LUNG CANCER

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Disclosure of Conflicts of Interest

Smitha Menon, MD, has the following financial relationships to disclose:

- Research Support (Institution): Eli Lilly, Merck, Mirati, Harpoon

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UPDATE IN NON-SMALL CELL LUNG CANCER MANAGEMENT

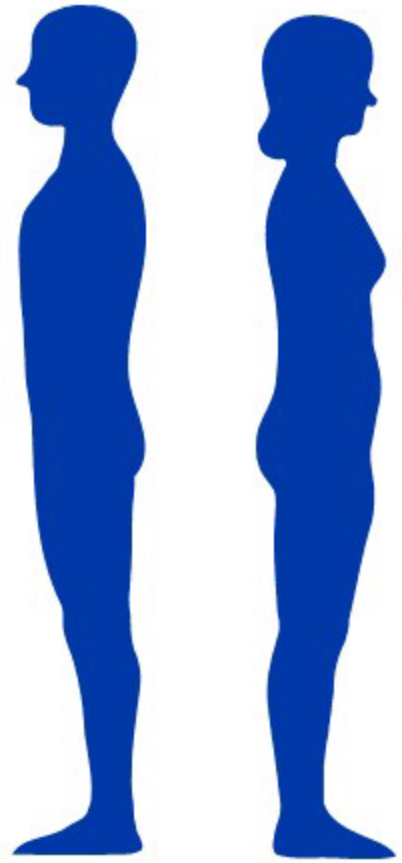
Froedtert & Medical College of Wisconsin

Outline

- Overview of advanced NSCLC
- Integration of immunotherapy in early-stage NSCLC
  - Neoadjuvant
  - Adjuvant
- Expanding Targeted therapy options
  - KRAS G12C
  - Her 2
  - EGFR exon 20

Estimated Cancer Deaths in the US in 2022

	Males 322,090	Females 287,270	
Lung & bronchus	21%	21%	Lung & bronchus
Prostate	11%		
Breast		15%	Breast
Colon & rectum	9%	8%	Colon & rectum
Pancreas	8%	8%	Pancreas
Liver & intrahepatic bile duct	6%	4%	Ovary
		4%	Uterine corpus
Leukemia	4%	4%	Liver & intrahepatic bile duct
Esophagus	4%		
Urinary bladder	4%	3%	Leukemia
Non-Hodgkin lymphoma	4%	3%	Non-Hodgkin lymphoma
Brain & other nervous system	3%	3%	Brain & other nervous system
All other sites	26%	25%	All other sites



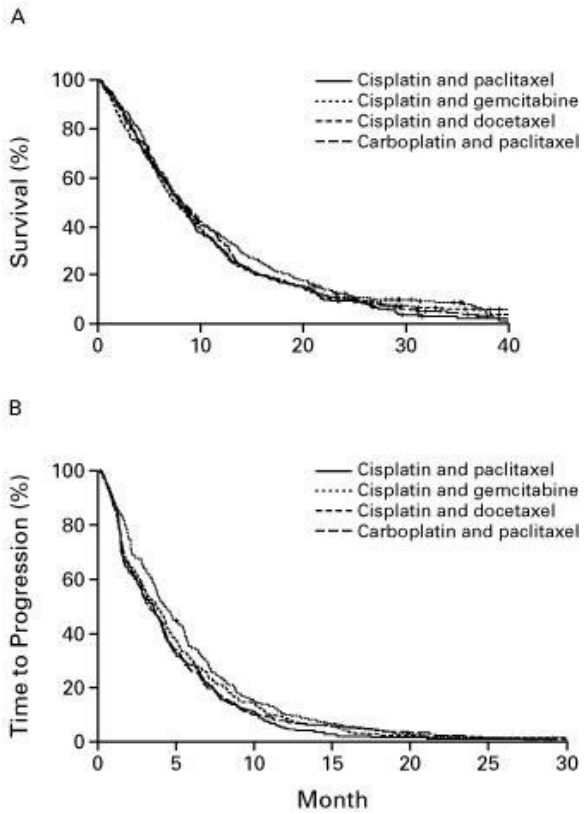
Siegel, RL, Miller, KD, Fuchs, HE, Jemal, A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022. https://doi.org/10.3322/caac.21708

Trends in Five-year Relative Survival Rates (%), 1975-2017

Site	1975-1977	1995-1997	2011-2017
All sites	49	63	68
Breast (female)	75	87	90
Colorectum	50	61	65
Leukemia	34	48	65
Lung & bronchus	12	15	22
Melanoma of the skin	82	91	93
Non-Hodgkin lymphoma	47	56	73
Ovary	36	43	49
Pancreas	3	4	11
Prostate	68	97	98
Urinary bladder	72	80	77

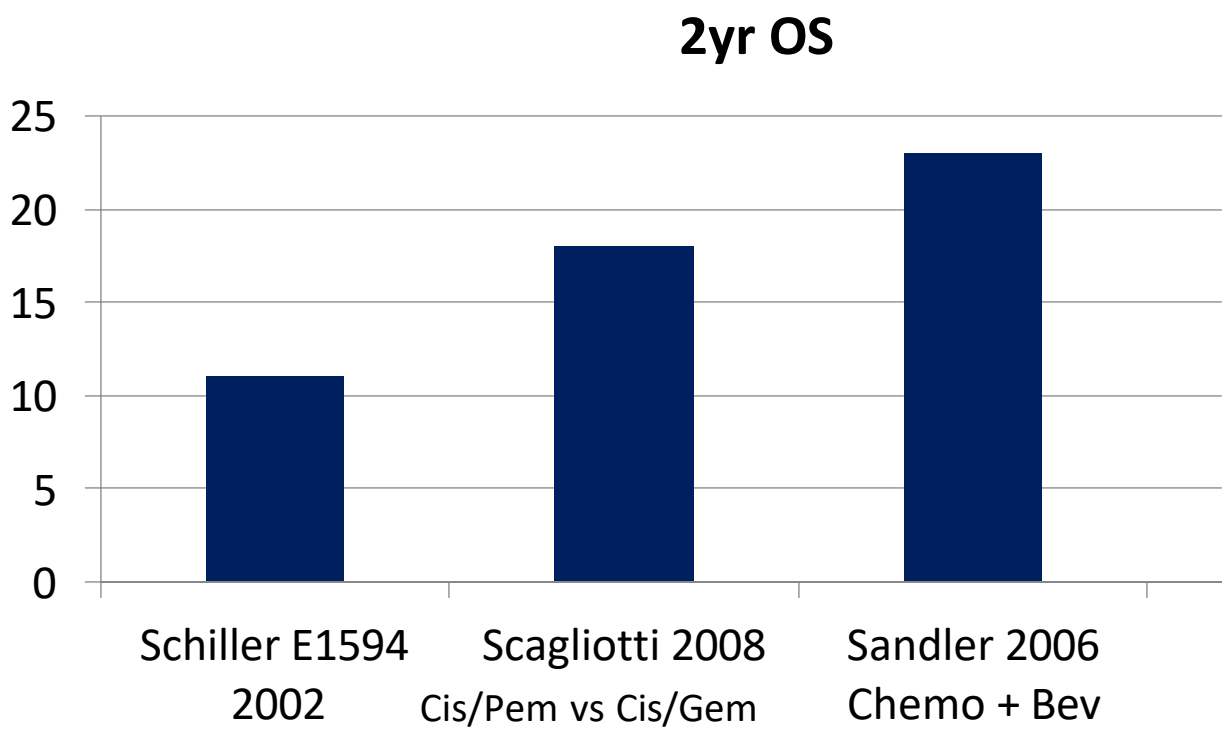
Siegel, RL, Miller, KD, Fuchs, HE, Jemal, A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022. https://doi.org/10.3322/caac.21708

Milestones in NSCLC before IO and Targeted Therapy 2000's -2010's

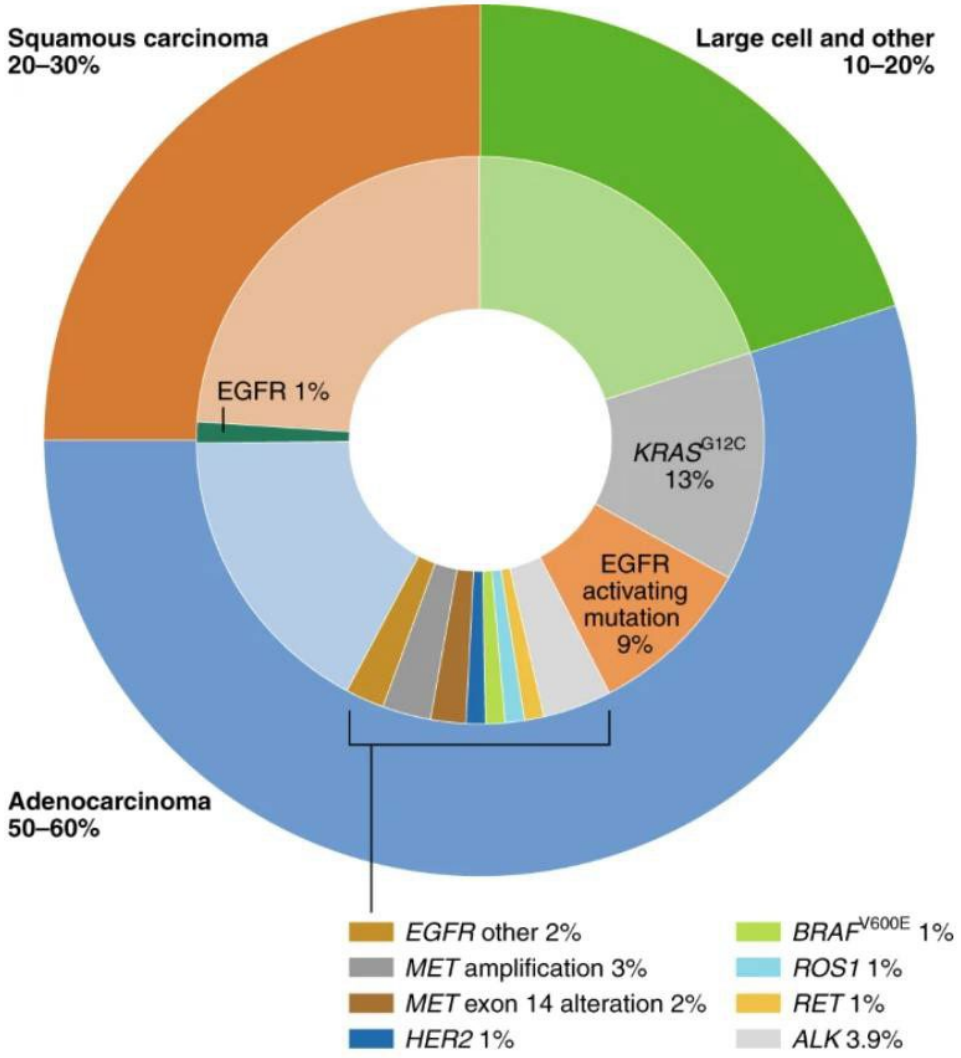


E1594, 1207 pt, 19% RR
MS: 7.9 months

Schiller JH et al. N Engl J Med 2002;346:92-98.

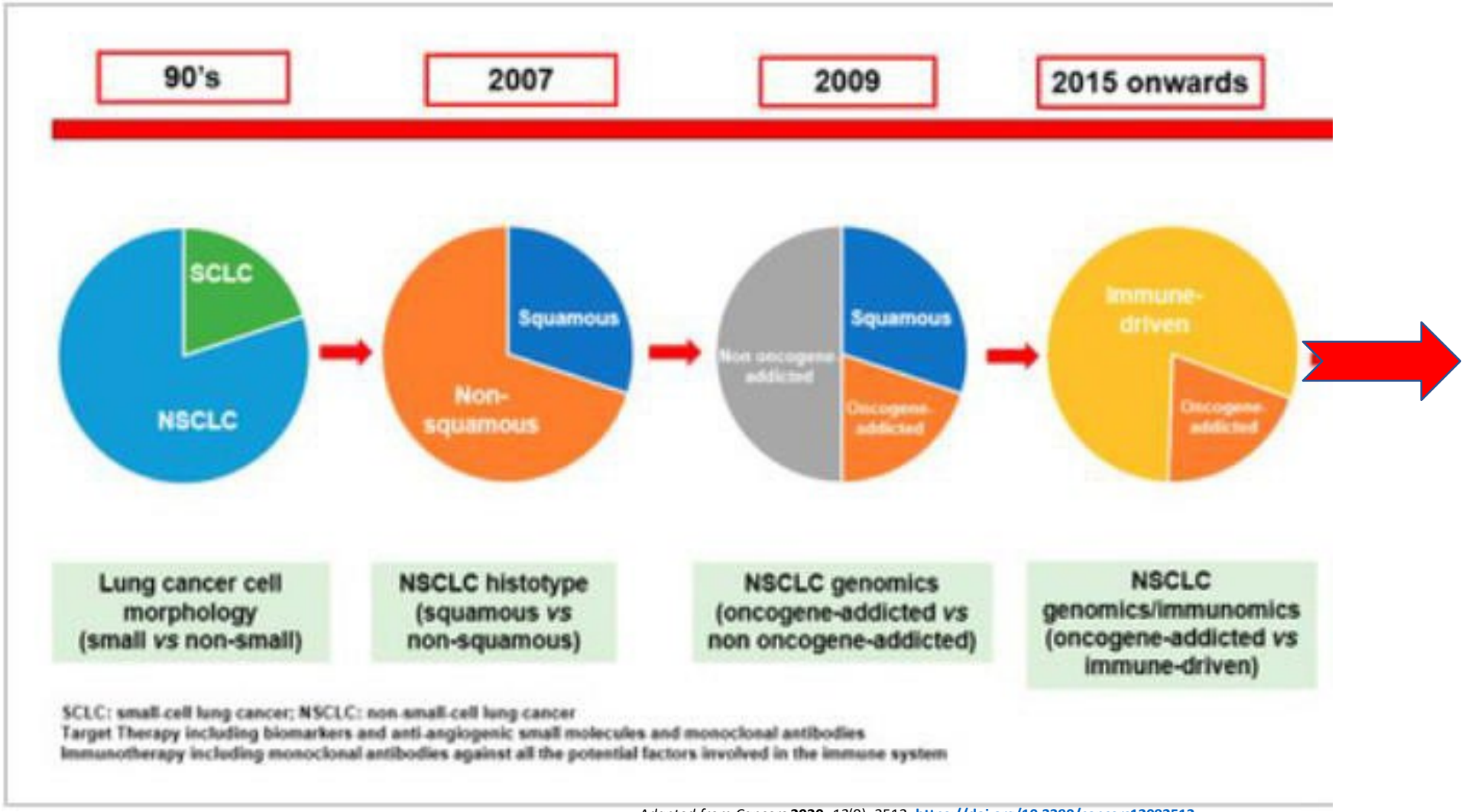


Molecular Landscape of Non -Small Cell Lung Cancer



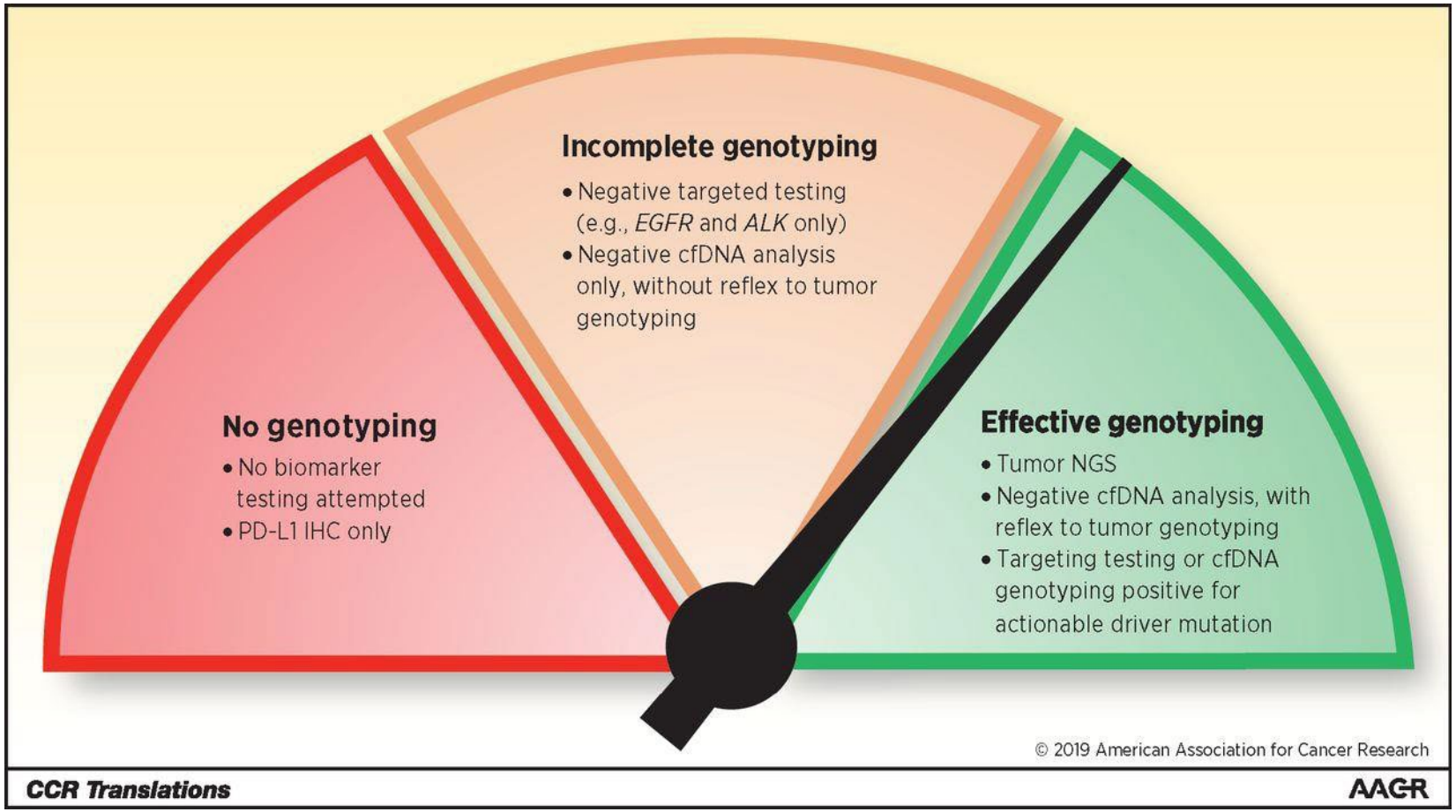
Wang, M., Herbst, R.S. & Boshoff, C. Toward personalized treatment approaches for non-small-cell lung cancer. *Nat Med* **27**, 1345–1356 (2021). https://doi.org /10.1038/s41591-021-01450-2

