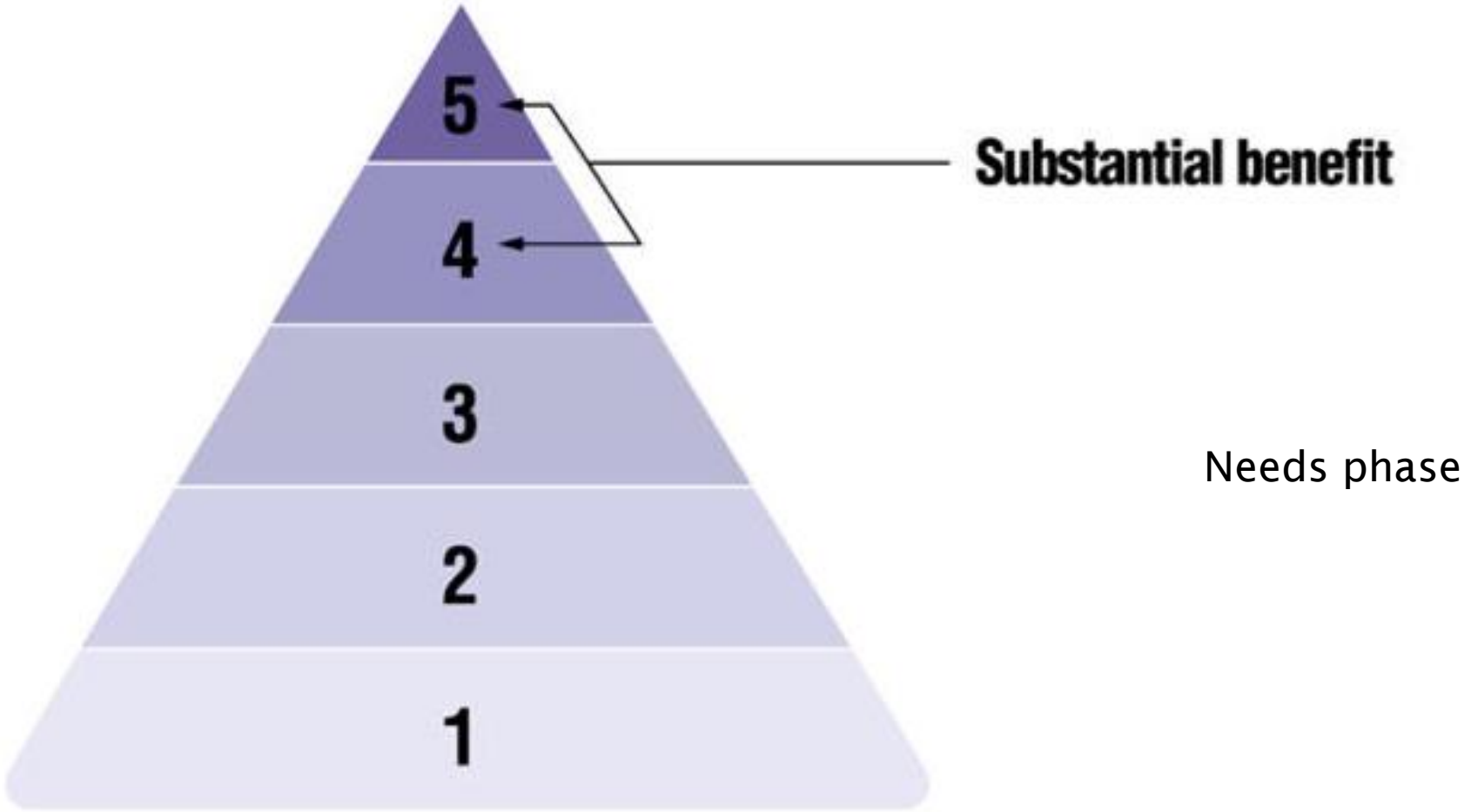
ESMO – Magnitude of Clinical Benefit Scale

