RESPIRATORNI EDUKATIVNI CENTAR

I MEDICAL NSCLC PRECEPTORSHIP

Karcinom pluća - Quo vadis?

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Beograd, Srbija

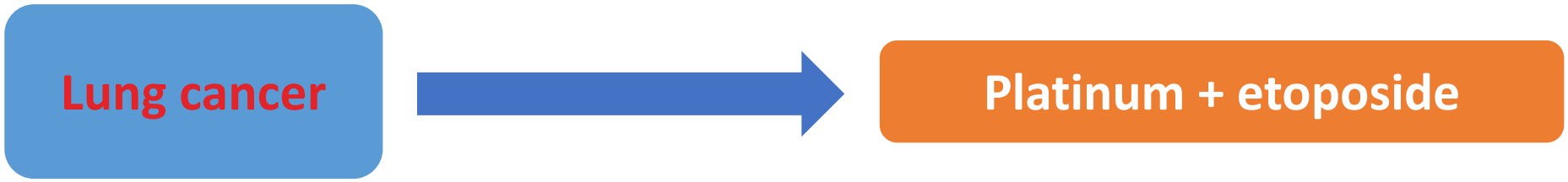
28/04/2023

Samo za stručnu javnost

ONCOLOGY

The meeting is initiated, organized and funded by Takeda

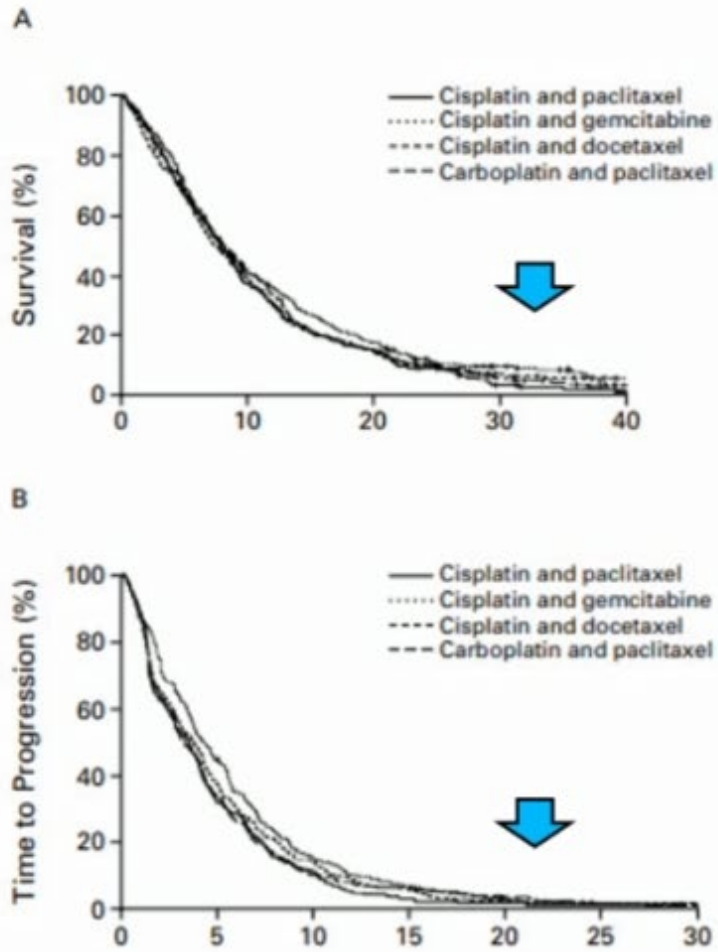
Until recently the life of a thoracic oncologist was simp



Very few treatment options

VIRTUAL 2020 ESMO congress

Status of Metastatic Lung Cancer Therapy in 2000



The New England Journal of Medicine

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

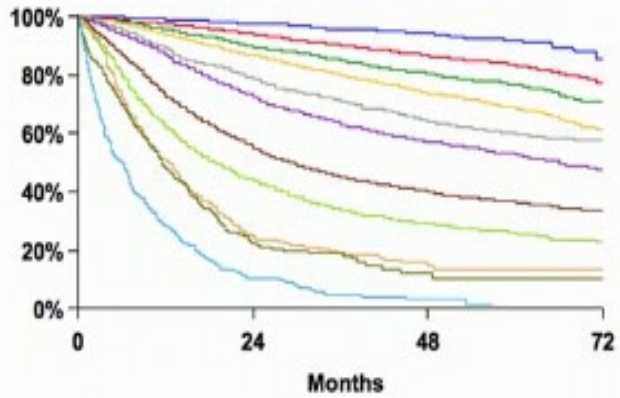
JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP

1 year survival 33%
Median Survival 7.9

- Platinum Chemotherapy Improved Survival
- All doublets with similar efficacy
- No predictive factors identified
- All regimens with significant toxicty

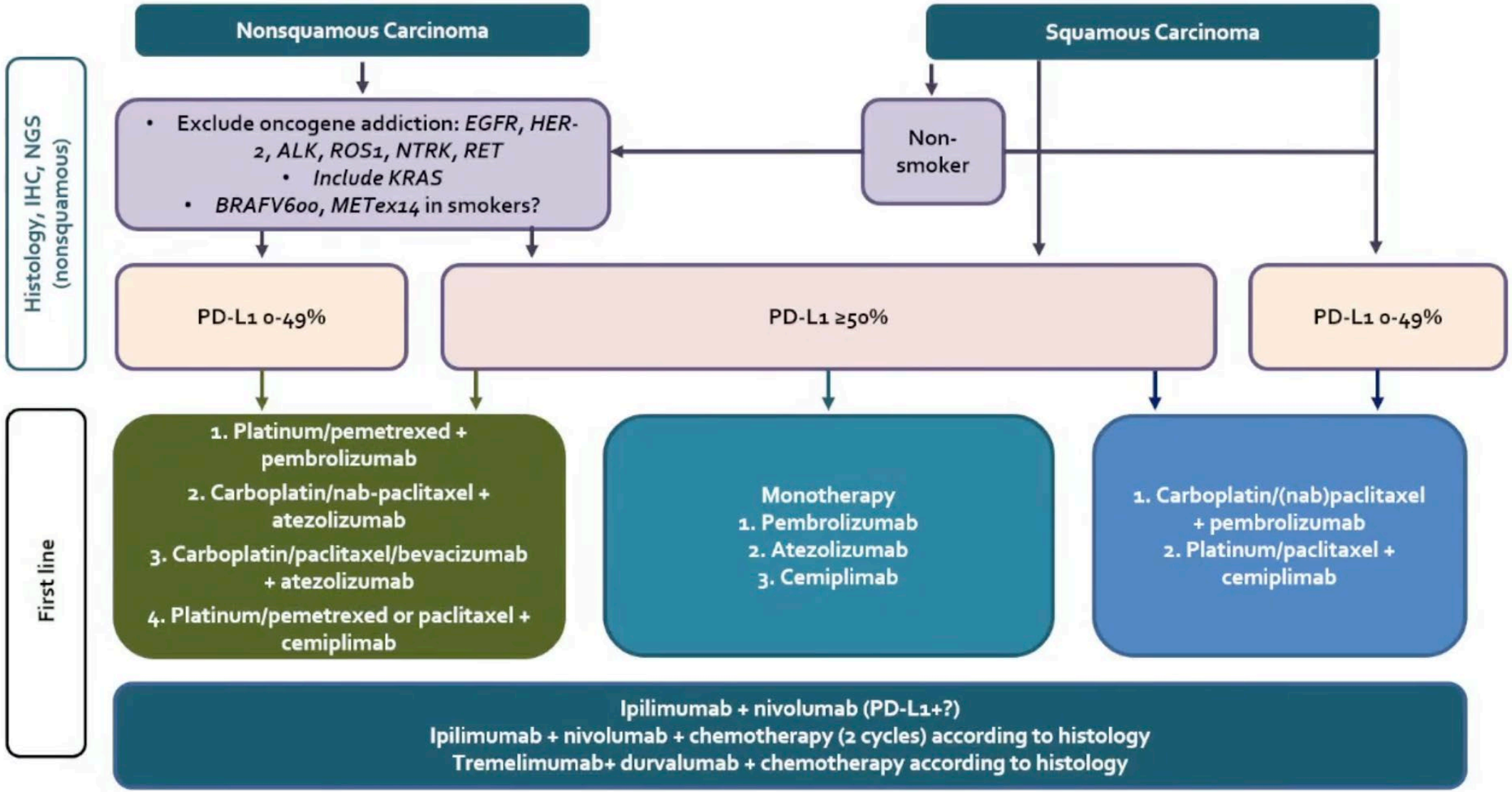
ECOG 1594 Schiller et al, NEJM 2000

NSCLC Outcome: 8th TNM



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

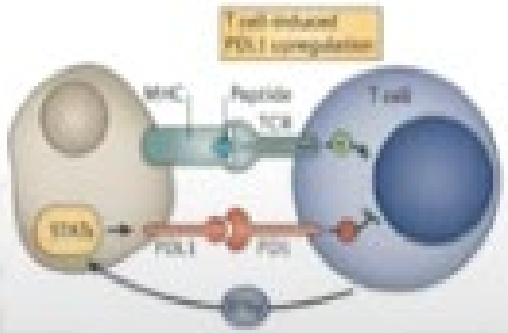
Frontline advanced NSCLC treatment landscape