Paradigm shift in the first-line treatment of fit metastatic non-small-cell lung cancer



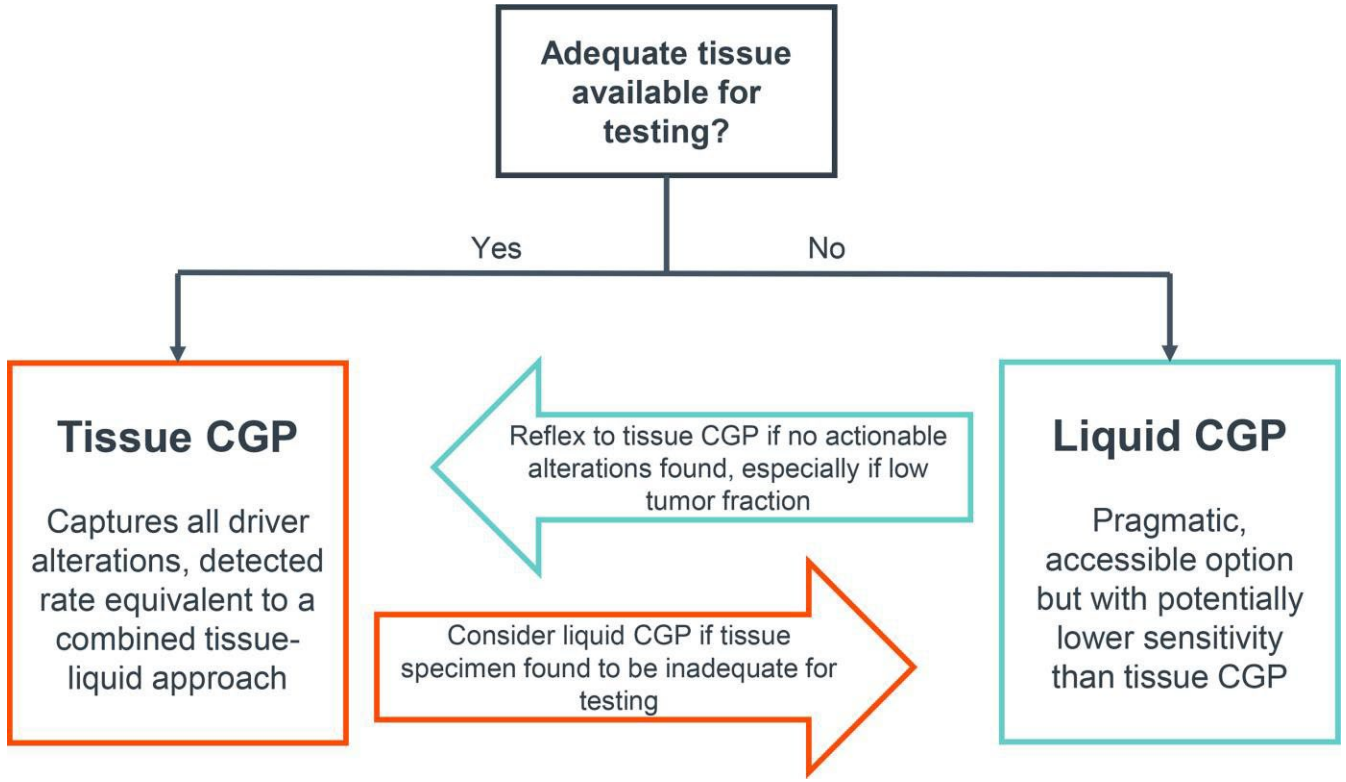
Adapted from Cancers **2020**, *12*(9), 2512; https://doi.org/10.3390/cancers12092512

Molecular Genotyping in Cancer



Clin Cancer Res. 2019;25(15):4583-4585.
doi:10.1158/1078-0432.CCR-19-1233

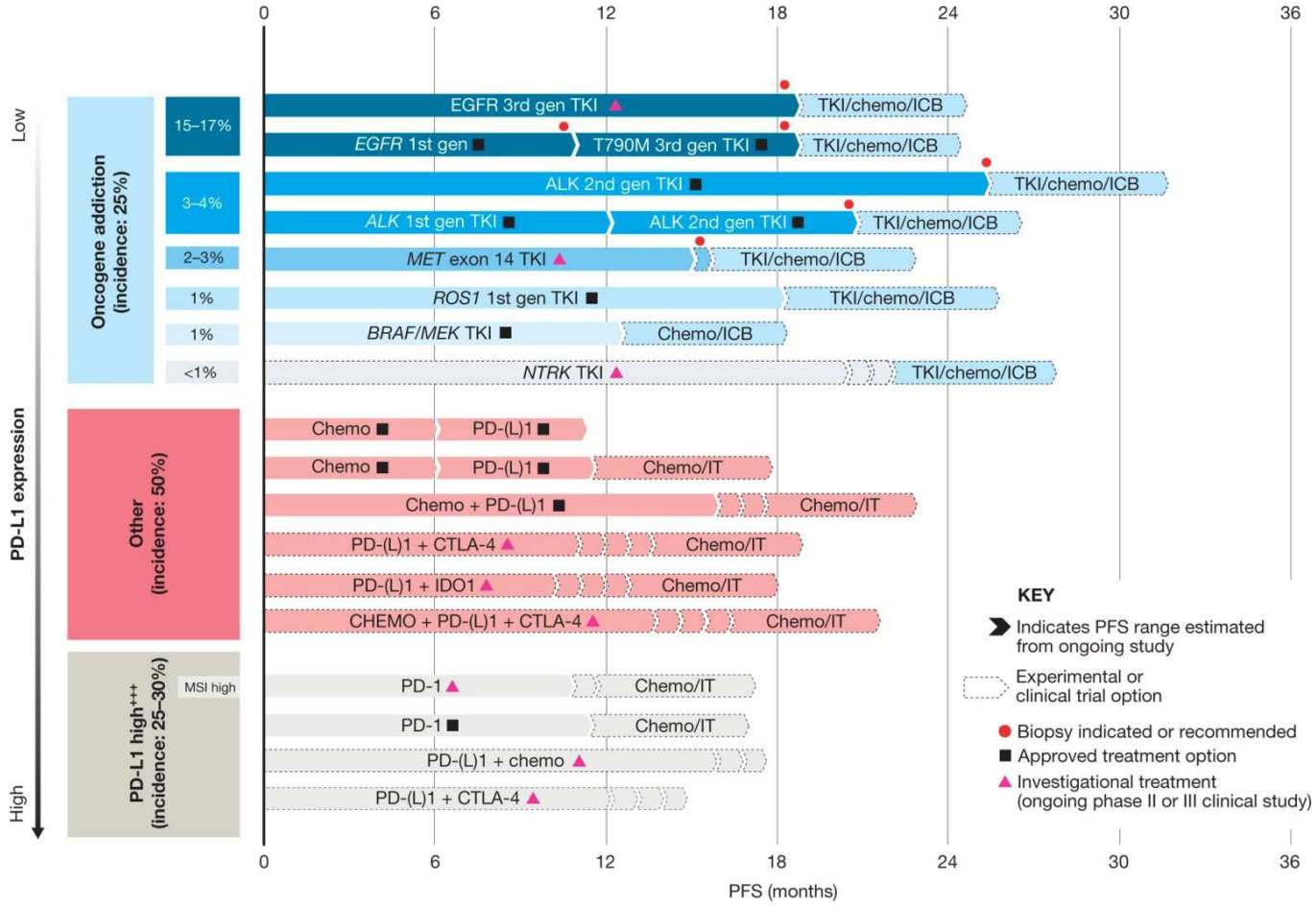
Complementary Role of Tissue and Blood Comprehensive Genomic Profiling (CGP)



Roles for Tissue- and Blood-Based Comprehensive Genomic Profiling for Detection of Actionable Driver Alterations in Advanced NSCLC Lee S. Schwartzberg, MD, et al.

JTO Clinical and Research Reports Volume 3 Issue 9 (September 2022)
DOI: 10.1016/j.jtocrr.2022.100386

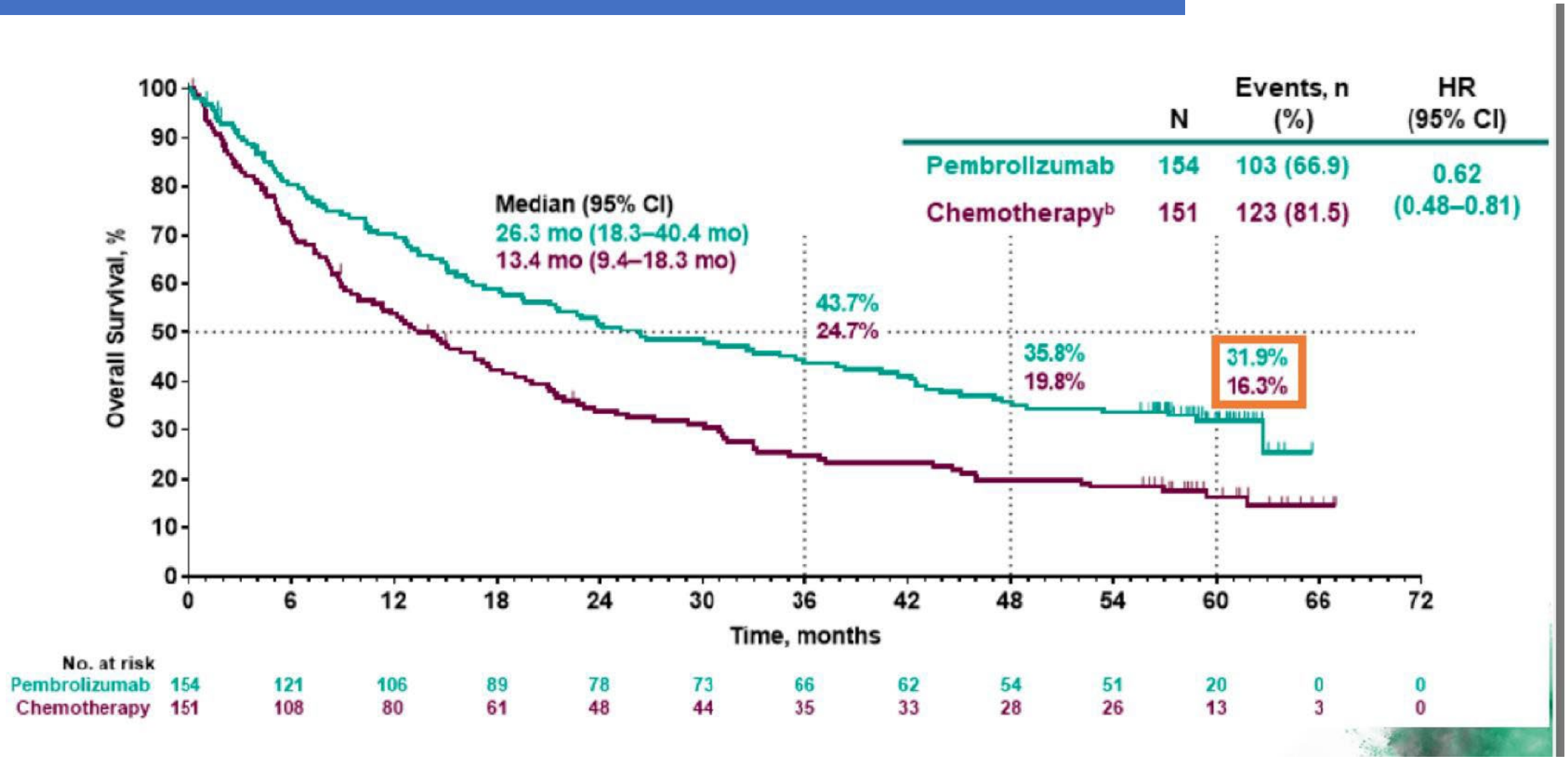
Current Treatment Paradigms in Metastatic NSCLC



R S Herbst *et al. Nature* **553,** 446–454 (2018) doi:10.1038/nature25183

nature

KEYNOTE-024 5-year OS update: first-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumor proportion score (TPS)≥50% : Brahmer et al. ESMO

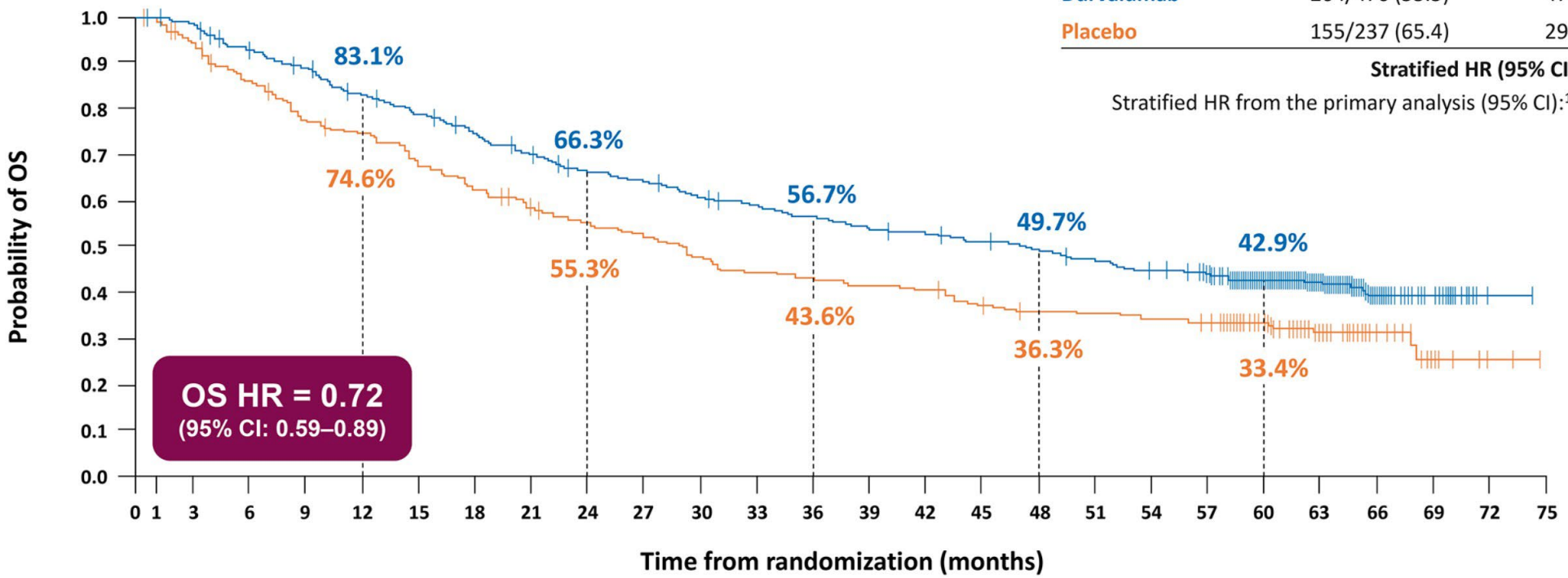


PACIFIC 5 yr OS results: Durvalumab in Unresectable Stage III NSCLC after concurrent chemoradiation