- **Aim 1:** to highlight treatments which bring substantial improvements to the duration of survival and/or the QoL of cancer patients
- **Aim 2**: to use the scale for accelerated reimbursement evaluation and decrease disparities across Europe



Underlying Premises for the MCBS Development

Cure takes precedence over deferral of death
Direct endpoints such as survival and QoL take precedence over surrogates such as PFS or RR
DFS in curative disease is a more valid surrogate than PFS or RR in non-curative disease
Interpretation of the evidence for benefit derived from surrogate outcomes (such as PFS) may be influenced by secondary outcome data
Priority to data of comparative trials with strong evidence (large randomized phase III trials)

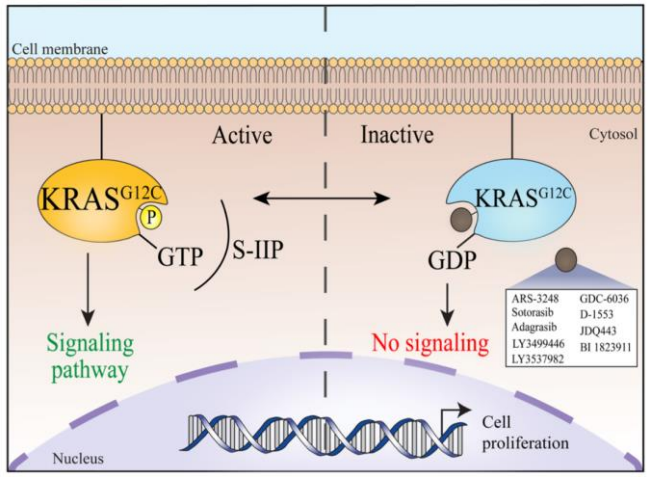


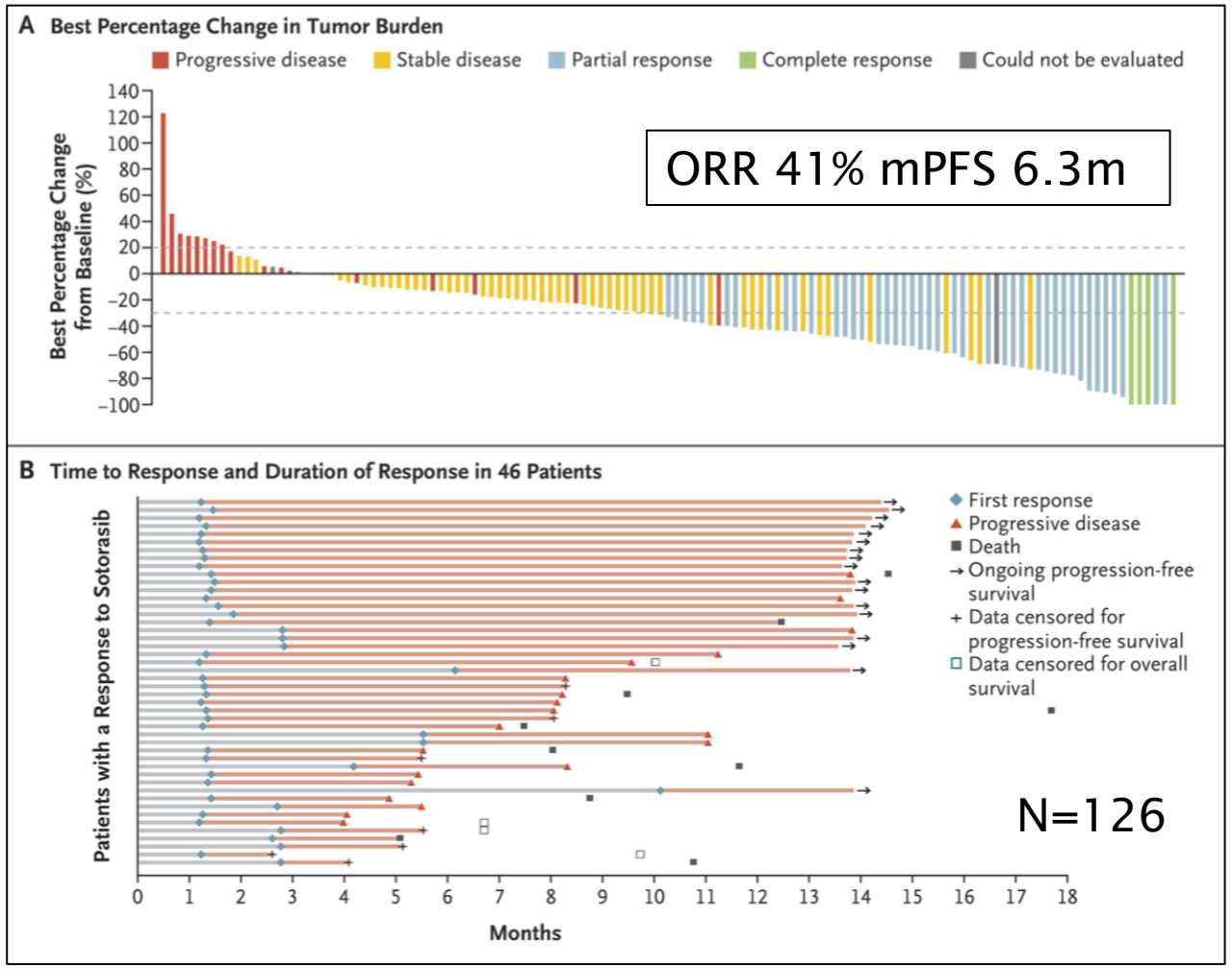
Needs phase III data

“Die Lanze brechen” für Phase III Studien

Sotorasib for NSCLC - CodeBreak 100 Phase I/II

- KRAS for decades untargetable
- pG12C common in NSCLC
- First approved KRAS inhibitor
- Approval based on CodeBreak 100





Skoulidis F et al, N Engl J Med 2021;384:2371-2381