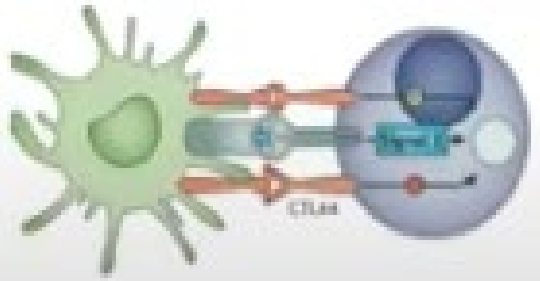


ICI : Nobel Prize 2018

Tasuku Honjo

James Allison



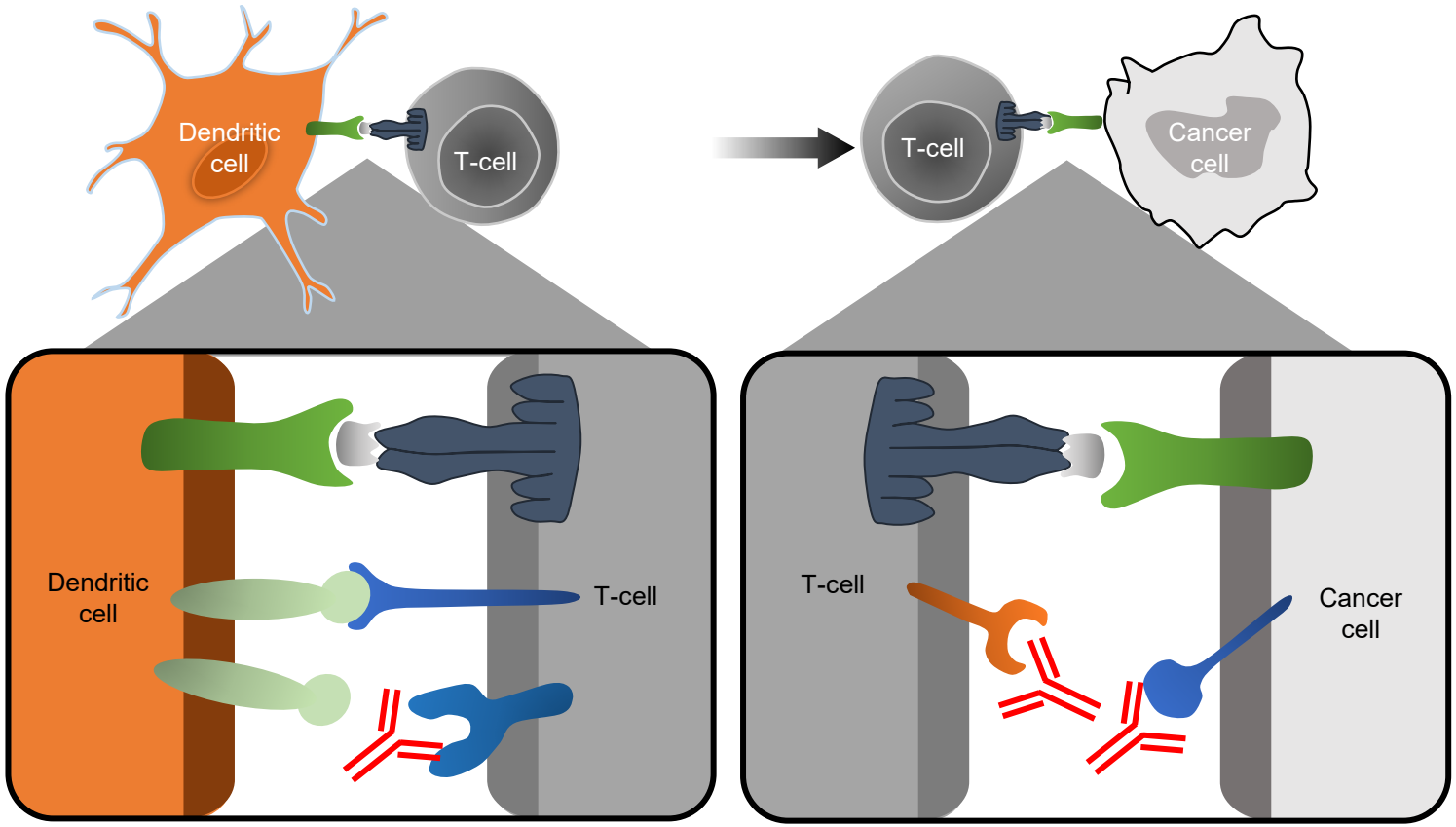


Ishida Y et al, EMBO J, 1992
Nishimura H, Immunity, 1999

Leach DR et al, Science, 1996
Kwon ED, Proc Natl Acad Sci U S A, 1997

CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

CTLA-4 mAbs:
Ipilimumab
Tremelimumab



PD-1 mAbs:
Nivolumab
Pembrolizumab

PD-L1 mAbs:
Atezolizumab
Avelumab
Durvalumab

Ribas A. N Engl J Med. 2012;366:2517-2519.

Slide credit: clinicaloptions.com

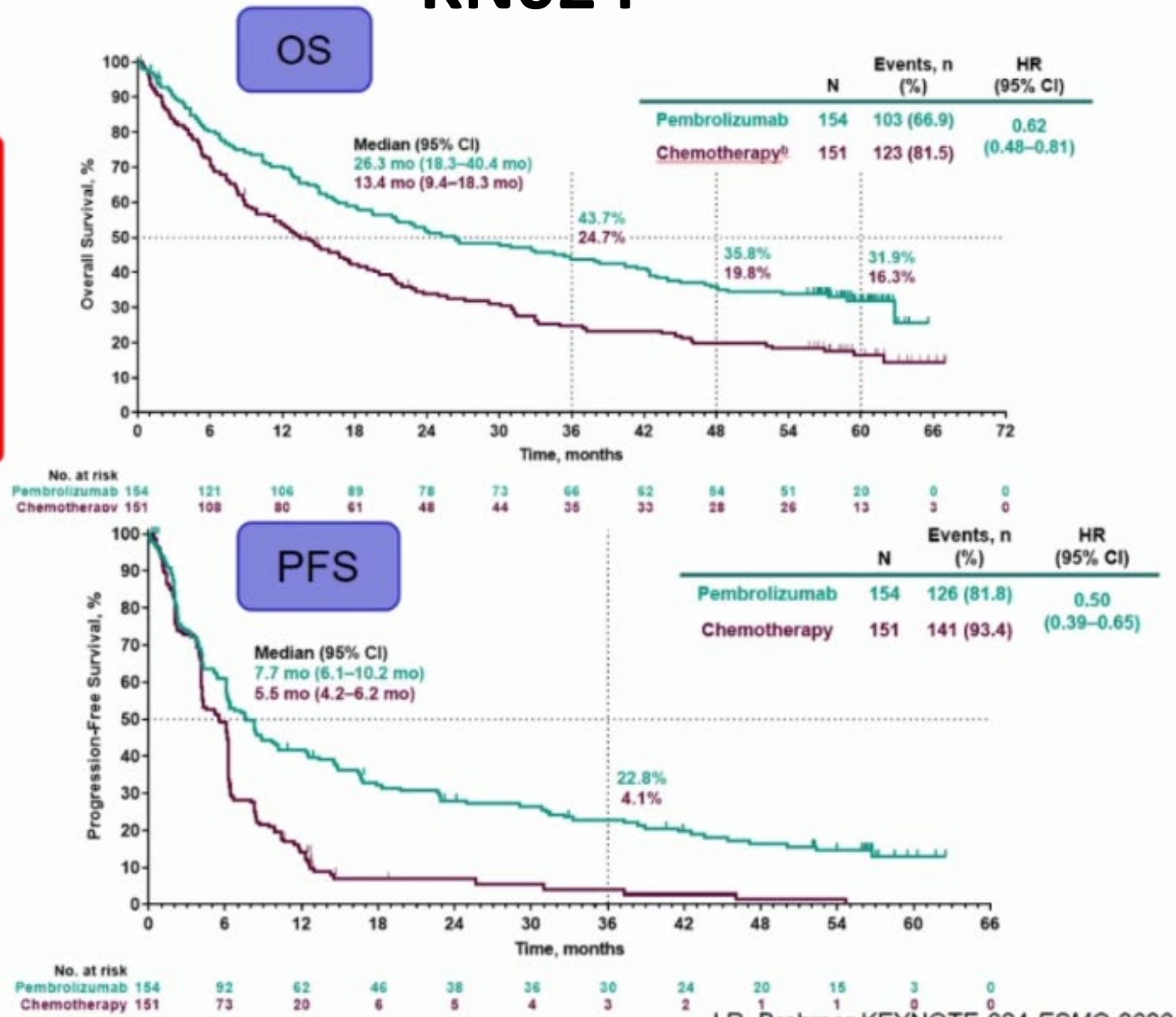
KN024

VIRTUAL 2020 ESMO congress

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

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

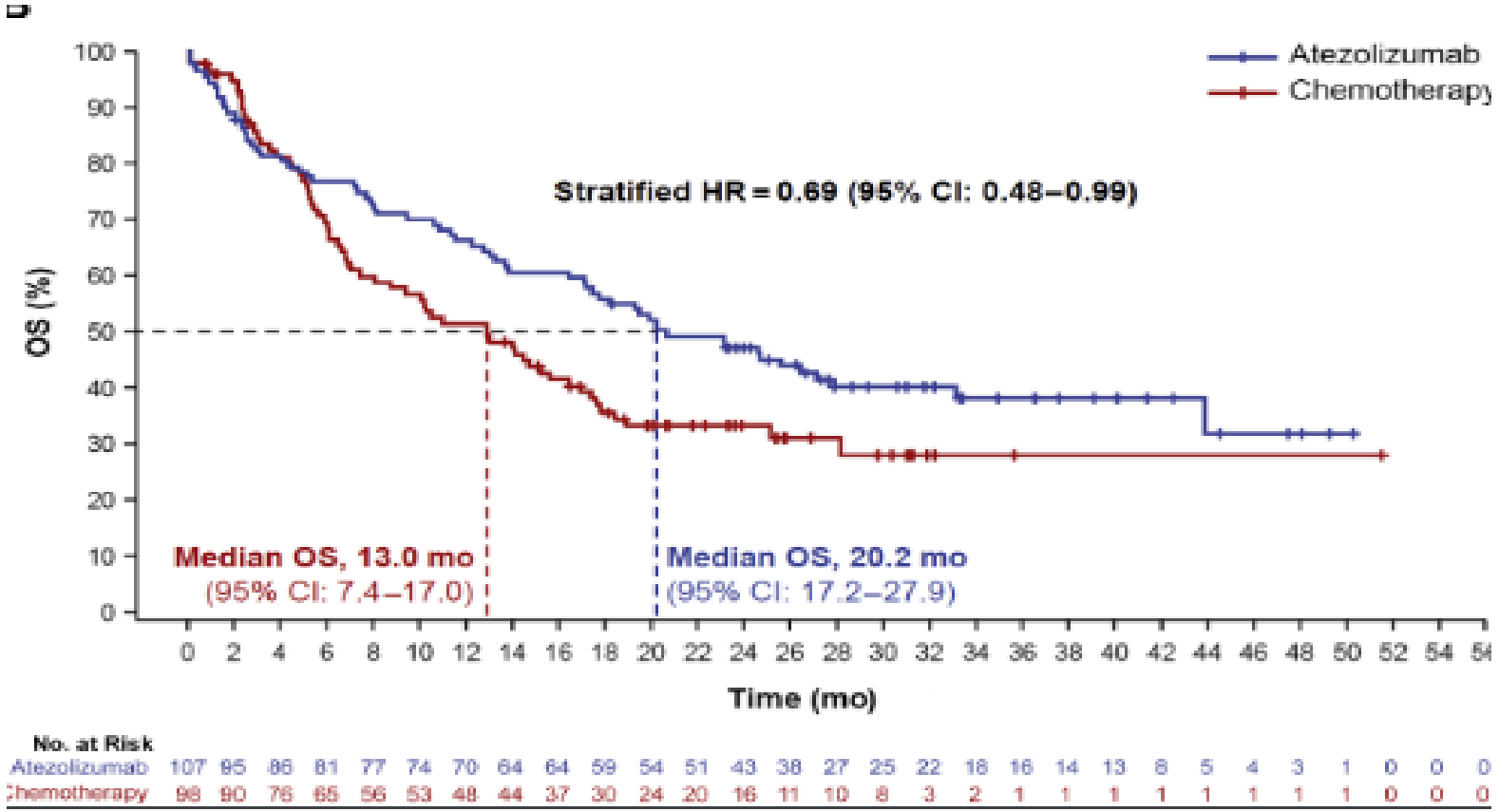
Overall Response Rate:
46.1% vs. 31.1%
Partial Response:
41.6% vs. 31.1%
Complete Response:
4.5% vs. 0