	No. of events/ total no. of patients (%)	Median OS (95% CI), months
Durvalumab	264/476 (55.5)	47.5 (38.1–52.9)
Placebo	155/237 (65.4)	29.1 (22.1–35.1)

Stratified HR (95% CI): 0.72 (0.59–0.89)

Stratified HR from the primary analysis (95% CI):[1,2] 0.68 (0.53–0.87)



No. at risk

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

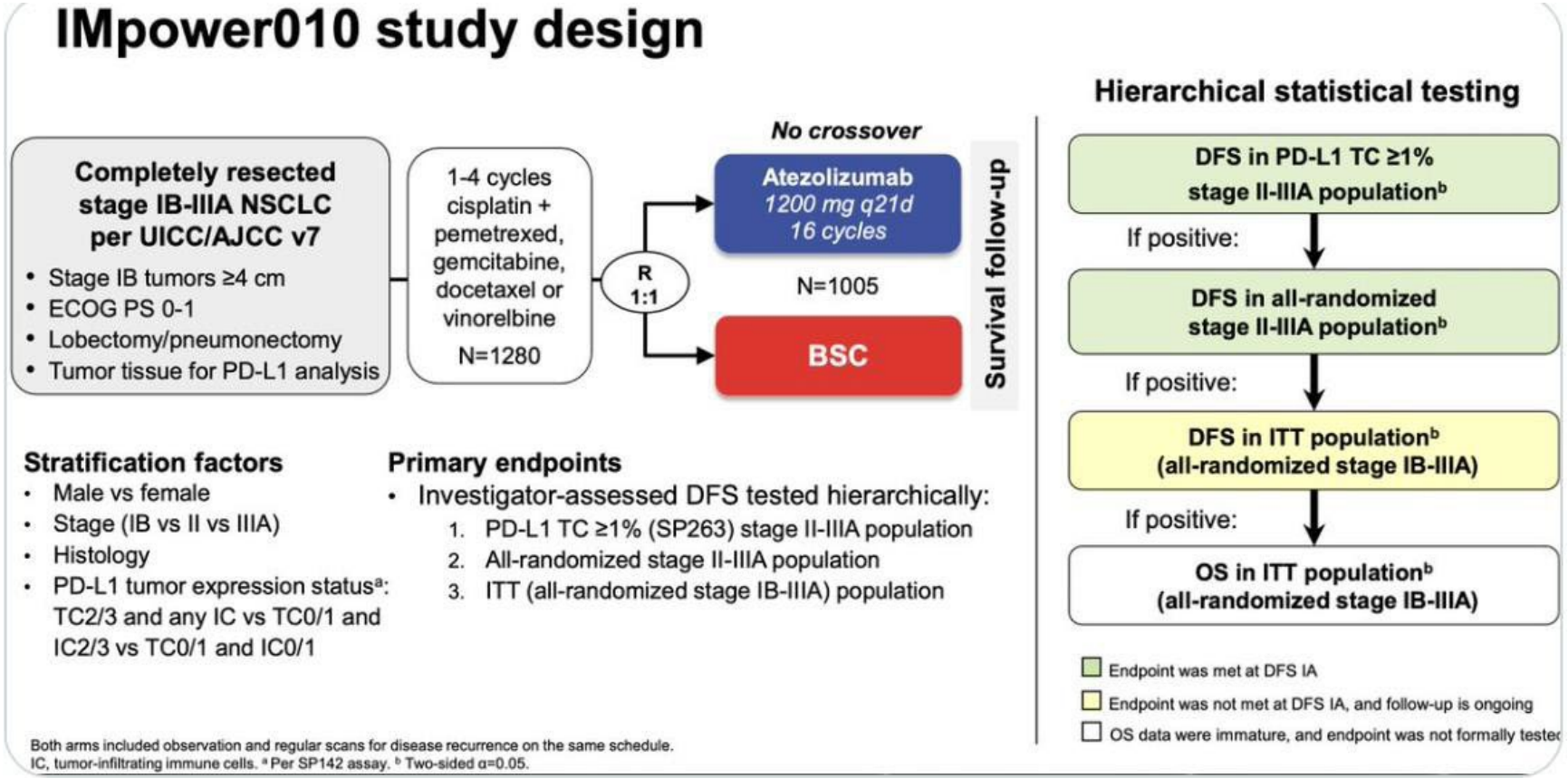
Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).

1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Integration of IO in stage1-3 NSCLC

- ~50% of NSCLC cases
- In eligible Stage 1-2 patients, surgery is the main modality
- Management of Stage 3 is variable, multi disciplinary discussion encouraged
- Modest and equivalent benefit of adjuvant and neoadjuvant chemotherapy
- Approval of adjuvant Osimertinib was based on a significant DFS benefit.

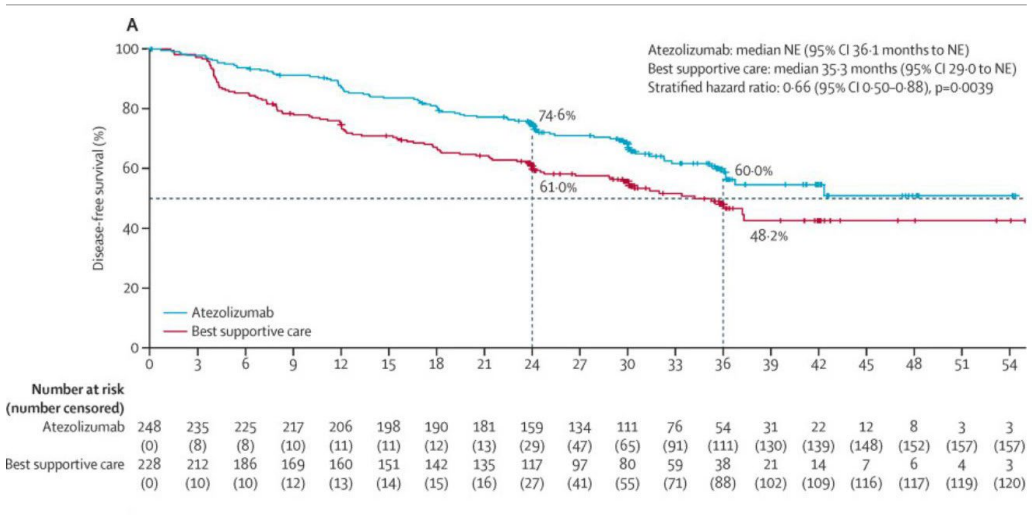
Impower 010: Adjuvant Atezolizumab



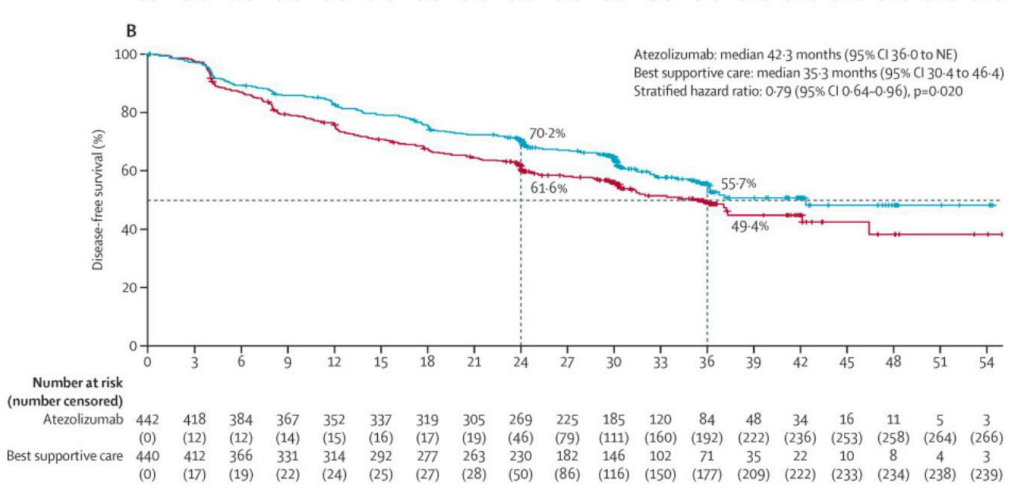
Slide by Nasser Altorki WCLC 2021

Impower 010 DFS benefit in PD-L1> 1%, II-IIIA

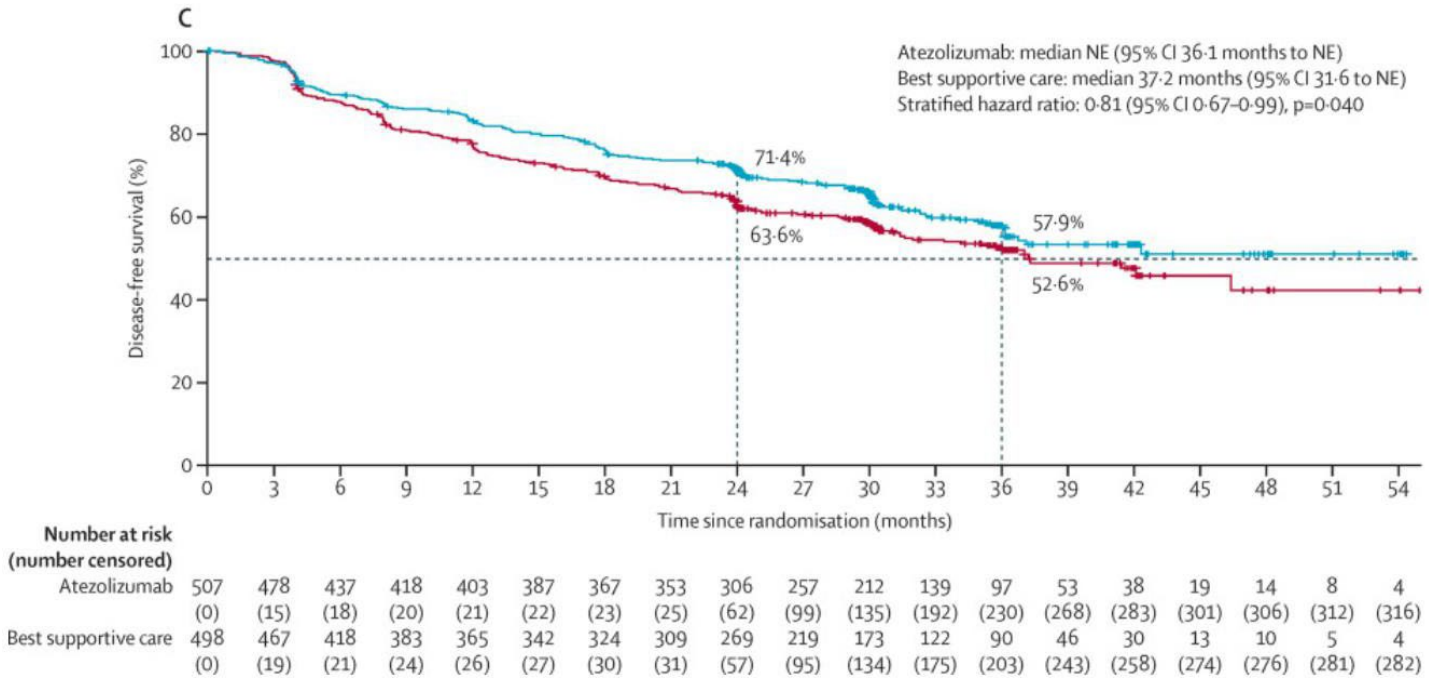
Patient with PD-L1> 1% tumors Stage II-IIA



All Stage II-IIA patients



Impower 010 DFS results: No benefit in the ITT population(Ib-IIIA)



	Ate.z.olizumabgroup		Best supportive care group		Ha.zard ratio (95,.CI)
	Event patient.s. n/N	Median DFS (95,.CI), monlhs	Eve1lts,lpa1ieots. n/N	Median DfS (95,.CI). month,	
Ago					
<6Sye•"	281/544	NE(JS·5--NEl	263/544	3S7 (304-464)	0·79 (0·61-1·03)
2::6Sye-m.	161/338	42·3(31·3-NE)	177/338	31-0(24-7-NE)	0·76 (0S4-HlS)
S..					
Malo	2951589	NE(36•7-NE)	294/589	36,0 (31•0-NE)	0-76 (0·59-0·99)
Ff>m;jlllt	147/293	34·9 (30·2-NE)	146/293	30·4 (25·1-37·3)	080(0·57-1-13)
RiilCe					
Wtlite	307/631	37-1 (35·3-NE)	324/631	JS 7 (304-41>4)	O 78 (0-61-1·00)
Asian	121/227	42·3(302-NE)	106/227	31-6(23-9-NE)	082 (0·5S-1·22)
U11kn()W11	9/16	NE(NE-NE)	7/16	28 6 (4•5-NE)	027 (0·0S-1·50)
Aegion					
Asia-Pacific	116/219	42·3(302-NE)	103/219	31·6 (24•0-NE)	0·83 (0·5S-1·2S)
Europeand the Middle East	270/560	NE (35•3-NE)	290/560	35-3(301-464)	073 (0·56-094)
NorthAmerir.1	55/101	35·5 (24•1-NE)	46/101.	35·7 (239-NE)	1·03 (0·57-1-89)
ECOG petfotmance status					
0	2391491	NE(JS•S-NE)	252/491	351(29·7-42·1)	072 (0·55-095)
	201/388	36-1(31-4-NE)	1871]88	NE(28-6-NE)	0-87 (0,6,t.-1,18)
Toba,r;co use history					
Never	100/196	301 (24·0-32·8)	96/196	30·4 (24·0-42-1)	1-13 (0 77-1·67)
Previous	277/547	NE(42•3-NE)	270/547	32·0 (297-NEJ	062 (0·47--0-81)
Current	6S/139	NE (30·l-NE)	74/139	NE(l4·2-NE)	1-01 (O·SS-1-?Sl
Histology					
Squamous	150/294	NE(36•1-NEJ	1441294	46·4(ll4-NE)	080(0·54-1-18)
Non-squamous	292/588	37-l(JJ.4-NE)	296/588	30·4(245-37·2)	0-78 (0,61--0·99)
St.Jge					
IIA	147/295	NE(l67-NE)	148/295	NE(1l·0-NE)	0-68 (0 46-100)
118	901174	37-1(32-J-NE)	841174	46·4 (32-0-NE)	0·88 (0·54-1-42)
IIIA	205/413	32·3 (25•4-NE)	208/413	29-7 (217-35·3)	0-81 (0·61-1·06)
Aegion;iil lymph node sbge (pN)					
NO	118/229	NE(35•5-NE)	1ll/229	46·4 (37-0-NE)	0-88 (0S7-l-3S)
NI	170/348	NE(JH-NE)	178/348	36-0 (304-NE)	0·67 (0·47--0-9S)
f'U·Llstatus by !tl'lb3					
TC<l%	**181/383**	36·1(30•2•NE)	2021383	370 (28,6-NE)	097 (0 72•1•31)
TCitl%	248/476	NE(l6•1-NE)	2281476	35·3 (29•0-NE}	0-66 (0·49-0•8n
TC1-49'"	133/247	32·8 (294-NE)	1l4/247	31- ◀ (240-NE)	0·87 (0,60-1·26)
TC::i:50%	115/129	NE(4H-NE)	1l4/1l9	357 (29•7-NE)	043 (0·27-0.68)
Tvrw, nf <1:11ml>rv					
8ilobectomy	30/47	367 (36.1-NE)	17/47	NE(6.2-NE)	1·02 (OJS-2•98)
Pneumolled:omy	72/150	36·1(30·1-NE)	781150	421 (234-NE)	0·91 (0·56-147)
Chemotherapy regimen					
Cisplatin plusdocetairel	59/124	36·1(31•3-NE)	65/124	37·3 (12•0-NE)	072 (0·42-1·23}
Cisplatin plU'i gemcitabine	77/138	36•1(301-NE)	61/138	46,4(2],8-NE)	094 (0·56-1·57)
Cisplatinplus pemetre:w1ed	172/349	42•3(32•8 El	177/349	31•4 (26,7-NE)	0 84 (0 61•H6)
Cisplatin plus virorelbine	134/171	NE(l6·0-NE)	1371271	37·0(301-NE)	0•67 (0 46-Q.99)
EGFR mutation stattlS					
Ve,	49/109	24-1(16-1-36·1)	60/109	24•0 (12-2-31·4)	099 (0·60-1·62)
No	229/463	NE(32·8-NE)	2341463	360(301-NE)	0·79 (059-105)
Unlmowri	164/310	NE(l6•1-NE)	146/)10	421 ()0·4-NE)	070(049-101)
AU' rearr.1ngement status					
Ve,	14/31	30·5(17-1-NE)	17/1l	37·2 (19·5-NE)	1·04 (0,38-2·90)
No	251/507	36•1(30•2•NE)	256/507	31·4 (24·7-NE)	085 (0-66-110)
Unknown	**177/344**	NE (36•1-NEJ	167f144	37·3 (31•0-NE)	0-66 (0·46-093)
Allpitients	**442/882**	42·3 (36•0-NE)	**440/882**	35-3 (30•4-46•4)	0·79(0-64-0.96)