PARIS 2022 ESMO congress

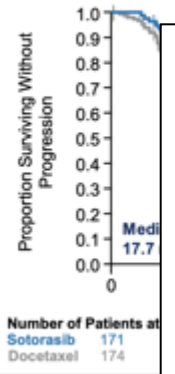
CodeBreaK 200

Sotorasib versus Docetaxel for Previously Treated Non-Small Cell Lung Cancer with *KRAS* G12C Mutation: CodeBreaK 200

Melissa L. Johnson,[1] Adrianus Jo… Waterhouse,[3*] Julien Mazieres,[4] An… Mountzios,[6] Miklos Pless,[7] Jürgen … Ferdinandos Skoulidis,[11] Isamu Ok… Linardou,[14] Silvia Novello,[15] Yuanbi… Obiozor,[18] Yang Wang,[18] Luis Paz-…

[1]Sarah Cannon Research Institute at Tennessee Oncol… Amsterdam, The Netherlands; [3]Oncology Hematology … Toulouse, Toulouse, France; [5]Erasmus MC Cancer Inst… [6]Henry Dunant Hospital Center, Athens, Greece; [7]Kanto… Integrated Oncology, University Hospital Cologne, Colo… Hospital Essen, Essen, Germany; [10]Centre Hospitalier … [11]University of Texas MD Anderson Cancer Center, Ho… [13]Asan Medical Center, Seoul, South Korea; [14]Metropol… Università Degli Studi Di Torino – San Luigi Hospital Or… Michigan, Grand Rapids, MI, USA; [17]Peter MacCallum … Thousand Oaks, CA, USA; [19]Hospital Universitario 12 d… University and Ciberonc, Madrid, Spain.
*Currently at Dana–Farber Cancer Institute, Boston, MA