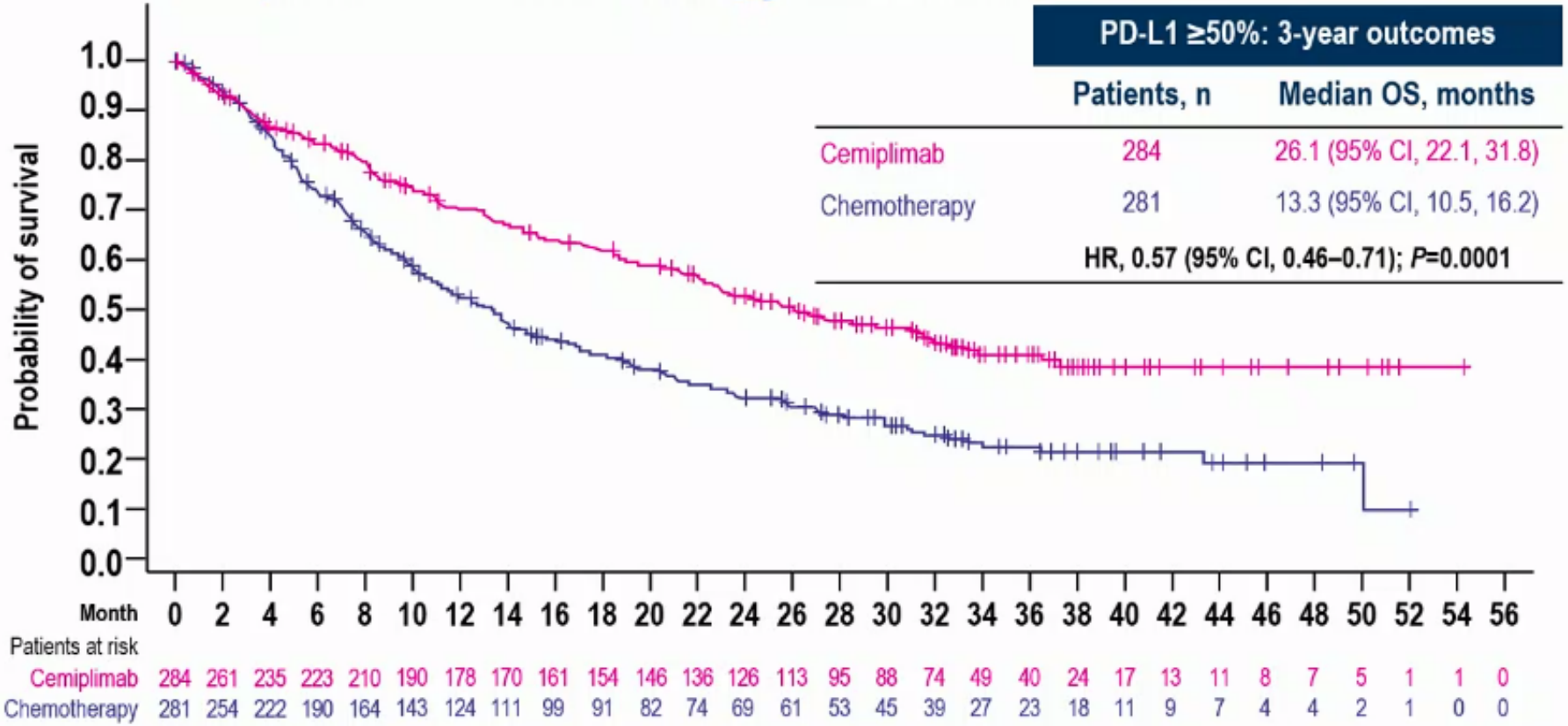
J.R. Brahmer KEYNOTE-024 *ESMO 2020: LBA 51*

Impower 110 update, PDL1 (SP142) ≥ 50%

J.Jassem et al, JTO 2021.



At 3-Year Follow-up Cemiplimab Produced Significantly Longer OS Compared to Chemotherapy in Patients with PD-L1 ≥50%



PD-L1 ≥50%: 3-year outcomes

	Patients, n	Median OS, months
Cemiplimab	284	26.1 (95% CI, 22.1, 31.8)
Chemotherapy	281	13.3 (95% CI, 10.5, 16.2)

HR, 0.57 (95% CI, 0.46–0.71); *P*=0.0001

PARIS 2022 ESMO congress

CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death-ligand 1

Data cutoff date: 4 March 2022

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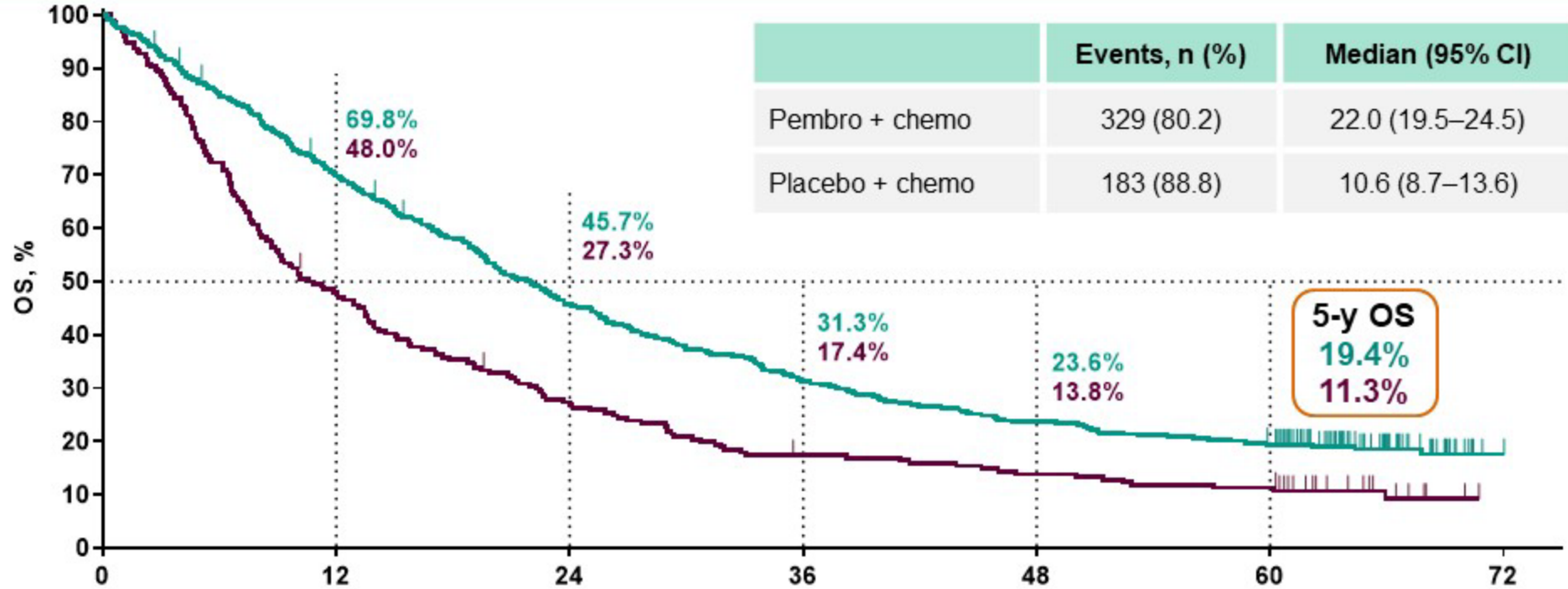
KN189

OS: ITT Population



	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

No. at risk

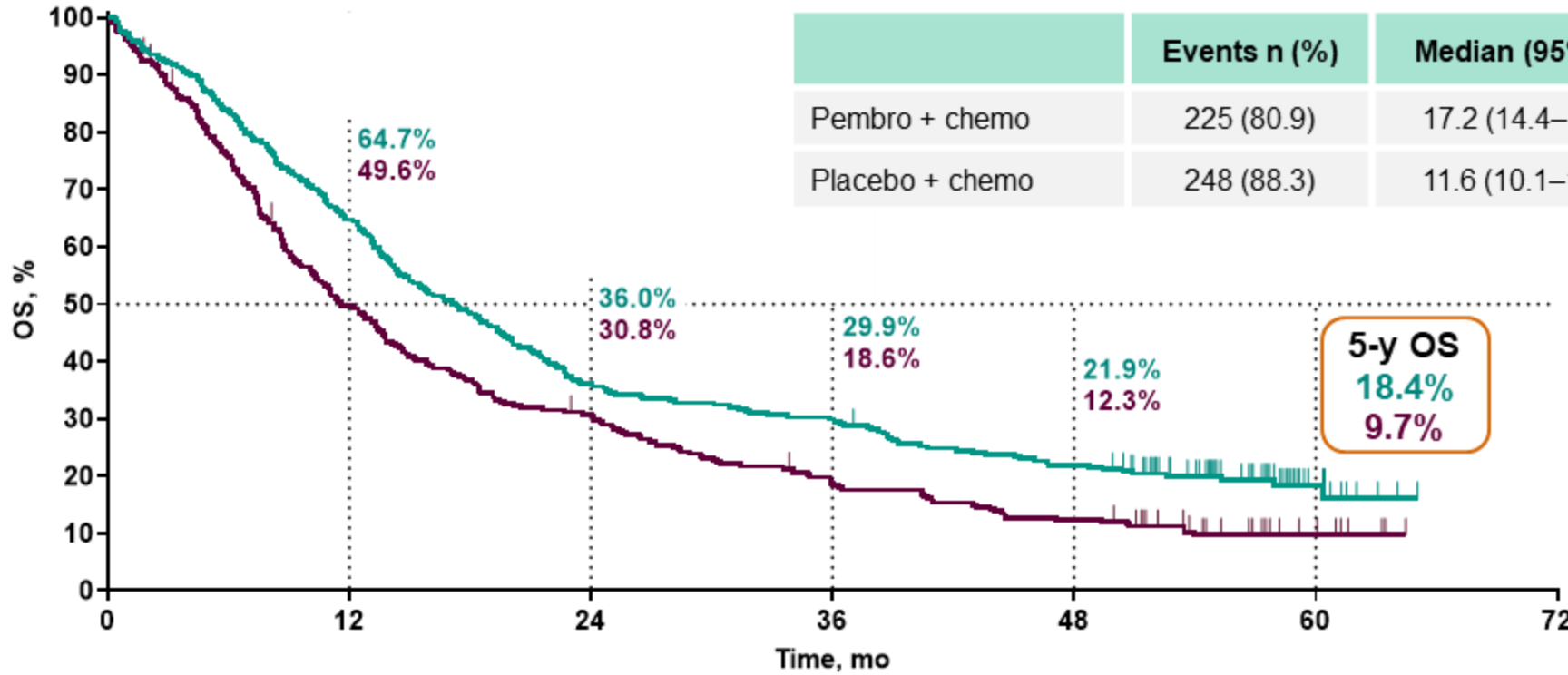
Pembro + chemo	410	283	184	126	95	77	0
Placebo + chemo	206	98	55	34	27	22	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

[a]Kaplan-Meier estimate. Data cutoff date: March 8, 2022.