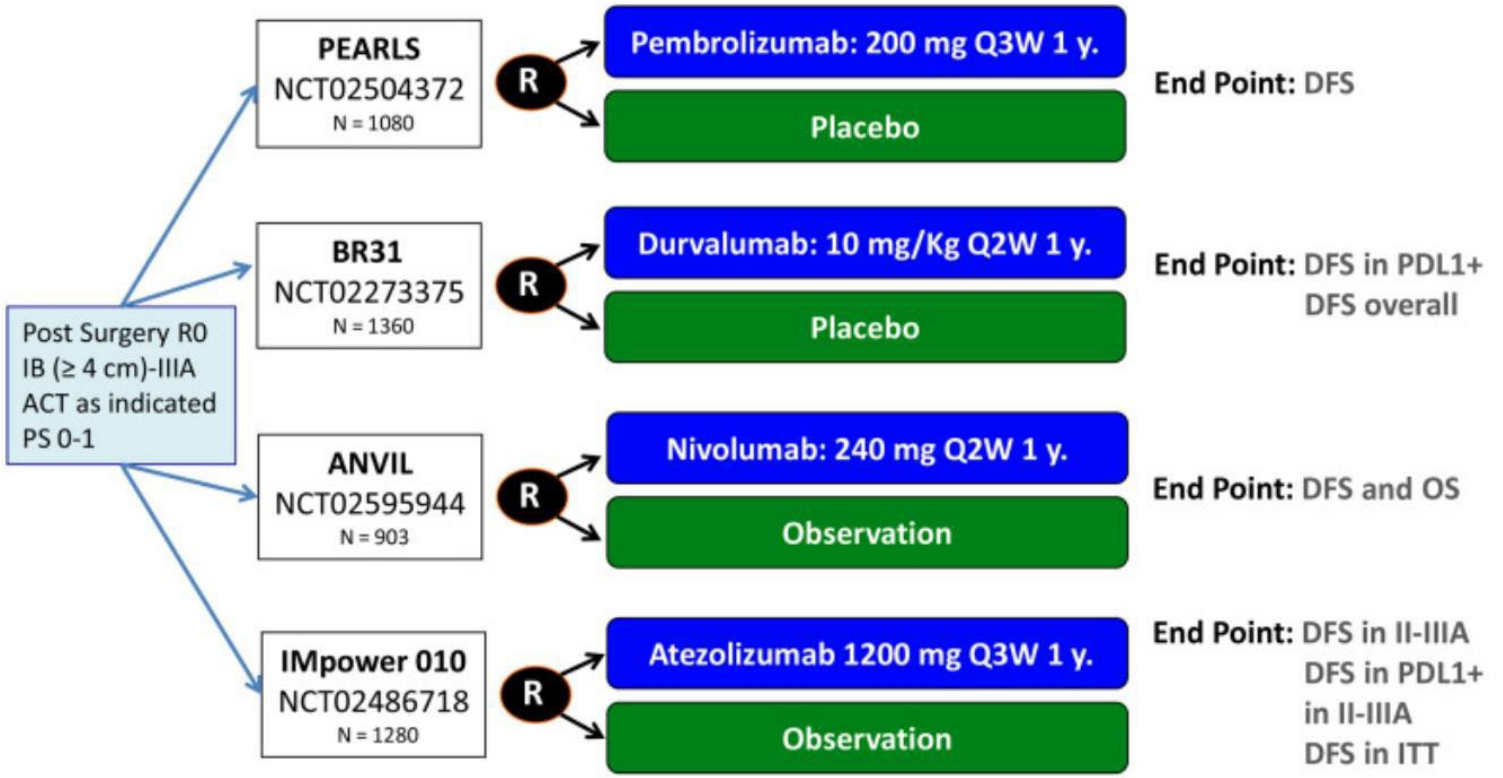
0·1 1·0 10-0

F.rvours ateiohzumab Favour best supportive care

Impower 010 Adverse Events

	(n=495)	(n=495)
Adverse event		
Any grade	459 (93%)	350 (71%)
Grade 3–4	108 (22%)	57 (12%)
Serious	87 (18%)	42 (8%)
Grade 5	8 (2%)*	3 (1%)†
Led to dose interruption of atezolizumab	142 (29%)	..
Led to atezolizumab discontinuation	90 (18%)	..
Immune-mediated adverse events		
Any grade	256 (52%)	47 (9%)
Grade 3–4	39 (8%)	3 (1%)
Required the use of systemic corticosteroids‡	60 (12%)	4 (1%)
Led to discontinuation	52 (11%)	0

Phase III NSCLC Adjuvant Immunotherapy Trials



DFS benefit but not in PD-L1 50% or higher.
Benefit in EGFR patients

Adjuvant Immunotherapy Take Home points

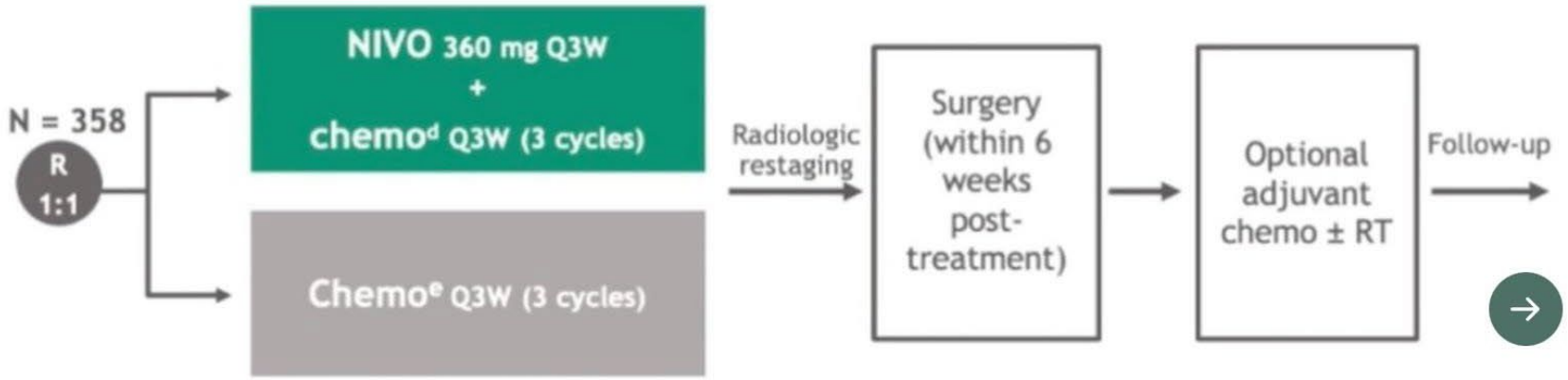
- FDA approval for 1 year of Atezolizumab in the PD-L1 1% or higher tumor. However, benefit is mostly driven by the PD-L1 50% or higher
- Matter of discussion in PD-L1 low patients. Consider Alliance ACCIO trial A01801 NCT04267848, in PD-L1 negative and low patients
- No benefit for adjuvant atezolizumab in EGFR and ALK mutated tumors. Adjuvant Osimertinib is the standard of care in EGFR mutated patients. Consider comprehensive molecular profiling in earlier stage NSCLC.

CheckMate 816 study design[a,1]

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0-1
- No known sensitizing *EGFR* mutations or *ALK* alterations

Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

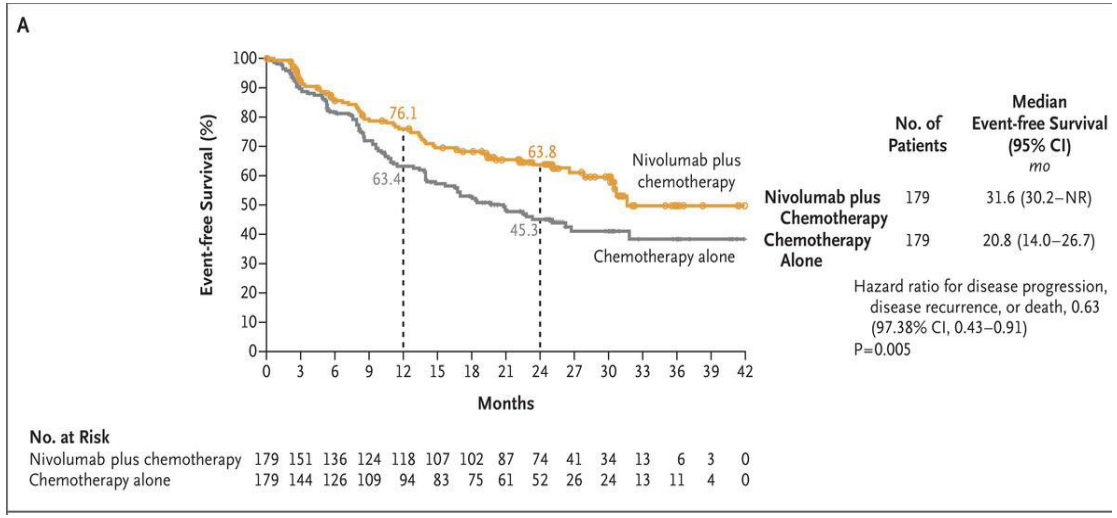
Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

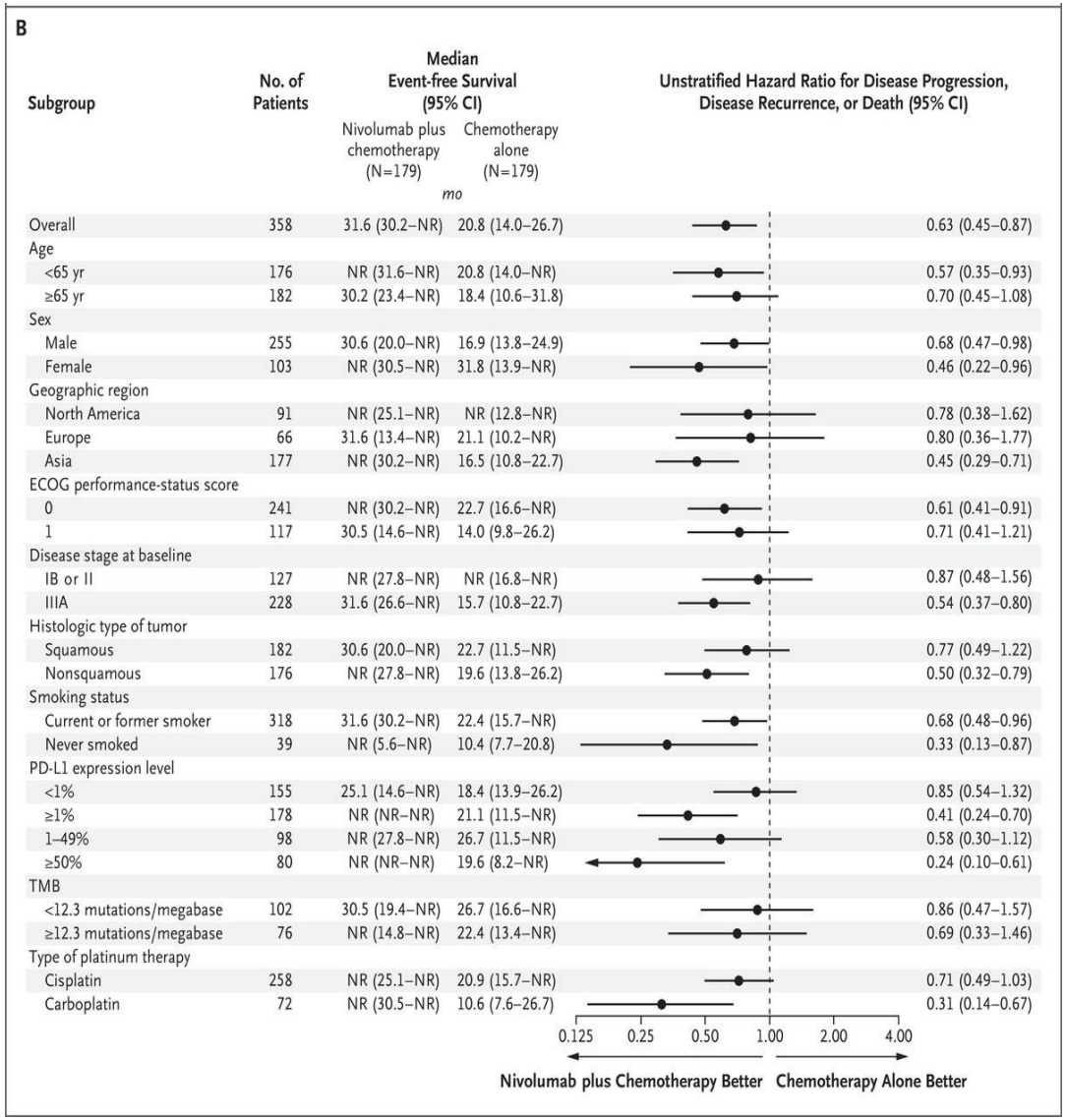
Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