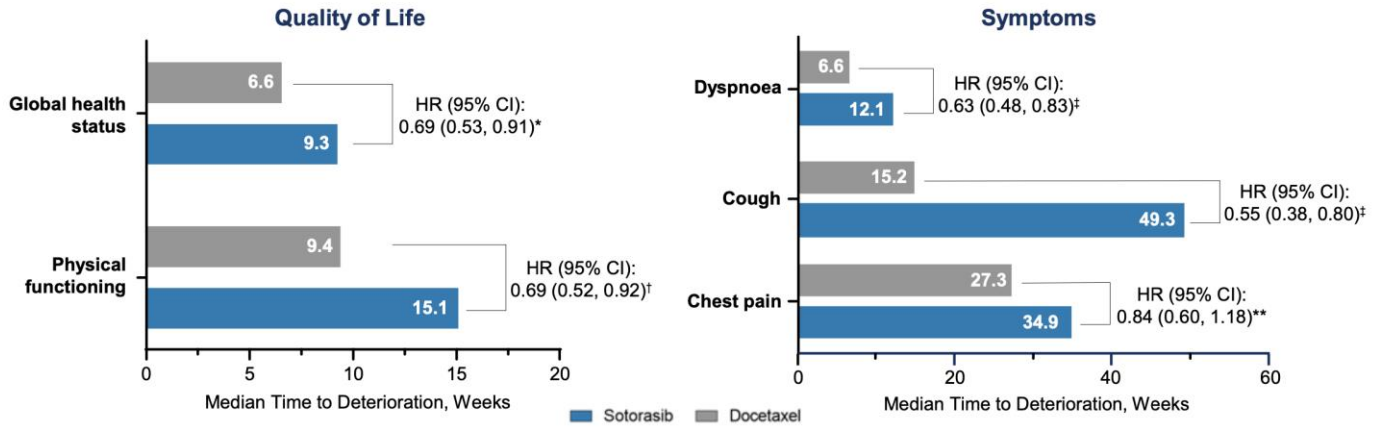
Sotorasib for NSCLC - CodeBreak 200 Phase III



CodeBreaK 200 me… docetaxel (HR 0.66…

Sotorasib 960 mg oral daily (N = 171) | Docetaxel 75 mg/m² IV Q3W (N = 174)

Patient-Reported Outcomes: Time to Deterioration



Time to deterioration in global health status, physical functioning, and cancer-related symptoms (dyspnoea and cough) were delayed with sotorasib compared to docetaxel

Baseline threshold: global health status: ≥ 8; physical functioning : ≥ 13; dyspnoea (composite score): ≤ 92, cough: ≤ 67, chest pain: ≤ 67.
* $P = 0.005$; † $P = 0.007$; ‡ $P < 0.001$; ** $P = 0.17$.