KN407

OS: ITT Population



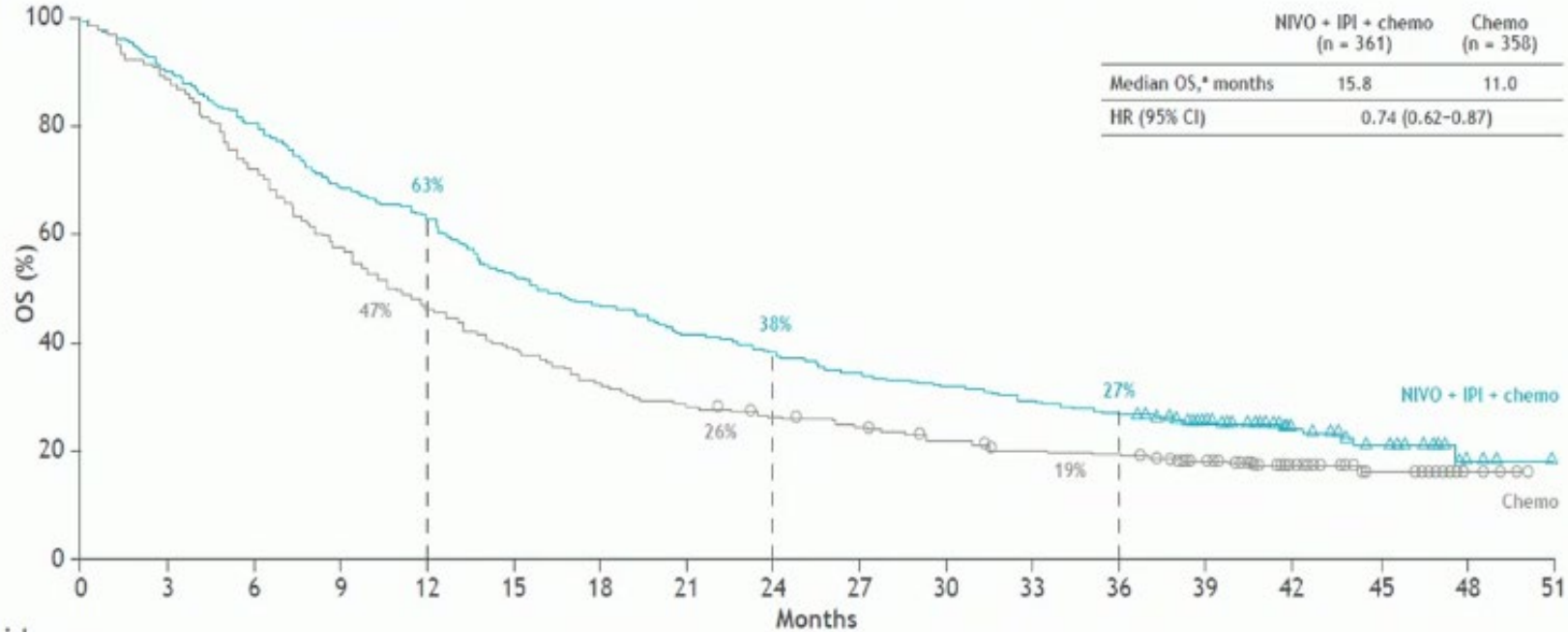
	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	**0.71 (0.59–0.85)**
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

No. at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

[a]Kaplan-Meier estimate. Data cutoff date: February 23, 2022.

9 LA Trial 3-Year update: OS in all randomized patients



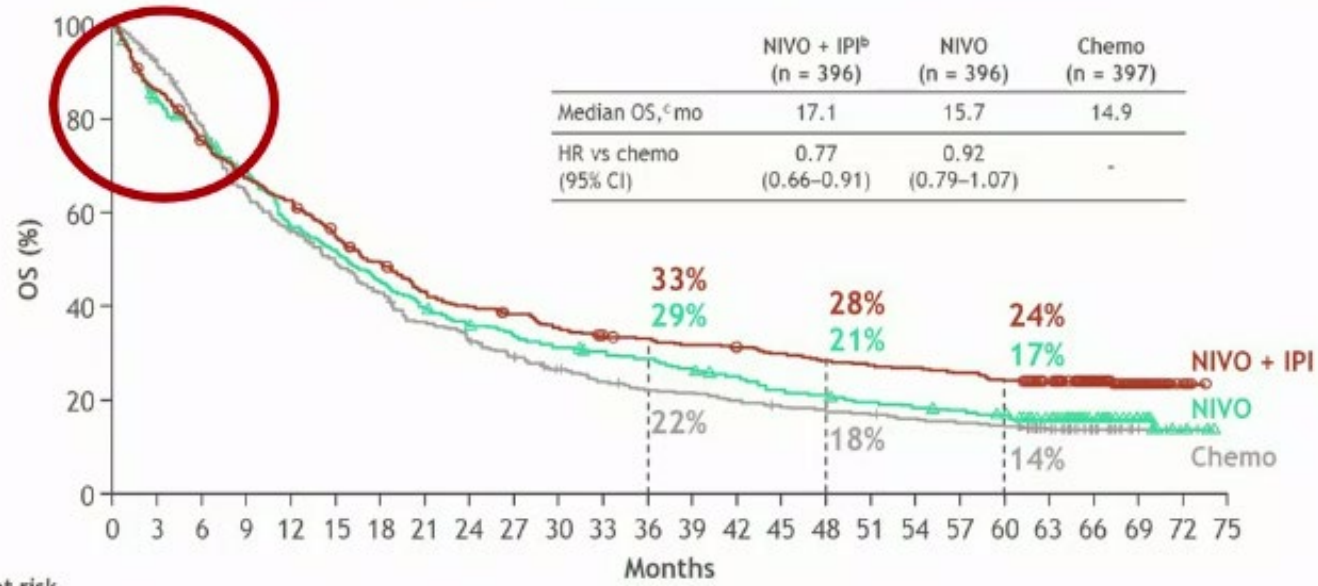
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS,[a] months	15.8	11.0
HR (95% CI)	0.74 (0.62–0.87)	

No. at risk																		
NIVO + IPI + chemo	361	326	292	250	227	191	170	151	138	125	115	106	96	65	27	16	4	0
Chemo	358	319	260	208	168	139	115	102	93	86	74	66	63	48	28	13	5	0

Database lock: February 15, 2022; minimum follow-up: 36.1 months.
[a]95% CI, 13.9-19.7 (NIVO + IPI + chemo) and 9.5-12.7 (chemo).

L Paz-Ares et al. ASCO 2022

CM 227 Trial: 5-year OS in patients with PD-L1 ≥ 1%



	NIVO + IPI[b] (n = 396)	NIVO (n = 396)	Chemo (n = 397)
Median OS,[c] mo	17.1	15.7	14.9
HR vs chemo (95% CI)	0.77 (0.66–0.91)	0.92 (0.79–1.07)	-

No. at risk

NIVO + IPI	396	341	296	265	246	214	192	166	154	146	134	126	123	118	115	110	104	101	99	95	89	74	47	20	3	0
NIVO	396	330	299	265	220	201	176	153	139	129	119	112	108	98	91	80	75	70	66	63	59	46	27	12	3	0
Chemo	397	358	306	250	218	190	166	141	126	112	98	87	80	78	72	66	63	60	56	53	50	37	18	5	2	0

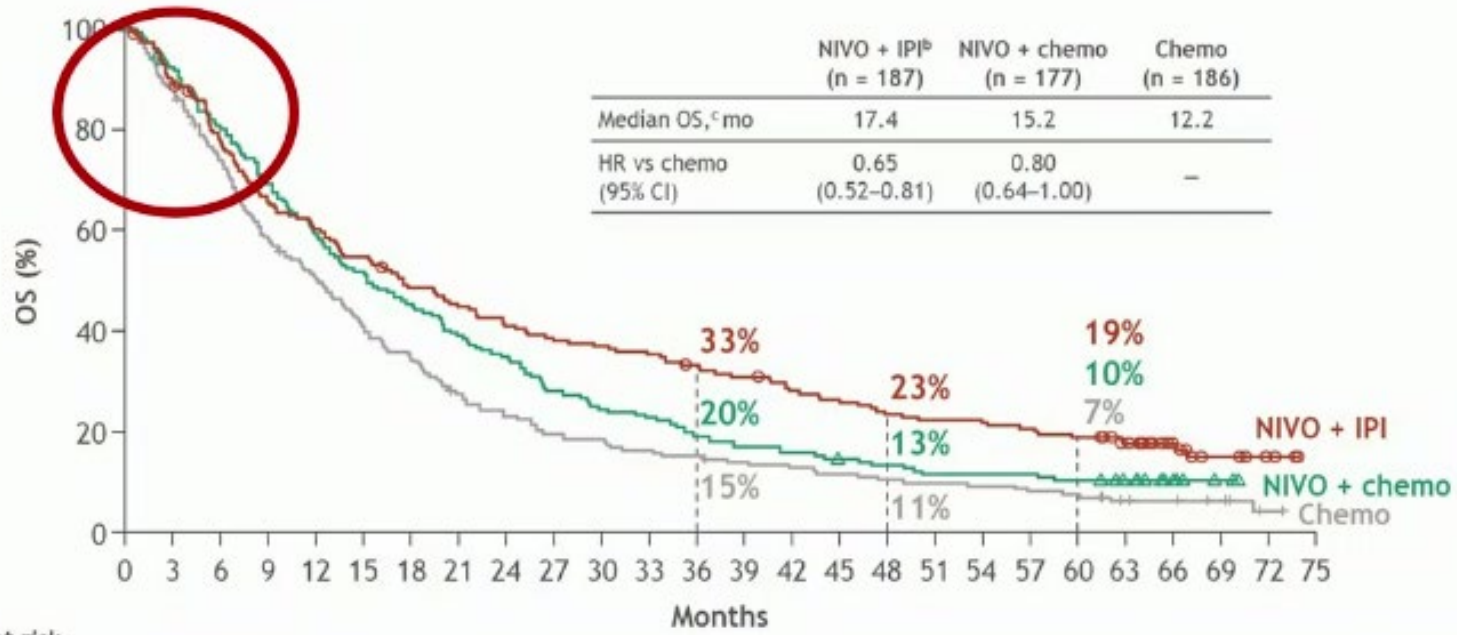
Database lock: February 15, 2022; minimum/median follow-up for OS: 61.3/66.7 months.