[a]NCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

PM Forde et al. N Engl J Med 2022;386:1973-1985

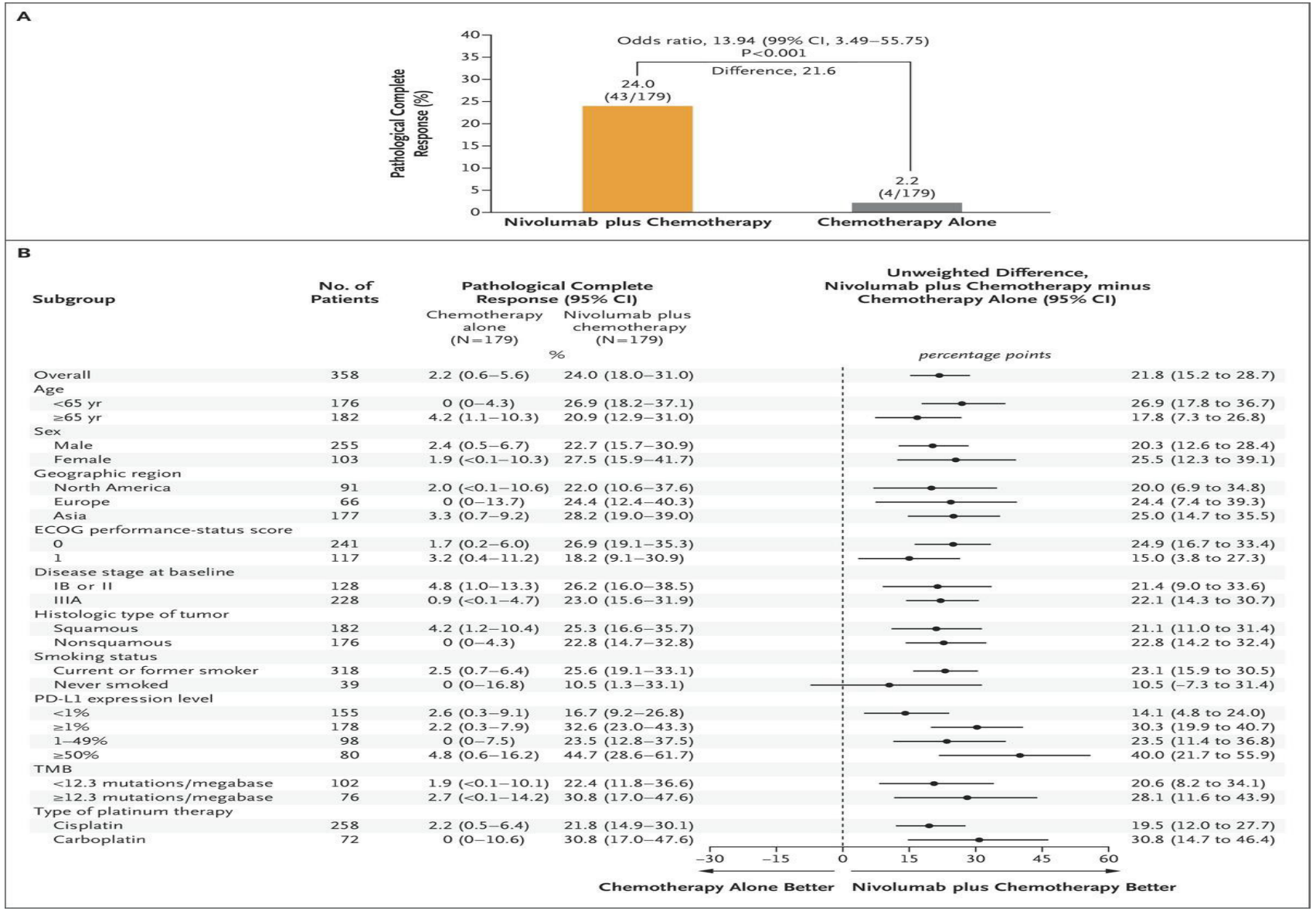
Checkmate 816:EFS





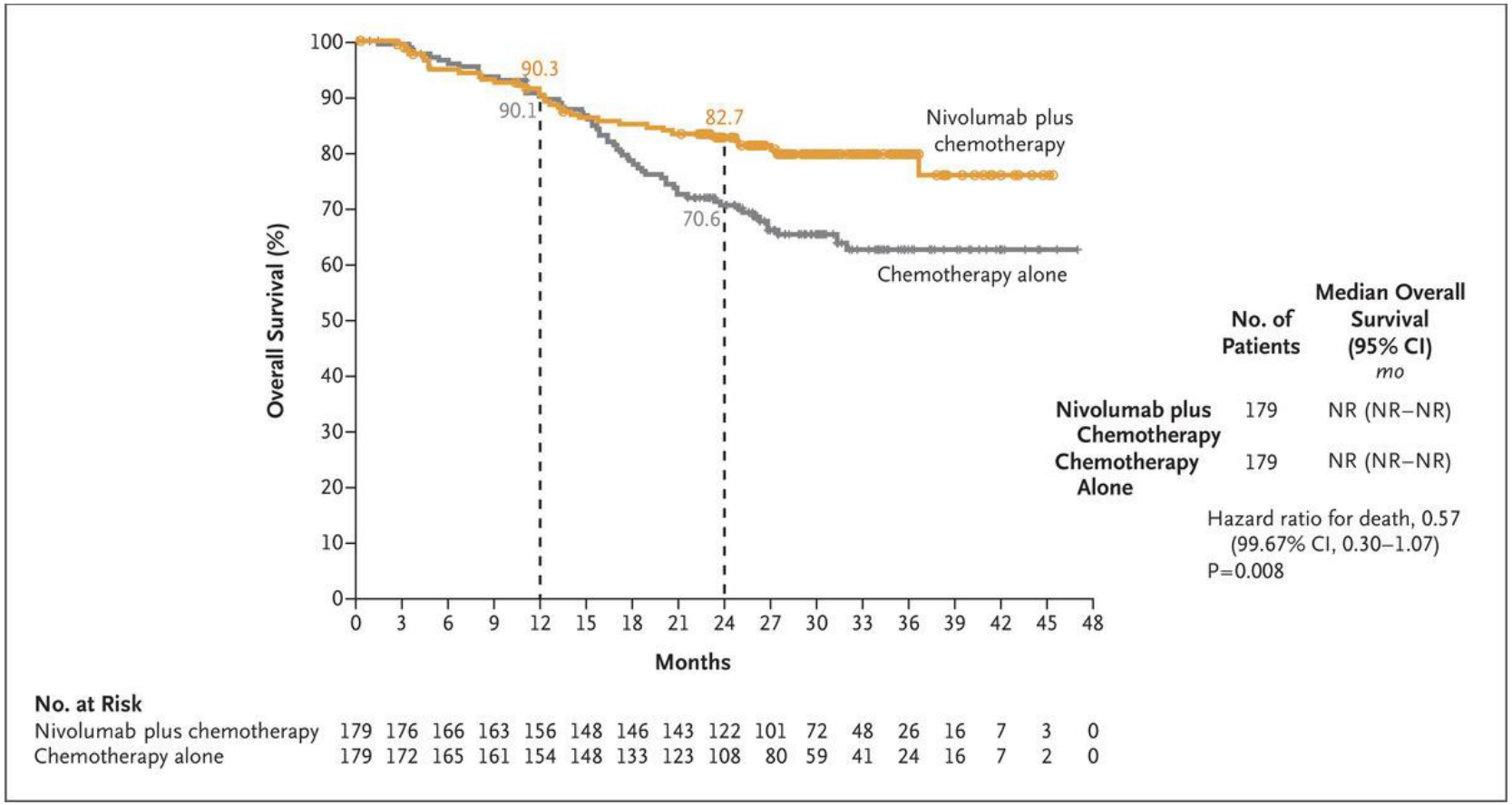
PM Forde et al. N Engl J Med 2022;386:1973-1985

Checkmate 816: Path CR



PM Forde et al. N Engl J Med 2022;386:1973-1985

Checkmate 816:OS



PM Forde et al. N Engl J Med 2022;386:1973-1985

Checkmate 816: Adverse Events

Table 2. Adverse Events.*

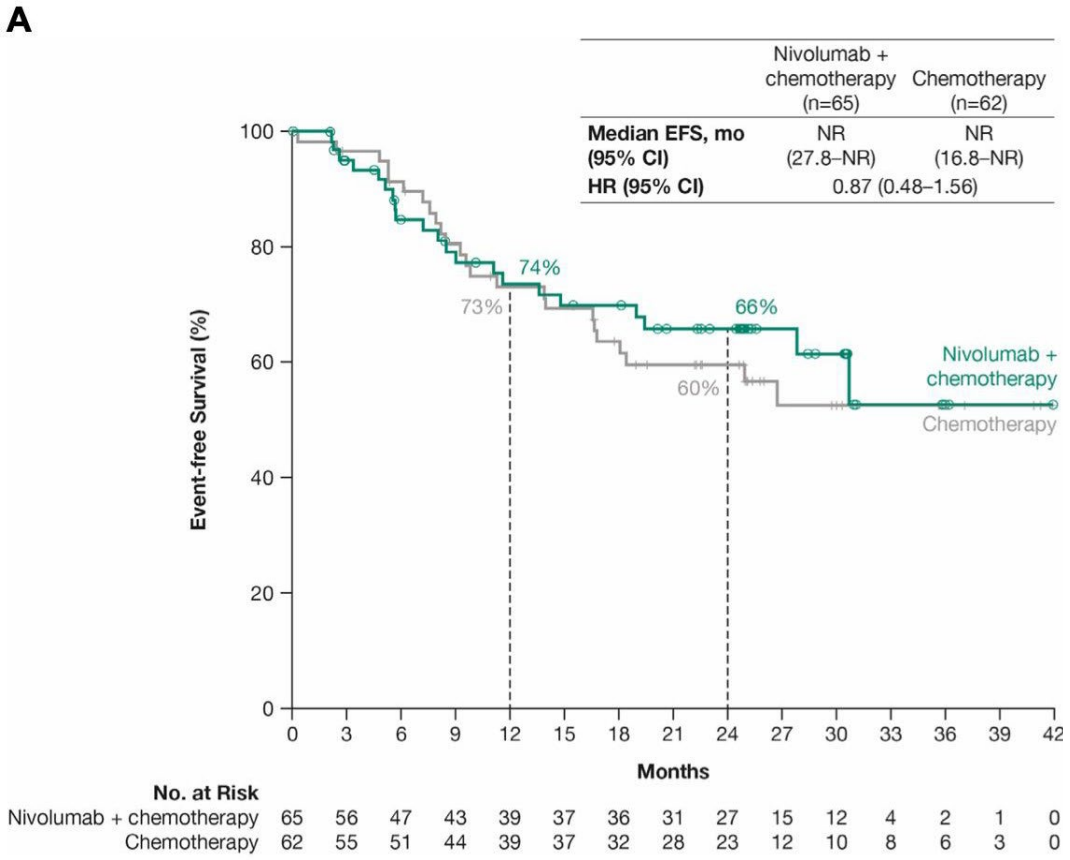
Event	Nivolumab plus Chemotherapy (N=176)		Chemotherapy Alone (N=176)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse events of any cause — no. (%)†				
All	163 (92.6)	72 (40.9)	171 (97.2)	77 (43.8)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	20 (11.4)	7 (4.0)
Serious	30 (17.0)	19 (10.8)	24 (13.6)	17 (9.7)
Treatment-related adverse events — no. (%)†				
All	145 (82.4)	59 (33.5)	156 (88.6)	65 (36.9)
Leading to discontinuation of treatment	18 (10.2)	10 (5.7)	17 (9.7)	6 (3.4)
Serious	21 (11.9)	15 (8.5)	18 (10.2)	14 (8.0)
Death‡	0	—	3 (1.7)	—
Surgery-related adverse events — no./total no. (%)§	62/149 (41.6)	17/149 (11.4)	63/135 (46.7)	20/135 (14.8)

* Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 24.0, and were graded according to the Common Terminology Criteria for Adverse Events, version 4.0.
† Included are events reported between the first neoadjuvant dose and 30 days after the last neoadjuvant dose.
‡ Treatment-related deaths in the chemotherapy-alone group were due to pancytopenia, diarrhea, acute kidney injury (all in one patient), enterocolitis, and pneumonia.
§ The denominators are based on patients who underwent definitive surgery. Included are events reported up to 90 days after definitive surgery. Grade 5 surgery-related adverse events (defined as events that led to death ≤24 hours after the onset of an adverse event) were reported in two patients in the nivolumab-plus-chemotherapy group and were deemed by the investigator to be unrelated to the trial drugs (one each due to pulmonary embolism and aortic rupture).

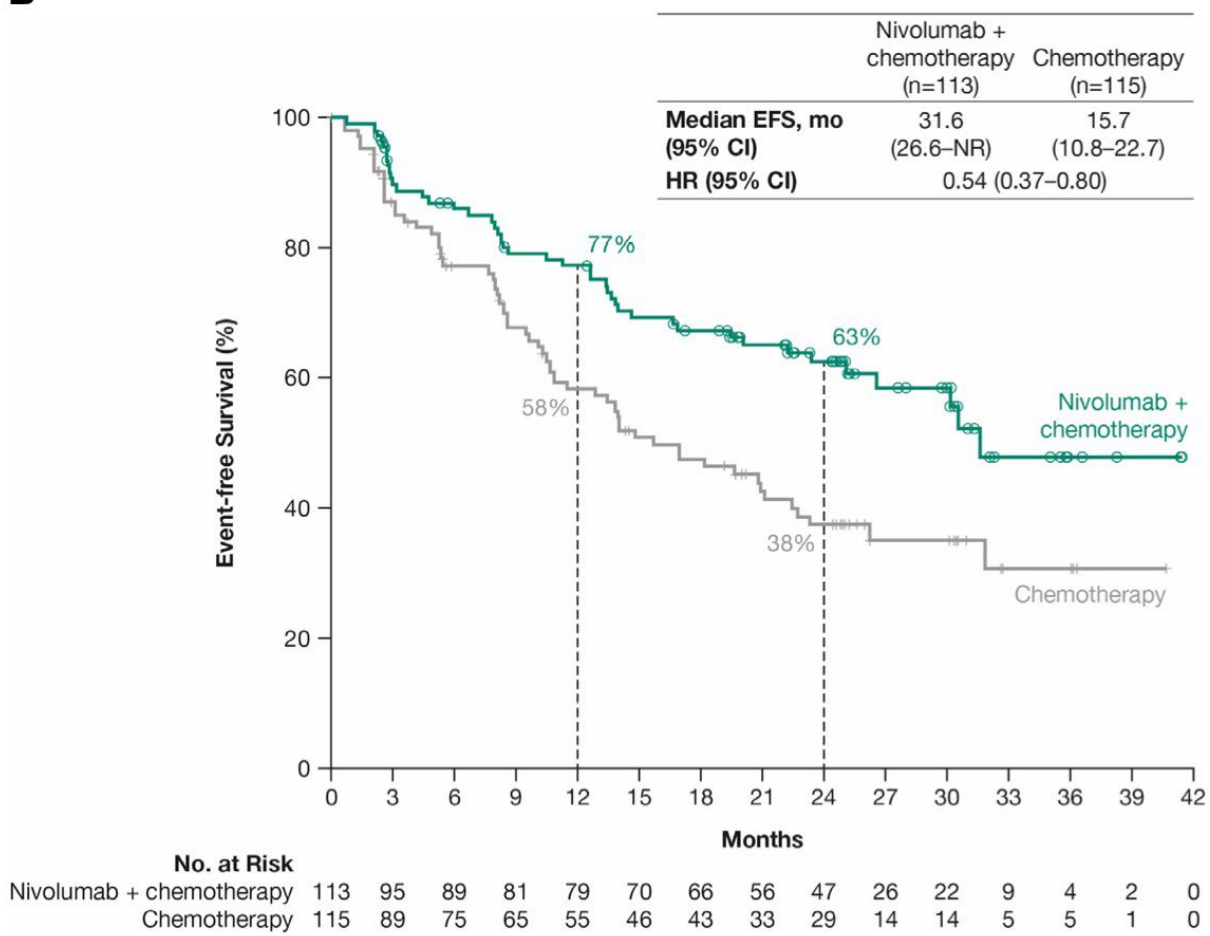
PM Forde et al. N Engl J Med 2022;386:1973-1985