MADRID 2023 ESMO congress

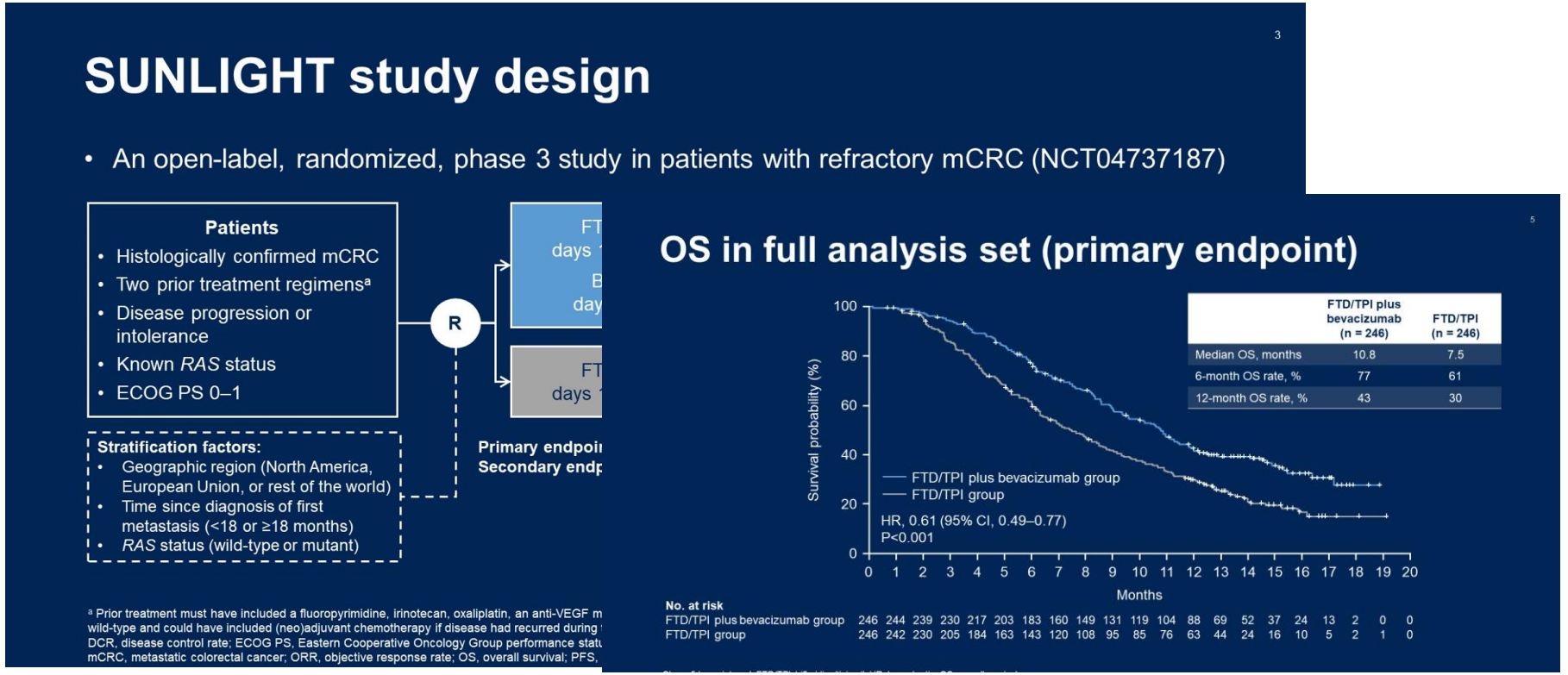
LBA10 - Sotorasib plus panitumumab versus standard-of-care for chemorefractory KRAS G12C-mutated metastatic colorectal cancer (mCRC): CodeBreak 300 phase 3 study

Presentation Number LBA10
Speakers Filippo Pietrantonio (Milan, Italy)
Lecture Time 17:50 - 18:02

Trifluridine–Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer

Gerald W. Prager, M.D., Julien Taieb, M.D., Ph.D., Marwan Fakih, M.D., Fortunato Ciardiello, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Elena Elez, M.D., Ph.D., Felipe M. Cruz, M.D., Ph.D., Lucjan Wyrwicz, M.D., Ph.D., Daniil Stroyakovskiy, M.D., Ph.D., Zsuzsanna Pápai, M.D., Pierre-Guillaume Poureau, M.D., Gabor Liposits, M.D., et al., for the SUNLIGHT Investigators*

The NEW ENGLAND JOURNAL of MEDICINE



Prof. Gerald Prager

„new standard of care for CRC patients after two lines of prior therapy“

TAS102

Prager GW et al, NEJM 2023;388:1657-1667

Best of Onkologie 2023 – mein Fazit

- **Novel Compounds** — ADC still number one hot topic
- **Novel Standards** — Optimizing perioperative care
- **Novel Strategies** — Agnostic vs. Personalized

MADRID 2023 ESMO congress
MADRID SPAIN
20-24 OCTOBER 2023

Acknowledgments

- Rupert Bartsch
- Anna Bergmeister-Berghoff
- Thorsten Füreder
- Aysegül Ilhan-Mutlu
- Gerald Prager
- Matthias Preusser
- Markus Raderer
- Team der Onkologie