[a]In patients with PD-L1 ≥ 1% with a PFS event (per BICR), subsequent systemic therapy was received by 34% in the NIVO + IPI arm, 46% in the NIVO arm, and 48% in the chemo arm; subsequent immunotherapies by 7%, 9%, and 40%; subsequent chemo by 33%, 45%, and 25%, respectively. [b]NIVO + IPI vs NIVO HR was 0.84 (95% CI, 0.72–0.99). [c]Median OS 95% CI are 14.95–20.17 (NIVO + IPI), 13.27–18.14 (NIVO), and 12.71–16.72 (chemo).

BICR, blinded independent central review.

Brahmer et al. Asco 2022

CM 227: 5-year OS in patients with PD-L1 < 1%



	NIVO + IPI[b] (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS,[c] mo	17.4	15.2	12.2
HR vs chemo (95% CI)	0.65 (0.52–0.81)	0.80 (0.64–1.00)	–

No. at risk																										
NIVO + IPI	187	165	142	120	110	100	88	81	74	69	67	64	59	55	49	45	41	39	38	36	33	27	15	8	3	0
NIVO + chemo	177	159	139	119	102	88	78	67	60	48	42	39	34	29	27	24	22	19	19	19	17	14	7	2	0	0
Chemo	186	164	135	107	92	74	62	49	41	35	33	29	27	24	22	20	18	17	16	14	12	8	7	5	1	0

Database lock: February 15, 2022; minimum/median follow-up for OS: 61.3/66.7 months.

[a]In patients with PD-L1 < 1% with a PFS event (per BICR), subsequent systemic therapy was received by 44% in the NIVO + IPI arm, 39% in the NIVO + chemo arm, and 48% in the chemo arm; subsequent immunotherapies by 8%, 5%, and 33%; subsequent chemo by 43%, 37%, and 33%, respectively. [b]NIVO + IPI vs NIVO + chemo HR was 0.80 (95% CI, 0.63–1.00). [c]Median OS 95% CI are 13.21–22.05 (NIVO + IPI), 12.29–19.78 (NIVO + chemo), and 9.17–14.32 (chemo).

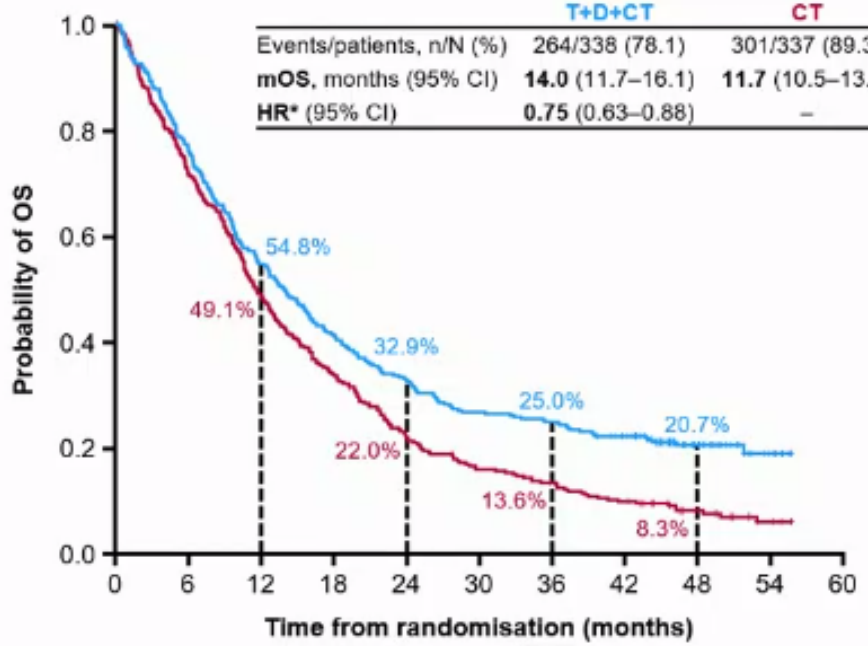
Brahmer et al. Asco 2022

OS Update

Durable long-term OS benefit for T+D+CT vs CT with HR 0.75 and estimated 25.0% alive at 3 yrs vs 13.6%

T+D+CT vs CT

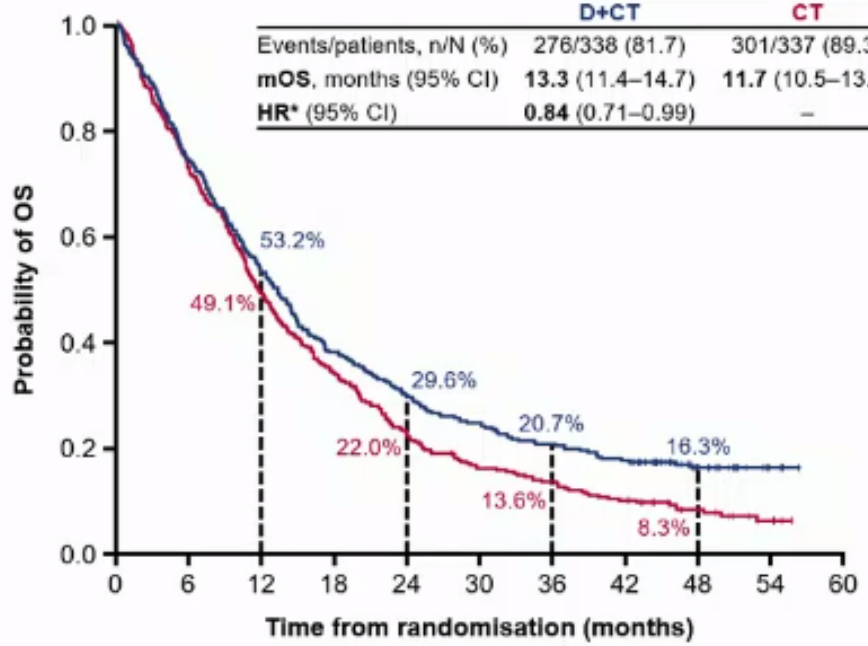
	T+D+CT	CT
Events/patients, n/N (%)	264/338 (78.1)	301/337 (89.3)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.75** (0.63–0.88)	–



No. at risk											
T+D+CT	338	256	183	137	109	89	83	70	32	6	0
CT	337	236	160	111	71	51	42	31	14	5	0

D+CT vs CT

	D+CT	CT
Events/patients, n/N (%)	276/338 (81.7)	301/337 (89.3)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR* (95% CI)	**0.84** (0.71–0.99)	–



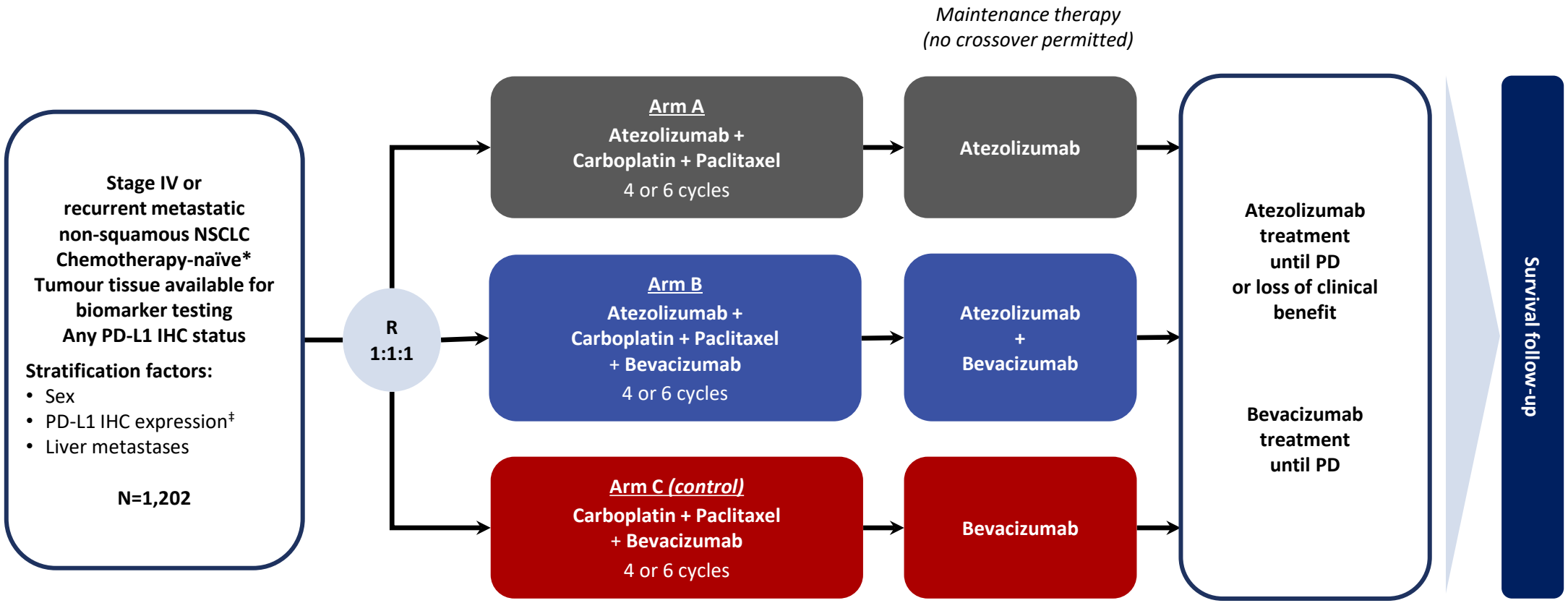
No. at risk											
D+CT	338	247	176	126	97	81	67	57	26	5	0
CT	337	236	160	111	71	51	42	31	14	5	0

Median follow-up in censored patients at DCO: 46.5 months (range 0.0–56.5)