Checkmate 816:EFS by Stage

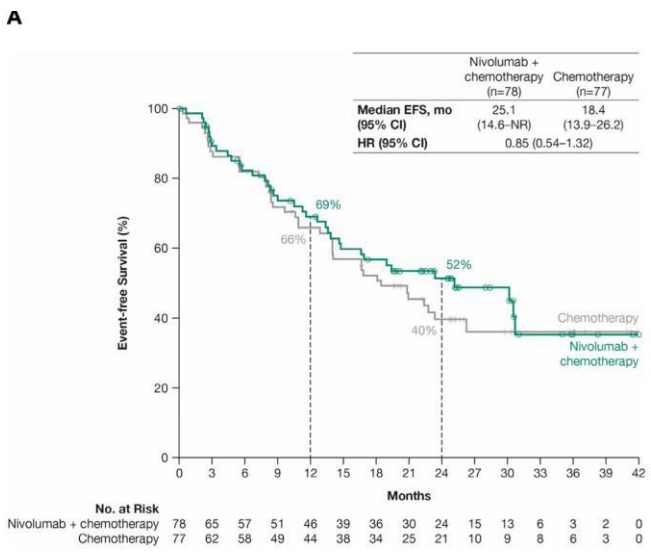
Stage 1-2



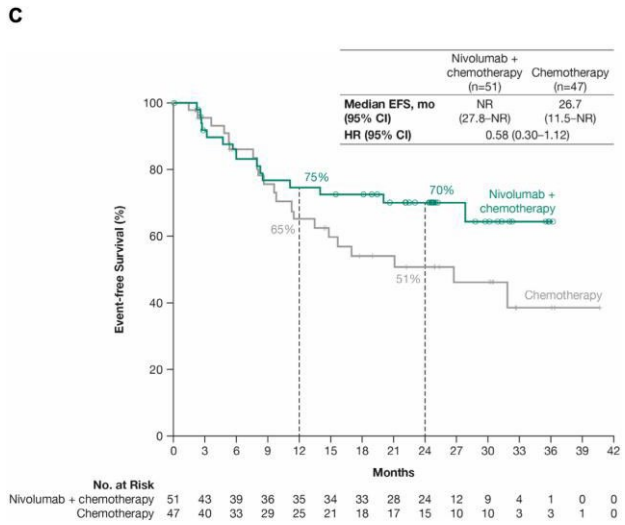
Stage 3A



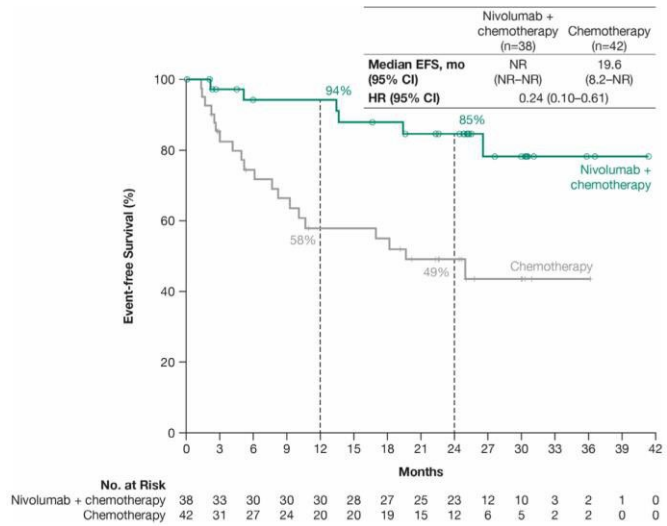
Checkmate 816:EFS by PD-L1



PD-L1
negative



PD-L1 1-49%

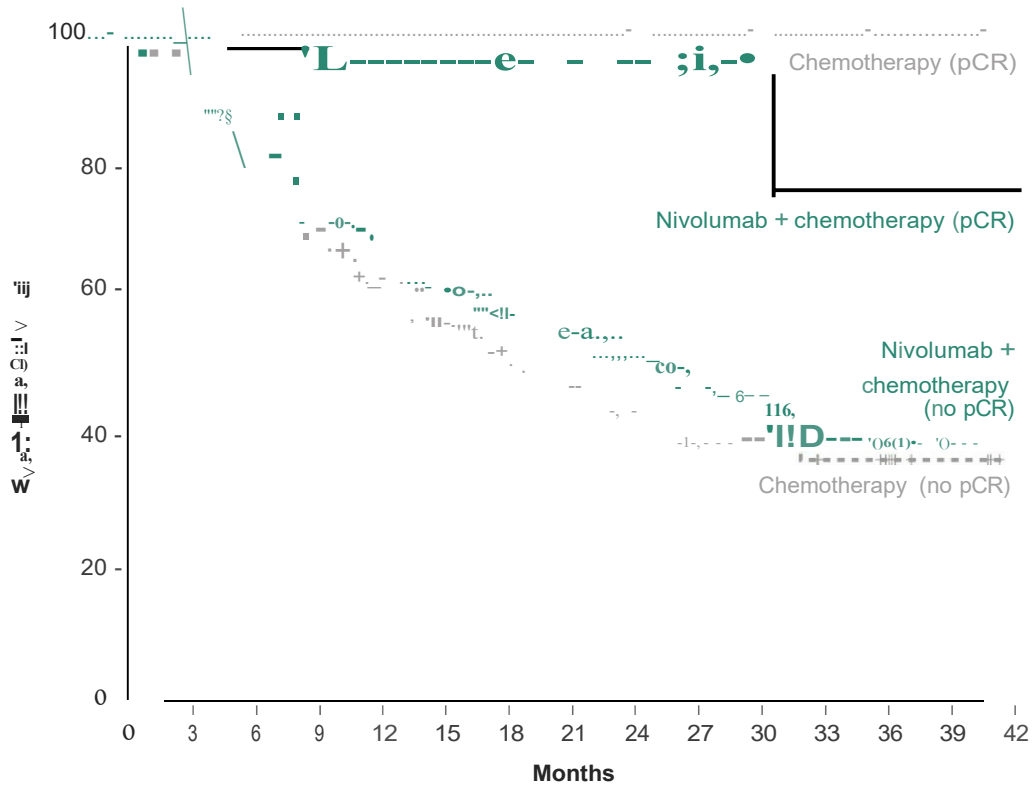


PD-L1 > 50%

PM Forde et al. N Engl J Med 2022;386:1973-1985

Checkmate 816: Event-free Survival in Patients with or without a Pathological Complete Response.

	pCR (n=43)	No pCR (n=136)	pCR (n=4)	No pCR (n=175)
Median EFS, mo {95% CI)	NR (30.6-NR)	26.6 (16.6-NR)	NR (NR-NR)	18.4 (13.9-26.2)
HR (95% CI)*	0.13 (0.05-0.37)		Not computedt	



No. at Risk

Nivolumab + chemotherapy (pCR)	43	43	41	40	40	40	40	35	32	19	14	6	3	2	0
Chemotherapy (pCR)	4	4	4	4	4	4	4	4	4	3	2	2	2	1	O
Nivolumab + chemotherapy (no pCR)	136	108	95	84	78	67	62	52	42	22	20	7	3	1	O
Chemotherapy (no pCR)	175	140	122	105	90	79	71	57	48	23	22	11	9	3	0

Checkmate 816: Surgical Outcomes

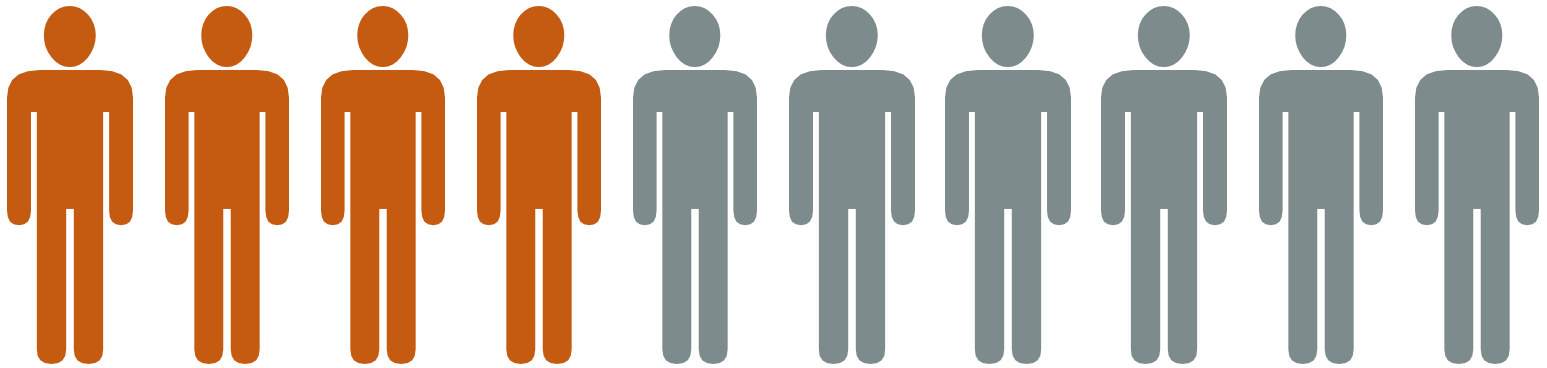
	Nivolumab plus Chemotherapy (N = 179)	Chemotherapy (N = 179)
Patients with definitive surgery* — no. (%)	149 (83.2)	135 (75.4)
Time from last neoadjuvant dose to definitive surgery — wk		
Median (IQR)	5.3 (4.6–6.0)	5.0 (4.6–5.9)
Patients with cancelled definitive surgery — no. (%)	28 (15.6)	37 (20.7)
Disease progression	12 (6.7)	17 (9.5)
Adverse event	2 (1.1)	1 (0.6)
Other†	14 (7.8)	19 (10.6)
Patients with delayed surgery‡,§ — no. (%)	31 (20.8)	24 (17.8)
Administrative reason	17 (11.4)	8 (5.9)
Adverse event	6 (4.0)	9 (6.7)
Other	8 (5.4)	7 (5.2)
Duration of surgery‖ — min		
Median (IQR)	185.0 (133.0–260.0)	213.5 (150.0–283.0)
Surgical approach§ — no. (%)		
Thoracotomy	88 (59.1)	85 (63.0)
Minimally invasive**	44 (29.5)	29 (21.5)
Minimally invasive to thoracotomy	17 (11.4)	21 (15.6)
Type of surgery§,†† — no. (%)		
Lobectomy	115 (77.2)	82 (60.7)
Sleeve lobectomy	2 (1.3)	10 (7.4)
Bilobectomy	3 (2.0)	4 (3.0)
Pneumonectomy	25 (16.8)	34 (25.2)
Other	24 (16.1)	21 (15.6)
Completeness of resection§ — no. (%)		
R0 (no residual tumor)	124 (83.2)	105 (77.8)
R1 (microscopic residual tumor)	16 (10.7)	21 (15.6)
R2 (macroscopic residual tumor)	5 (3.4)	4 (3.0)
Rx (unknown)	4 (2.7)	5 (3.7)

PM Forde et al. N Engl J Med 2022;386:1973-1985

Checkmate 816: Take Home Points

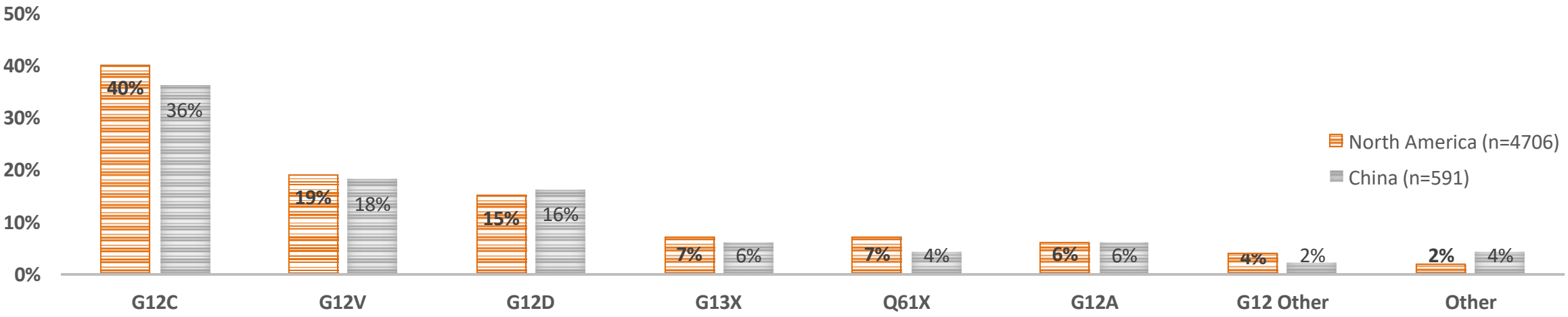
- 3 cycles of neoadjuvant chemo immunotherapy improved outcomes (EFS, pCR) in EGFR/ALK negative resectable Stage 1b-3a NSCLC
- Most benefit derived by Stage IIIA , PD-L1 high, Non squamous subsets
- No detriment to surgical outcomes due to immunotherapy
- 17% did not proceed to surgery, 6.7% from progression, 1.1% from toxicity.
- Consider/Preferred choice for resectable Stage IIIA patients
- Post surgical management of patients who do not have path CR is unclear
- Is 3 cycles of neoadjuvant chemo/immunotherapy enough?
- Logistics of molecular profiling before neoadjuvant therapy needs to be worked out.

KRAS G12C is the most common KRAS variant in NSCLC



KRAS G12C

40% of KRAS mutations in NSCLC



Infographic generated from data
Judd MCT 2021; Loong TLCR 2020

Slide courtesy: Dr Grace DY

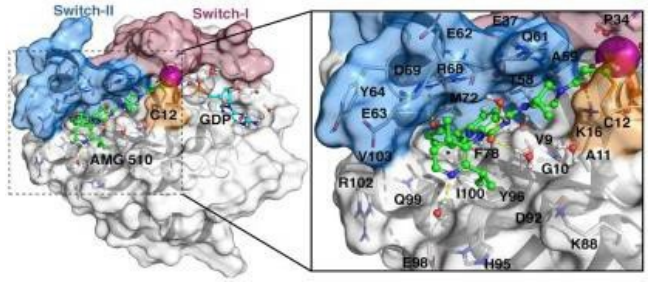
Development of KRAS-Targeting Therapies in NSCLC

2009-2017: MEKi (SELECT), CDK4/6i (JUNIPER) failed clinical testing in KRAS mutant NSCLC

2000-2003: FTIs failed clinical testing in lung cancer

1982: Discovery of KRAS oncogene in LC cell line

2013: Shokat team revealed crystallographic insights on allosteric site for developing KRAS G12Ci

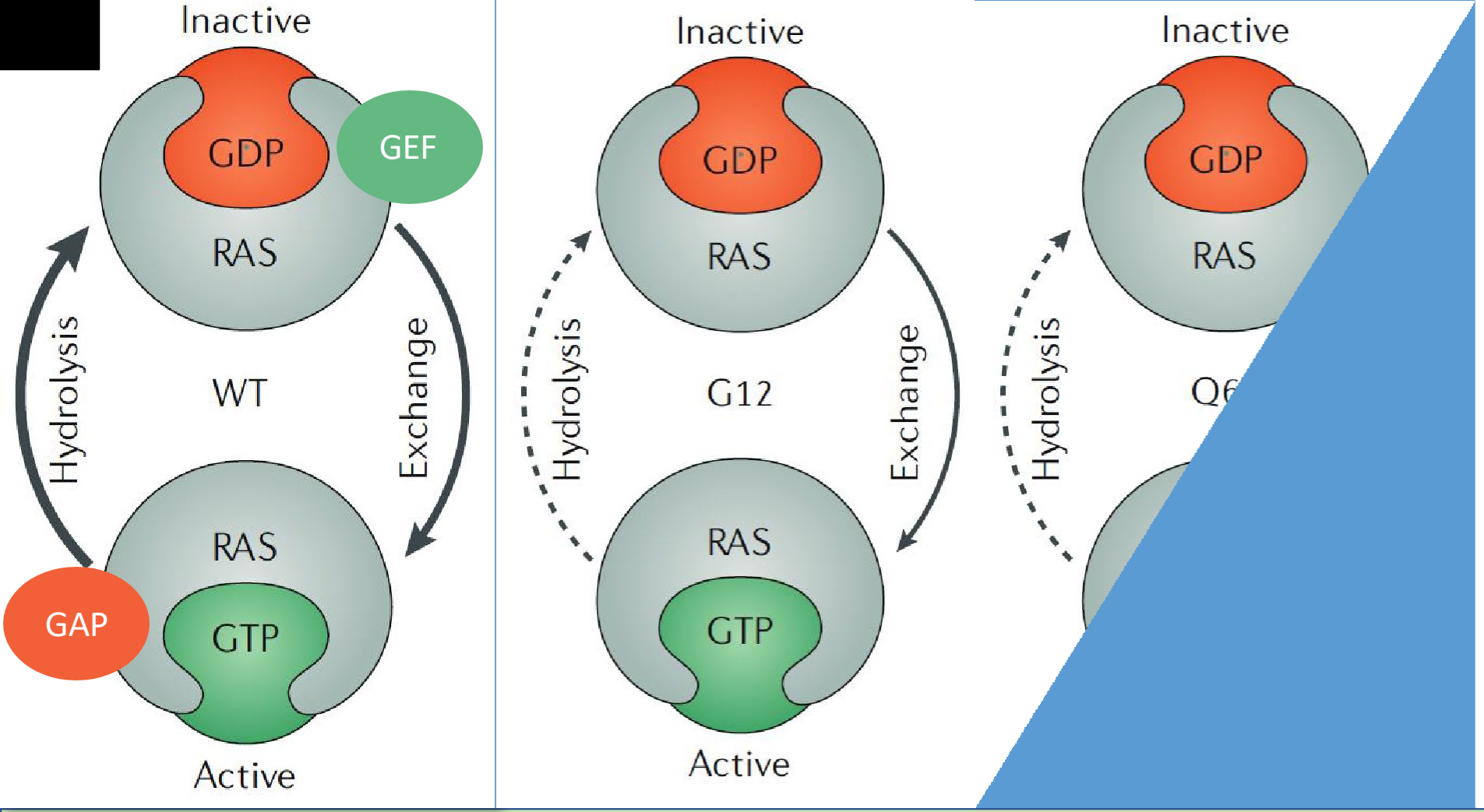


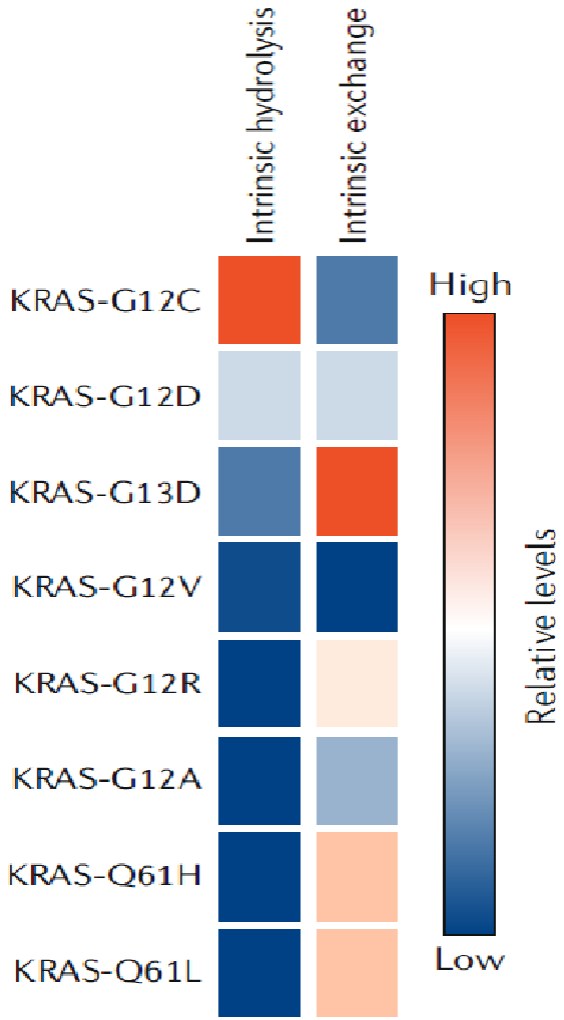
2018: Sotorasib FIH trial started
2021: Sotorasib received US FDA accelerated approval as 2/3L NSCLC with KRAS G12C