*HR <1 favours D(±T)+CT vs CT (stratified analysis); DCO, 11 Mar 2022

mOS, median OS

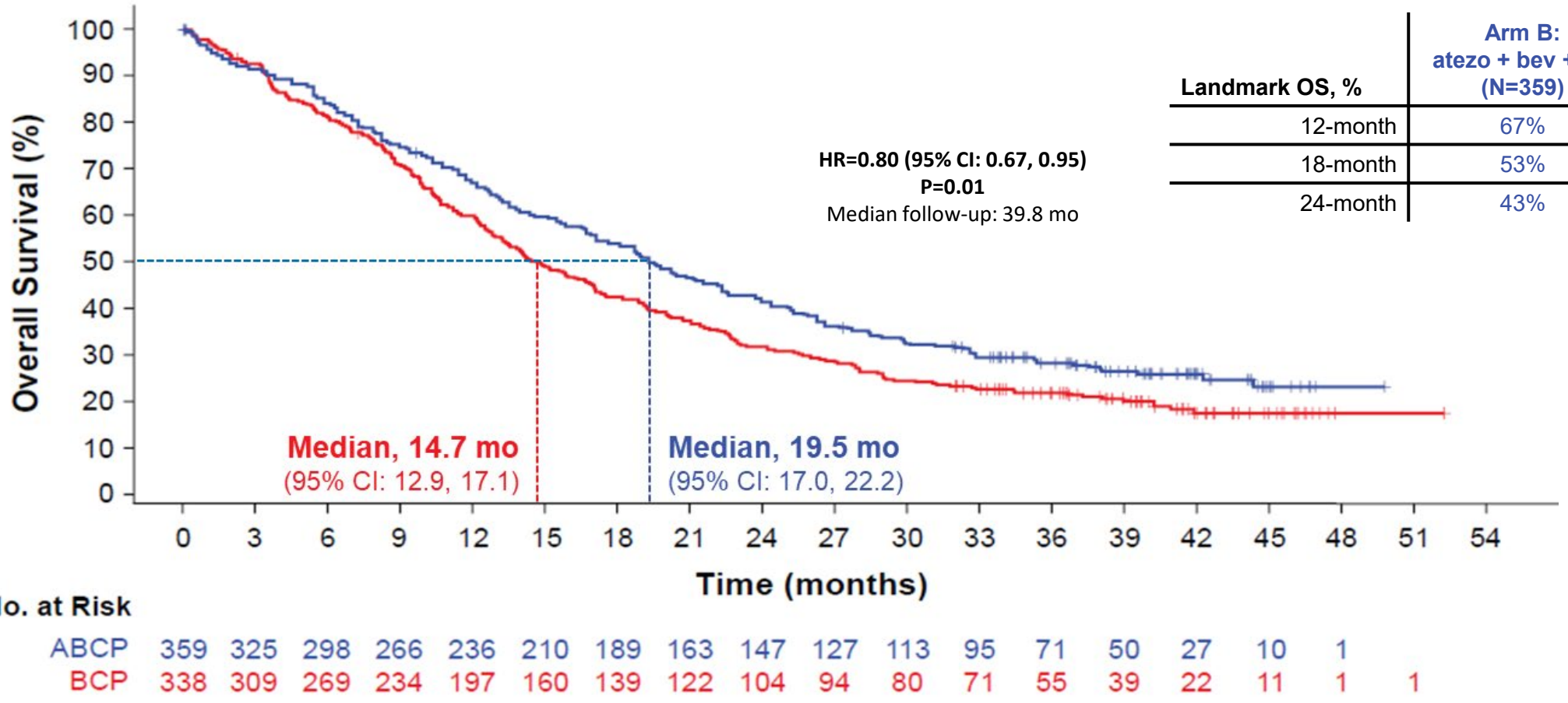
IMpower150 is a randomised, phase III global trial



*Patients with a sensitising EGFR mutation or ALK translocation must have disease progression or intolerance to treatment with one or more approved targeted therapies
‡PD-L1 testing by SP142 IHC assay
Atezolizumab: 1,200mg IV q3w; Carboplatin: AUC 6 IV q3w
Paclitaxel: 200mg/m2 IV q3w; Bevacizumab: 15mg/kg IV q3w

Reck, et al. ESMO IO 2017 (Abs LBA_PR1)

This OS benefit in the ITT-WT was maintained at the updated analysis (Arm B vs Arm C)



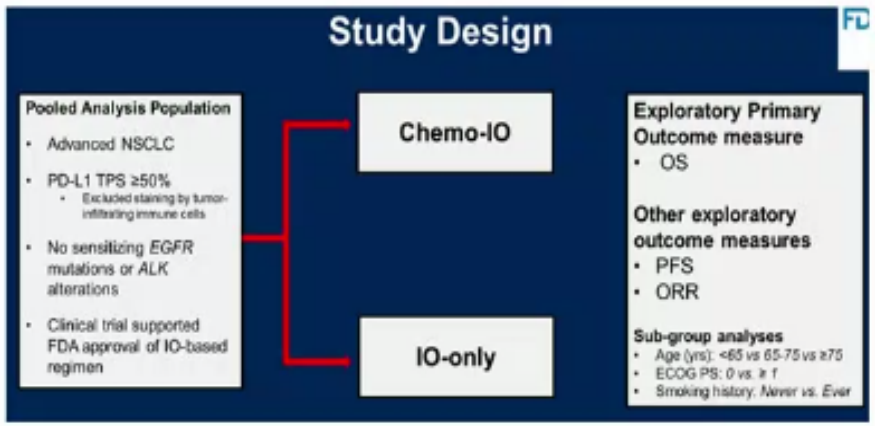
HR=0.80 (95% CI: 0.67, 0.95)
P=0.01
Median follow-up: 39.8 mo

Landmark OS, %	Arm B: atezo + bev + CP (N=359)	Arm C: bev + CP (N=337)
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

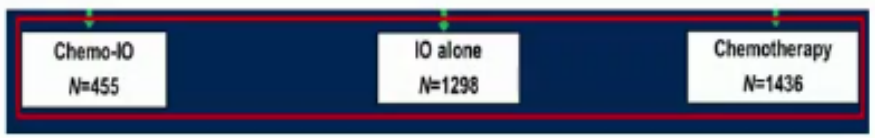
Median follow-up 39.8 months (updated OS analysis)
OS analysis for Arm B vs Arm C was considered final at the second interim analysis: data are shown for descriptive purposes only
Data cut-off: 13 September, 2019

Socinski, et al. ASCO 2018 (Abs 9002)

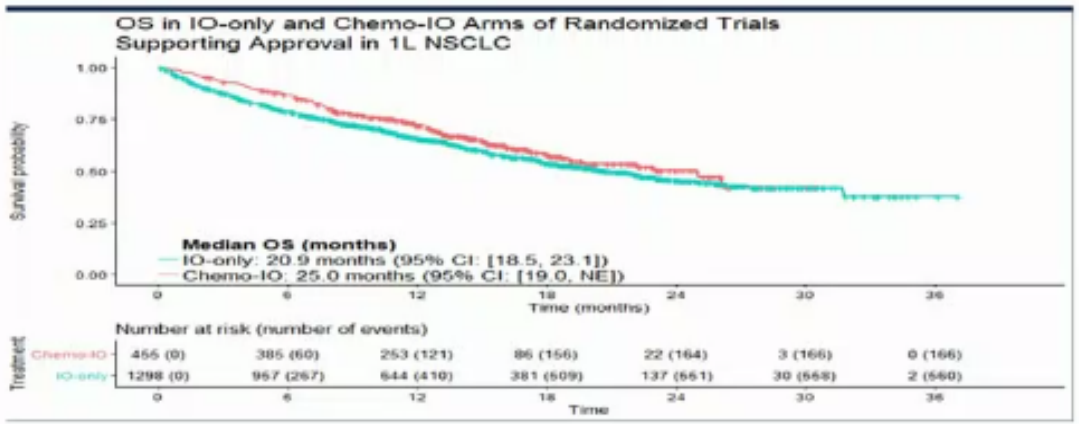
IO vs Chemo-IO in NSCLC PD-L1≥ 50%



Chemo-IO Trials		IO-only Trials	
Trial	Investigational Regimen	Trial	Investigational Regimen
KEYNOTE-021*	**Pembrolizumab** + Chemo**	CheckMate 026	**Nivolumab****
KEYNOTE-189	**Pembrolizumab** + Chemo**	KEYNOTE-024	**Pembrolizumab****
KEYNOTE-407	**Pembrolizumab** + Chemo**	KEYNOTE-042	**Pembrolizumab****
IMpower150	**Atezolizumab** + Bevacizumab + Chemo***	IMpower110	**Atezolizumab****
IMpower130	**Atezolizumab** + Chemo**	CheckMate 227	**Nivolumab** + **Ipilimumab****
CheckMate-9LA	**Nivolumab** + **Ipilimumab** + Chemo**	EMPOWER-Lung 1	**Cemiplimab****

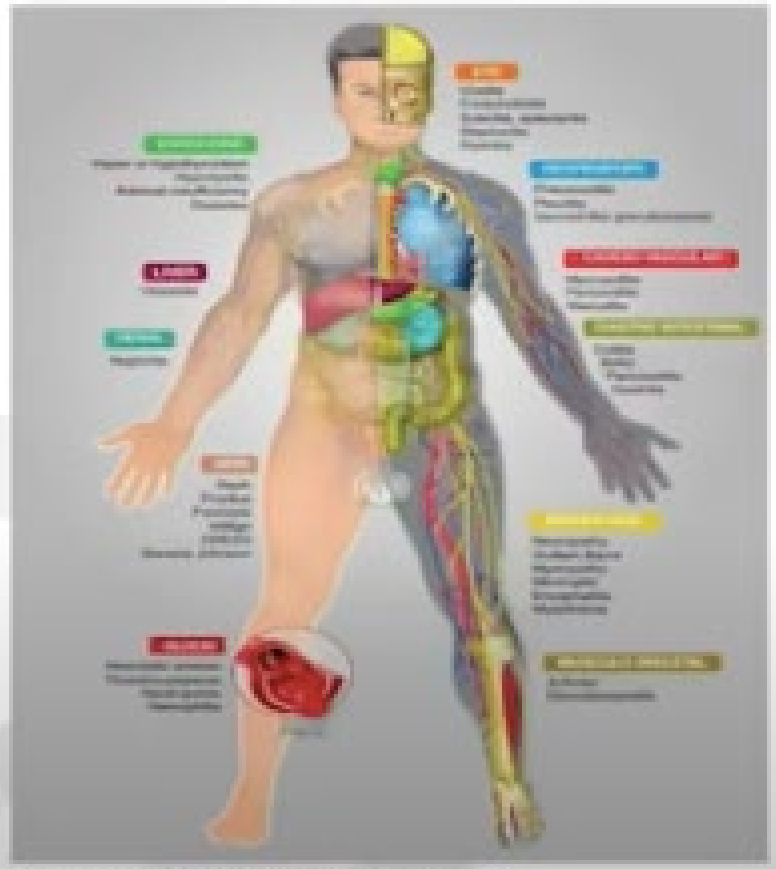


	Chemo-IO (*N*=455)	IO-alone (*N*=1,298)
OS		
Median, months (95% CI)	25.0 (19.0, NE)	20.9 (18.5, 23.1)
HR (95% CI)	0.82 (0.62, 1.08)	
PFS		
Median, months (95% CI)	9.6 (8.4, 11.1)	7.1 (6.3, 8.3)
HR (95% CI)	0.69 (0.55, 0.87)	
ORR		
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio	1.2 (1.1, 1.3)	



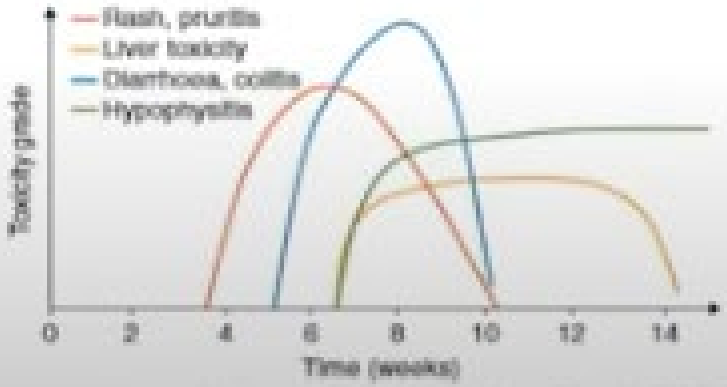
Akinboro et al. ASCO 2022

Immune-related adverse events (irAEs)



Champiat S et al, Ann Oncol., 2016

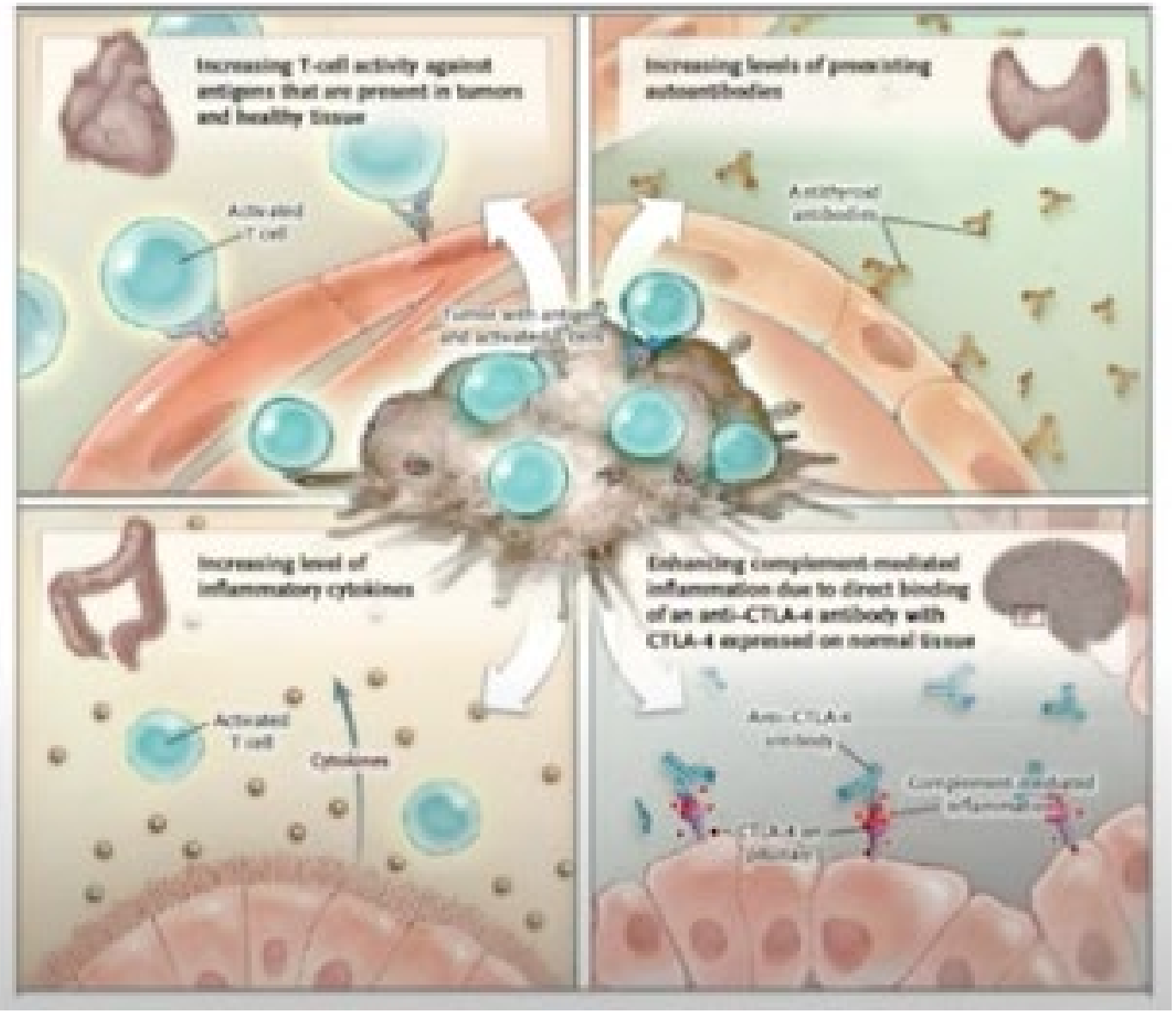
- Up to 70% of patients, rarely severe (<10%)
- Can affect any organ system
- ≠ between CTLA-4 and anti PD-1/PD-L1, and increased risk with combination



Haanen JBAG et al, Ann Oncol., 2017

irAEs mechanisms

Postow et al. NEJM, 2018



Is there a difference in irAE between PD-1 and PD-L1 inhibitors?

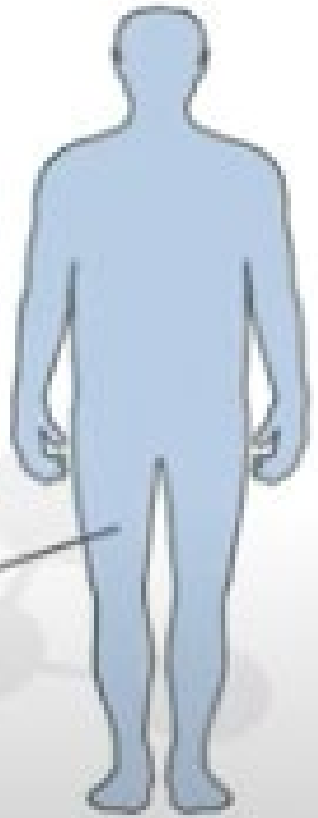
	PD-1 Inhibitors N = 3284	PD-L1 Inhibitors N = 2460	*P*
Overall AEs, %	64	66	.8
Grade 3-5 AEs, %	13	21	.15
Fatigue of any grade, %	19	21	.4
Diarrhea of any grade, %	9	12	.4
Rash of any grade, %	9	7	.8
IRAEs, %	16	11	.07
Grade 3-5 IRAEs, %	3	5	.4
Hypothyroidism of any grade, %	6.7	4.2	.07
Pneumonitis of any grade, %	4	2	.01
Colitis of any grade, %	1.7	1	.4
Overall response rate, %	19	18.6	.17

Meta analysis of 23 studies

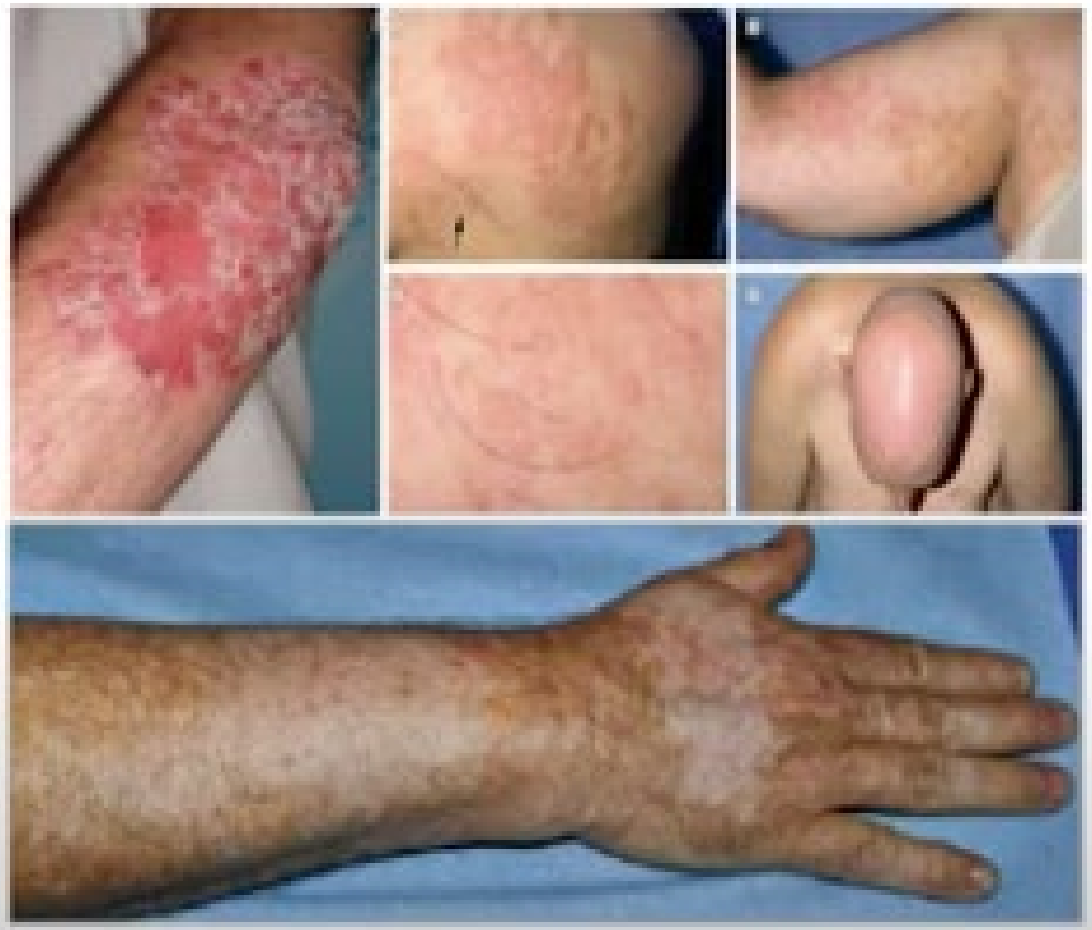
- 5744 patients:
- 3284 patients treated with PD-1 inhibitors
- 2460 patients with PD-L1 inhibitors