- Sotorasib is a first-in-class, oral targeted therapy that selectively inhibits the $KRAS^{G12C}$ protein
- Sotorasib locks the $KRAS^{G12C}$ protein in an inactive state, preventing oncogenic signaling without affecting wild type KRAS

Slide courtesy: Dr Grace DY

Der PNAS 1982
Adjei JCO 2003
Janne JAMA 2017
Goldman Front Oncol 2020
Ostrem Nature 2013
Skoulidis NEJM 2021
Canon Nature 2019
Lanman AACR 2019
Ryan Nat Rev Clin Oncol. 2018





Biochemical Heterogeneity of KRAS Mutations

Modifed from
Moore Nat Rev Drug Discov 2020
Hunter Mol Cancer Res 2015

Slide courtesy: Dr Grace DY

CodeBreaK 100 Long-term Update in NSCLC: Study Schema
SOTORASIB

Screening/ enrollment → **Pooled Phase 1/2: Advanced NSCLC, sotorasib 960 mg orally once daily (N = 174)**
Radiographic scan every 6 weeks up to week 48; once every 12 weeks thereafter → **Safety and long-term follow-up**

Key eligibility criteria

- Locally advanced or metastatic *KRAS* p.G12C-mutated solid tumors
- 1+ prior systemic therapy or ineligible/intolerant
- Stable brain mets allowed

PHASE 1 (n = 48)

Primary endpoint
- Safety and tolerability

Key secondary endpoints
- PK, ORR, DoR, PFS, duration of stable disease

PHASE 2 (n = 126)

Primary endpoint
- ORR by RECIST 1.1 by BICR

Key secondary endpoints
- DoR, DCR, PFS, OS, time to response, safety

Data cutoff: February 22, 2022

Median Follow-up for Overall Survival: 24.9 months

Dy et al AACR 2022

BICR, blinded independent central review; DCR, duration of complete response; DoR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria In Solid Tumors.

Efficacy Analysis: Code Break 100 Long-Term Update (AACR)

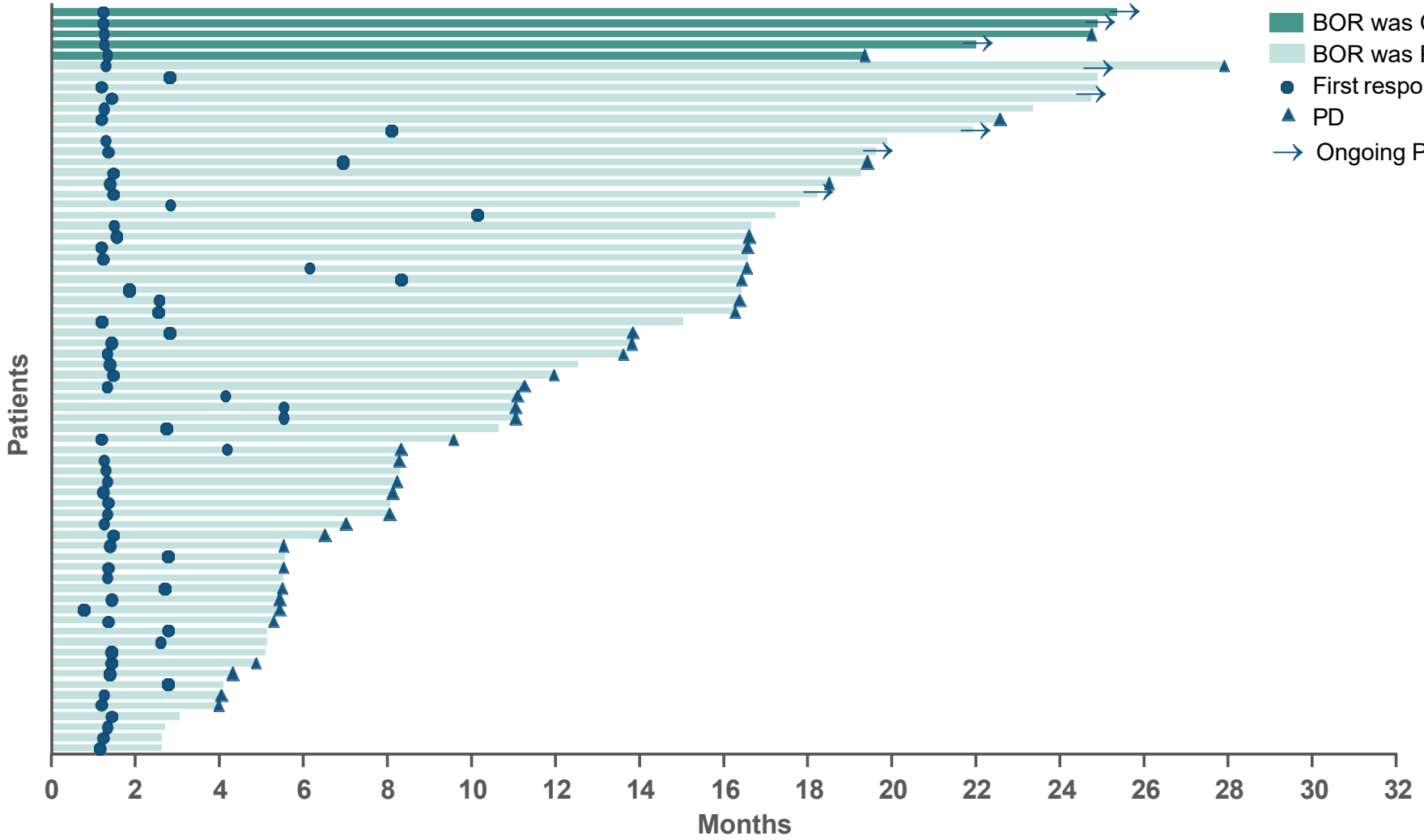
Response by Central Review	Phase 1/2 NSCLC N = 172*
Objective response rate, % (95% CI)	**40.7 (33.3, 48.4)**
Best overall response, n (%)	
Complete response	5 (2.9)
Partial response	65 (37.8)
Stable disease	74 (43.0)
Progressive disease	23 (13.4)
Not evaluable or missing scan	5 (2.9)
Disease control rate, % (95% CI)	**83.7 (77.3, 88.9)**
Median progression-free survival, months (95% CI)	**6.3 (5.3, 8.2)**

CI = Confidence Interval.
95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival Estimate Follow-up time is summarized by reversing the status indicator for censored and events. Time to response and duration of response are calculated among confirmed responders.
*2 patients are not included in the efficacy set as they did not have measurable lesions at baseline and were ineligible for response assessment

Dy et al AACR 2022

Slide courtesy: Dr Grace DY

Durability of Response: CodeBreak 100 Long-Term Update (AACR)



Median time to response: 6 weeks

- 70% of patients had a response at their first scan

Median duration of response: 12.3 months (95% CI: 7.1, 15.0)

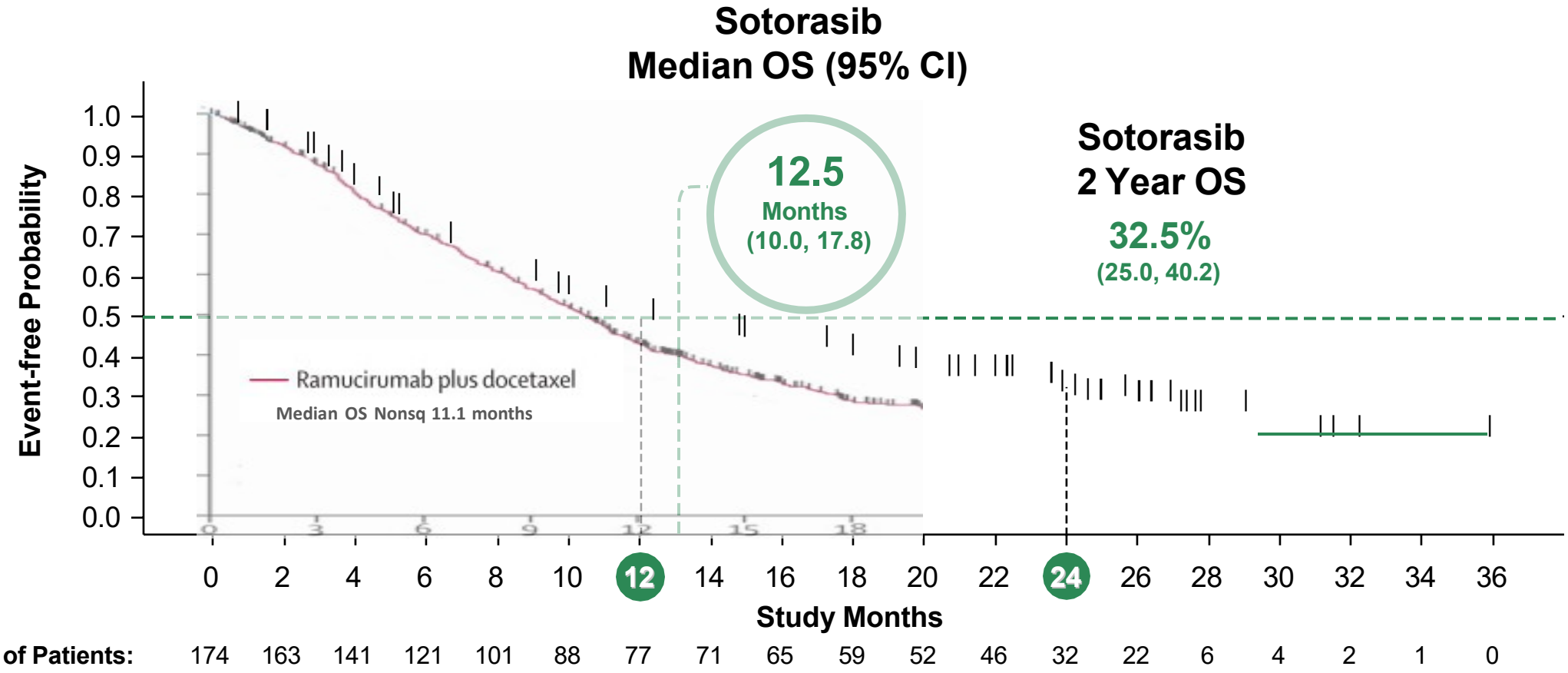
50.6% (95% CI: 37.4, 62.4) **of responders remained in response for 12+ months**

BOR, best overall response; CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response.

Dy et al AACR 2022

Slide courtesy: Dr Grace DY

Updated Overall Survival: CodeBreak 100 Long-Term Update



2-year overall survival observed in 32.5% of patients

Median follow-up time for OS was 24.9 months

95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.

Dy et al AACR 2022

Slide courtesy: Dr Grace DY

CodeBreak 200 Randomized Phase III

Screening/ enrollment

Key eligibility criteria

- Locally advanced or metastatic *KRAS* p.G12C-mutated NSCLC
- 1+ prior systemic therapy or ineligible/intolerant
- Stable brain mets allowed

RANDOMIZATION N=345

Sotorasib 960mg QD

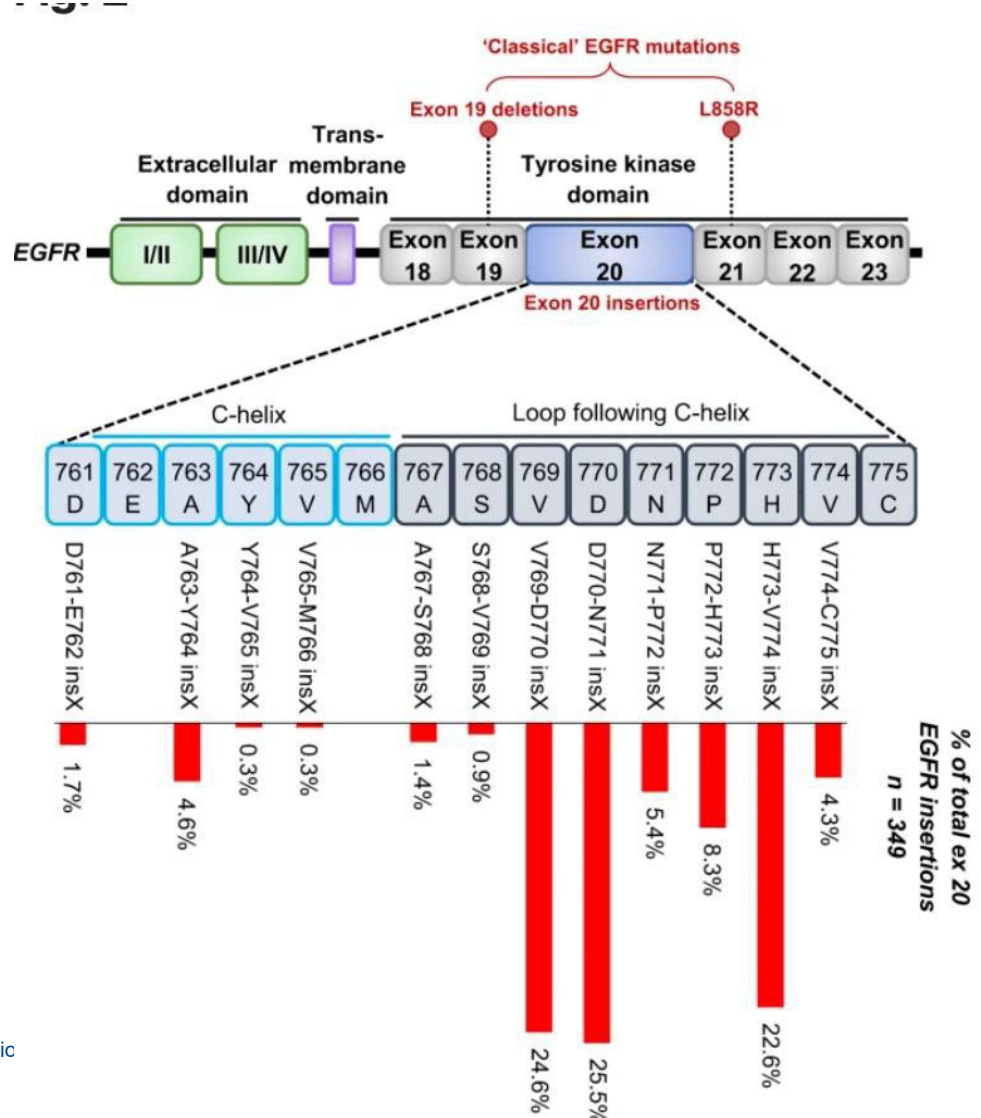
Docetaxel 75mg/m2 every 21 days

Primary endpoint
- PFS

Key secondary endpoints
- ORR, OS, DOR, QOL, DCR

Slide courtesy: Dr Grace DY

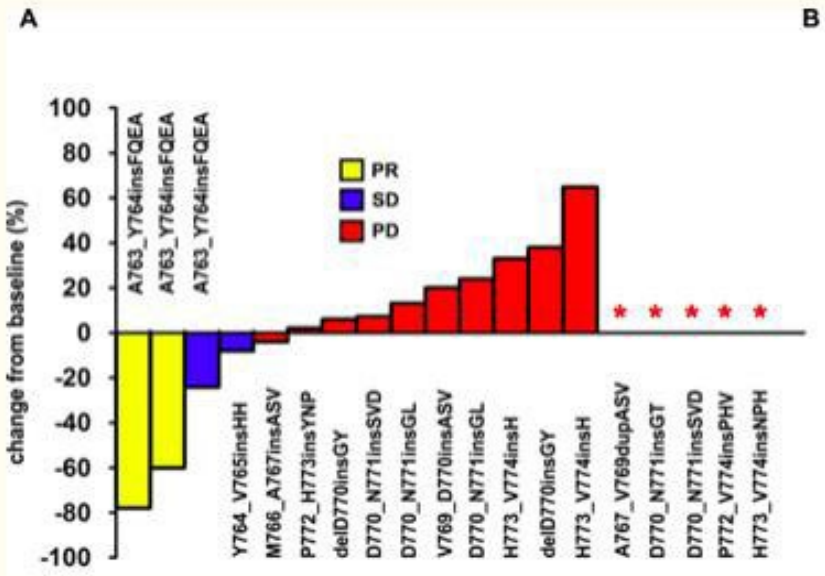
EGFR exon 20 insertions



Vyse, S., Huang, P.H. Targeting *EGFR* exon 20 insertic
https://doi.org/10.1038/s41392-019-0038-9

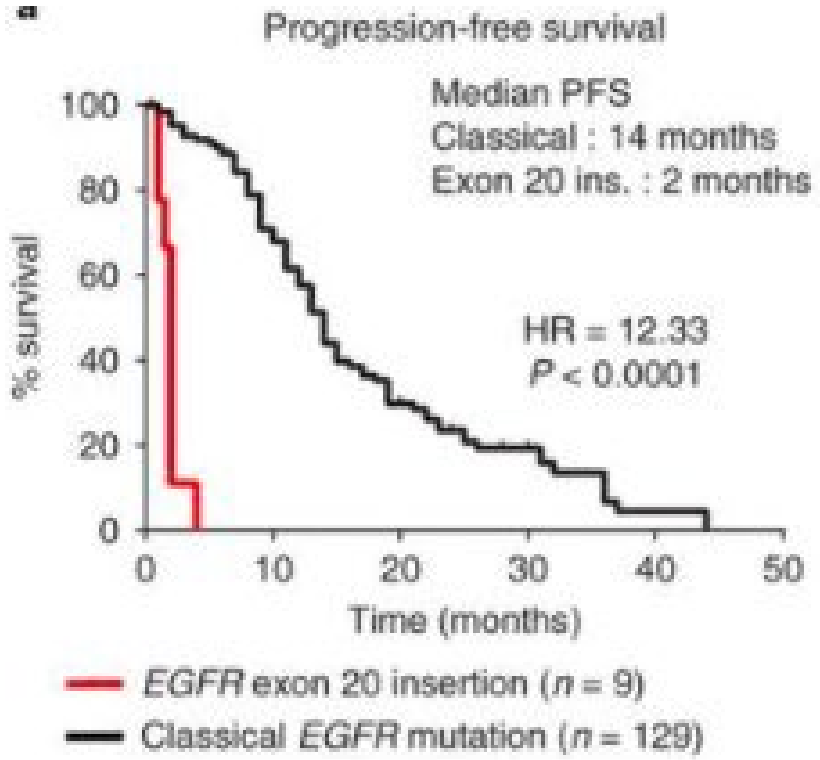
Froedtert & Medical College of Wisconsin

Poor Response to EGFR TKI in NSCLC with Exon 20



	Best response to reversible EGFR TKI				
EGFR mutation	drug	PR	SD	PD	RR [%]
A763_Y764insFQEA	erlotinib	2	1	-	66.6%
Y764_V765insHH	gefitinib	-	1	-	0%
M766_A767insASV	erlotinib	-	-	1	0%
A767_V769dupASV	gefitinib	-	-	1	0%
V769_D770insASV	erlotinib	-	-	1	0%
D770_N771insGL	erlotinib	-	-	2	0%
D770_N771insGT	erlotinib	-	-	1	0%
D770_N771insSVD	erlotinib	-	1	1	0%
delD770insGY	erlotinib	-	-	2	0%
P772_H773insYNP	gefitinib	-	-	1	0%
P772_V774insPHV	erlotinib	-	-	1	0%
H773_V774insH	gefitinib/ erlotinib	-	-	2	0%
H773_V774insNPH	erlotinib	-	-	1	0%

Figure 2



Yasuda H, Park E, Yun CH, et al. Structural, biochemical, and clinical characterization of epidermal grow th factor receptor (EGFR) exon 20 insertion mutations in lung cancer [published correction appears in Sci Transl Med. 2014 Feb 26;6(225):225er1]. *Sci Transl Med*. 2013;5(216):216ra177. doi:10.1126/scitranslmed.3007205
Robichaux, J.P., Elamin, Y.Y., Tan, Z. *et al.* Mechanisms and clinical activity of an EGFR and HER2 exon 20–selective kinase inhibitor in non–small cell lung cancer. *Nat Med* **24,** 638–646 (2018).

Froedtert & Medical College of Wisconsin

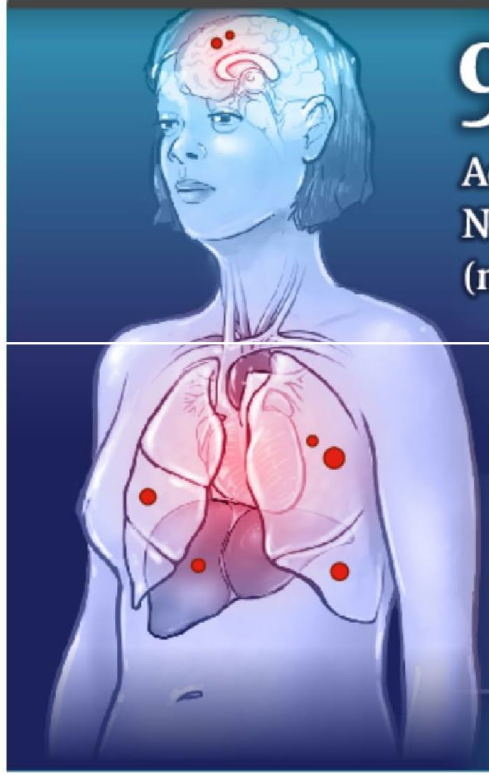
Summary of active agents in EGFR exon 20

Drug	Type	Study	ORR/ DCR	PFS	DOR	Common AE	DCR
Poziotinib	Oral TKI 16 mg qd	Zenith Cohort 3 79 pts	27.8%	7.2 months	6.5 months	Grade 3 Rash (33%) diarrhea (23%) mucositis	8% (94% had dose interruption)
Mobocertinib FDA APPROVED Sep 2021	Oral TKI 160 mg daily	114pts Exclaim NCT02716116	28 %	7.3 months	17.5months	diarrhea (83%), nausea (43%), rash (33%), and vomiting (26%),	25%
Amivantamab FDA APPROVED May 2021	IV EGFR-MET bispecific antibody	Chrysalis 81 pts	40%	8.3 months	11 months	Rash (86%) Infusion reaction (66%) Paronychia (45%)	4%
Osimertinib 160 mg	Phase 2	ECOG /ACRIN 5162 21 pts	25%	9.7 months	5.7	Anemia, fatigue, prolonged QT	

The NEW ENGLAND JOURNAL of MEDICINE

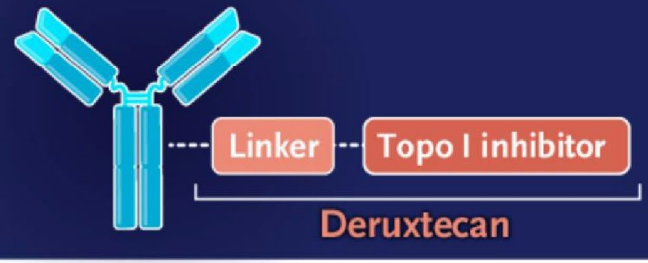
Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer

MULTICENTER, INTERNATIONAL, PHASE 2 STUDY



91

Adults with metastatic *HER2*-mutant NSCLC refractory to standard treatment (median follow-up, 13 mo)



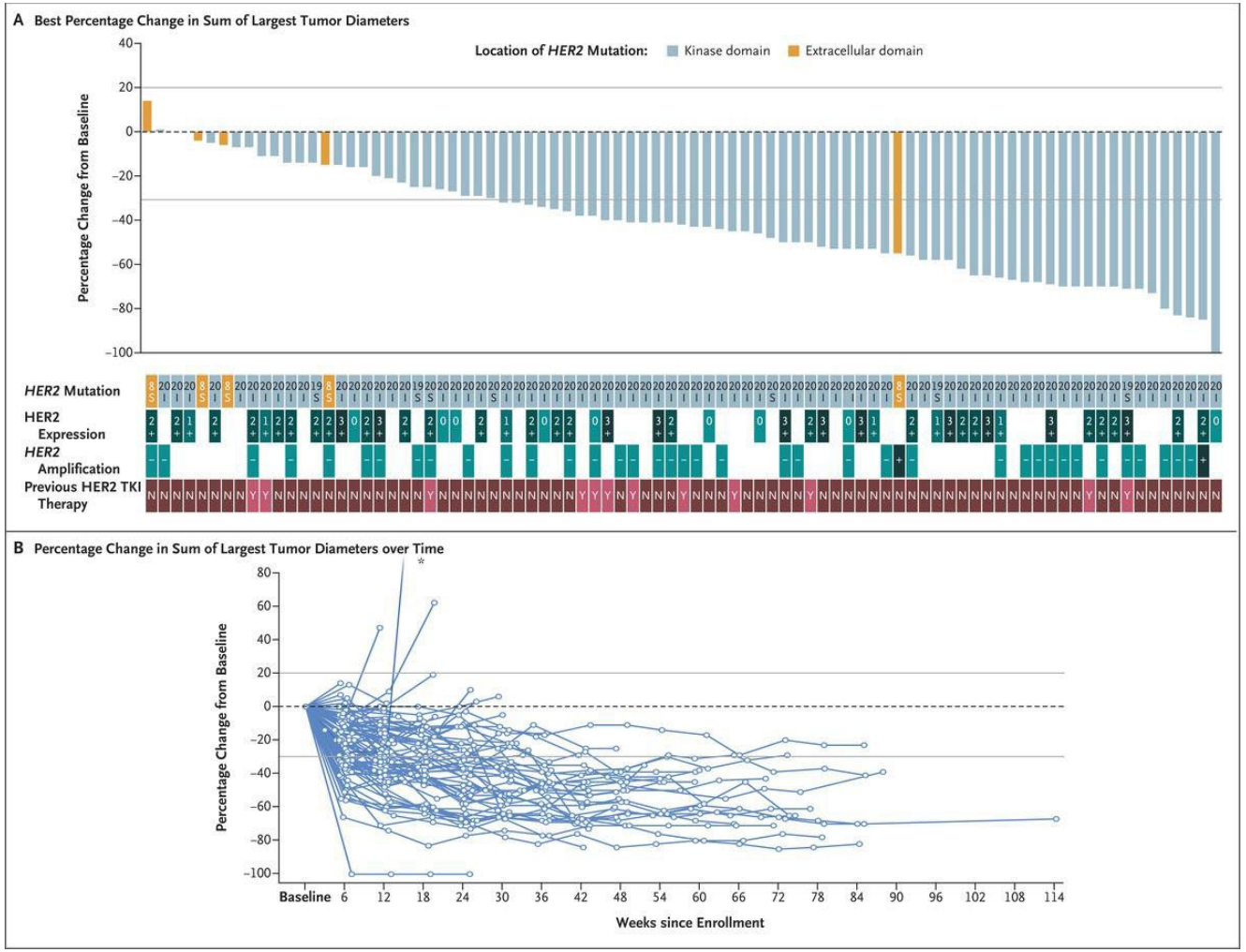
Confirmed objective response (assessed by independent central review)	55% (95% CI, 44-65)
Duration of response	9.3mo
Progression-free survival	8.2mo
Overall survival	17.8 mo

Grade 3 or higher drug-related adverse events occurred in 46% of patients.

Trastuzumab deruxtecan showed durable anticancer activity.

B.T. Li et al. 10.1056/NEJMoa2112431

Anti Tumor Activity of Trastuzumab Deruxtecan in Her 2 mutated NSCLC



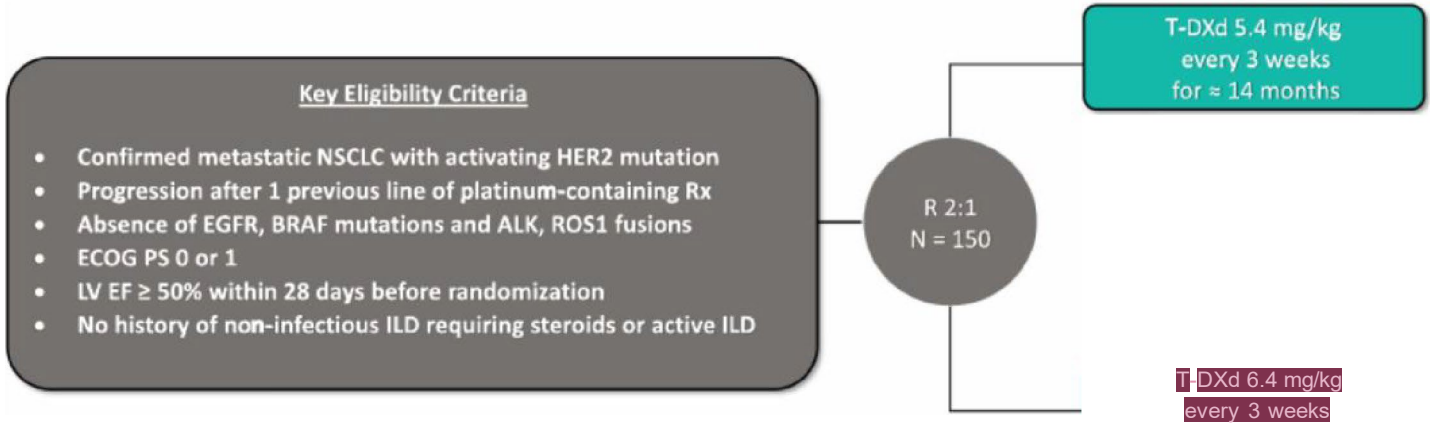
BT Li et al. N Engl J Med 2022;386:241-251

Trastuzumab related ILD

Table S5. Adjudicated Drug-related Interstitial Lung Disease.

	Patients (N = 91)					
	Grade 1	**Grade 2**	**Grade3**	**Grade4**	**Grade 5**	**Total**
Adjudicated drug-related interstitial lung disease, n (%)*	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)t	24 (26.4)

DESTINY-Lung02



ECOG PS, Eastern Cooperative Oncology Group performance status; LV EF, lert ventricular ejection fraction; ILD. interstitial lung **disease;** T-DXd. trastuzumab d ruxtecan; ORR, obj ctlve respo s rate; R CIST, r sponse valuation criteria In solid tumors; BICR, blinded independent central review; OCR, disease control rate; DOR, duration of response; PFS, progression-free survhr.11; OS ov rail survival.

Primary end point
- ORR (RECIST v1 I per BICR)

Key secondary end points
- ORR (RECIST v1.I per investigator)
- DCR, DOR, and PFS (RECIST vl.1per 81CR)
- OS
- Safety

ORR:57.7%
DoR : 8.7 months

FDA approval Aug 2022

iUUMti54--

Conclusions

- Treatment Landscape of NSCLC has changed dramatically in the last decade with the advent of immunotherapy and targeted therapy

- Novel combinations and immunotherapy approaches are being studied