What do we see ? Cutaneous irAEs

40-50% with ipilimumab
30-40% with anti PD-1



Cutaneous:
Rash, erythema, vitiligo, psoriasis, bullous pemphigoid

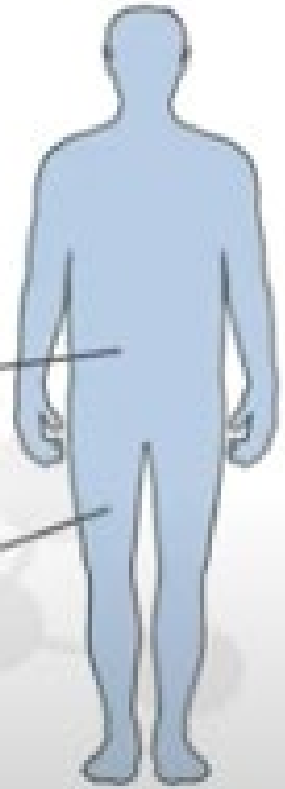


What do we see ? Digestive irAEs

Diarrhea 30%

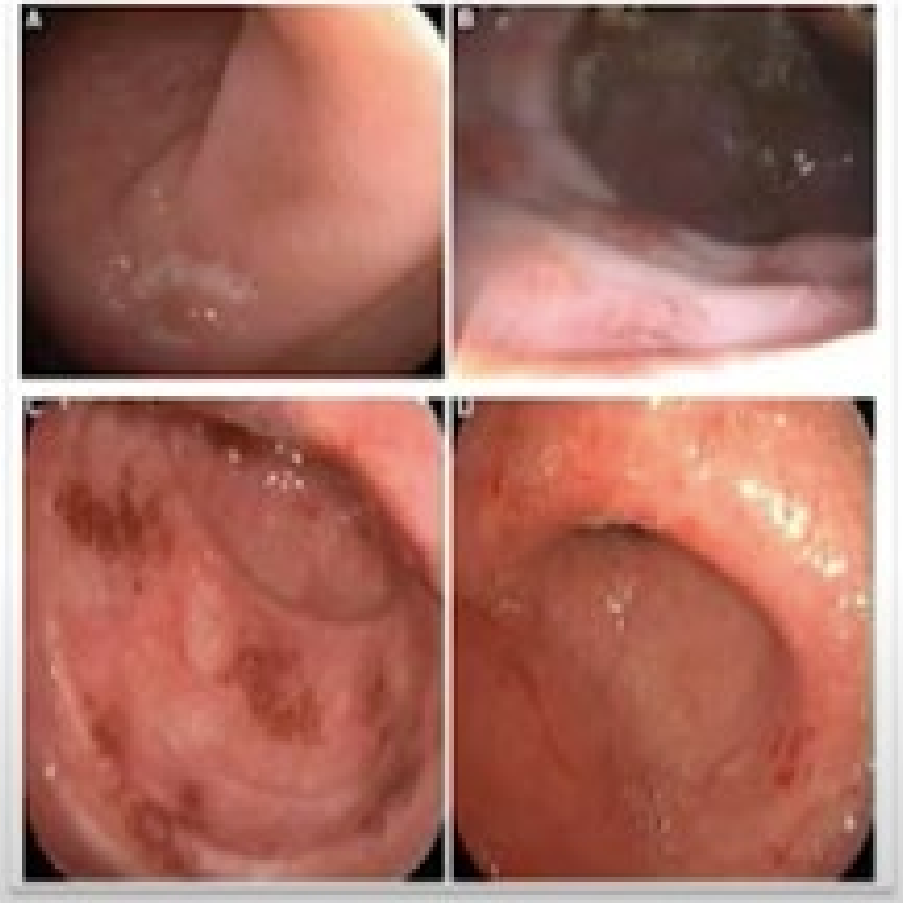
Colitis 8-20%

Mostly with ipilimumab



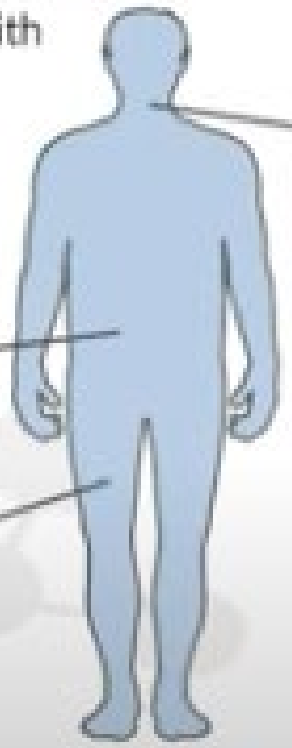
Digestive:
Diarrhea, colitis, pancreatitis, hepatitis

Cutaneous:
Rash, erythema, vitiligo, psoriasis, bullous pemphigoid



What do we see ? Endocrine irAEs

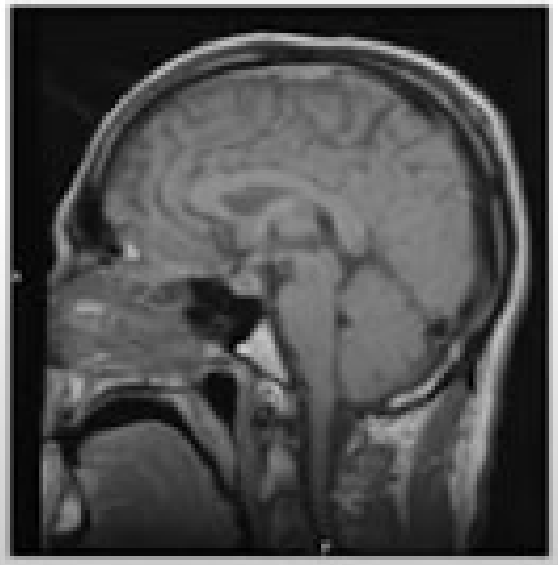
Hypophysitis 1-4% with ipilimumab
Thyroid dysfunction 6-20% mostly with anti PD-1



Endocrine:
hypophysitis, thyroid dysfunction, diabetes mellitus, adrenal insufficiency

Digestive:
Diarrhea, colitis, pancreatitis, hepatitis

Cutaneous:
Rash, erythema, vitiligo, psoriasis, bullous pemphigoid



What do we see ? Pulmonary irAEs

5% with anti PD-(L)1

More rarely with ipilimumab

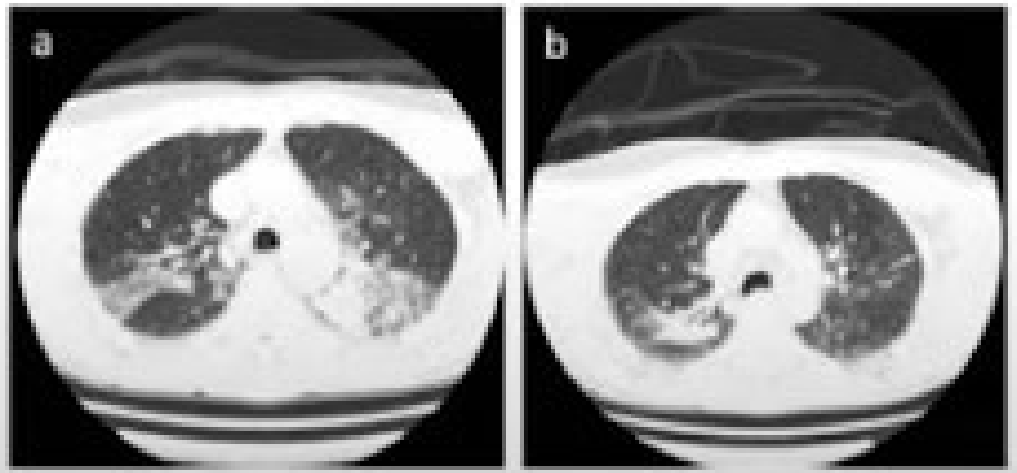
10% with combination

Pulmonary:
Pneumonitis, sarcoidosis

Endocrine:
hypophysitis, thyroid dysfunction, diabetes mellitus, adrenal insufficiency

Digestive:
Diarrhea, colitis, pancreatitis, hepatitis

Cutaneous:
Rash, erythema, vitiligo, psoriasis, bullous pemphigoid



What do we see ? Cardiac irAEs

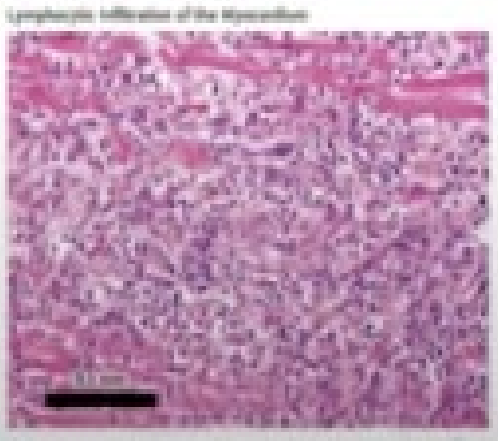
Pulmonary:
Pneumonitis, sarcoidosis

Endocrine:
hypophysitis, thyroid dysfunction, diabetes mellitus, adrenal insufficiency

Cardiac:
myocarditis, pericarditis, vasculitis

Digestive:
Diarrhea, colitis, pancreatitis, hepatitis

Cutaneous:
Rash, erythema, vitiligo, psoriasis, bullous pemphigoid

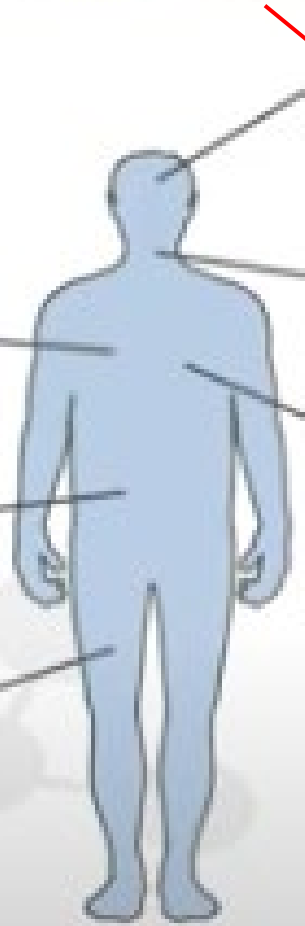


What do we see ? Neurologic irAEs

3-4% sous ipilimumab

6% sous anti PD-1

12% si combinaison



Neurologic:
encephalitis, myelitis, meningitis, Guillain-Barre syndromé, myasthenia, peripheral neuropathy

Endocrine:
hypophysitis, thyroid dysfunction, diabetes mellitus, adrenal insufficiency

Pulmonary:
Pneumonitis, sarcoidosis

Cardiac:
myocarditis, pericarditis, vasculitis

Digestive:
Diarrhea, colitis, pancreatitis, hepatitis

Cutaneous:
Rash, erythema, vitiligo, psoriasis, bullous pemphigoid

What do we see ? Renal irAEs

Environ 2%, plutôt avec combinaison

Neurologic:
encephalitis, myelitis, meningitis, Guillain-Barre syndrome, myasthenia, peripheral neuropathy

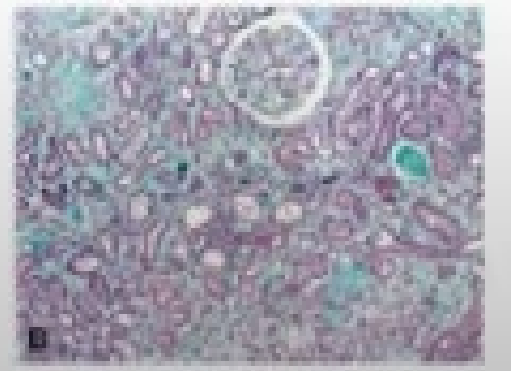
Endocrine:
hypophysitis, thyroid dysfunction, diabetes mellitus, adrenal insufficiency

Pulmonary:
Pneumonitis, sarcoidosis

Cardiac:
myocarditis, pericarditis, vasculitis

Digestive:
Diarrhea, colitis, pancreatitis, hepatitis

Renal:
Lupus nephritis, glomerulonephritis



Cutaneous:
Rash, erythema, vitiligo, psoriasis, bullous pemphigoid

What do we see ? Ophthalmic irAEs

Ophthalmic:
uveitis, conjonctivitis, scleritis

Neurologic:
encephalitis, myeliti
Barre syndromé, my
neuropathy

Endocrine:
hypophysitis, thy
adrenal insufficie

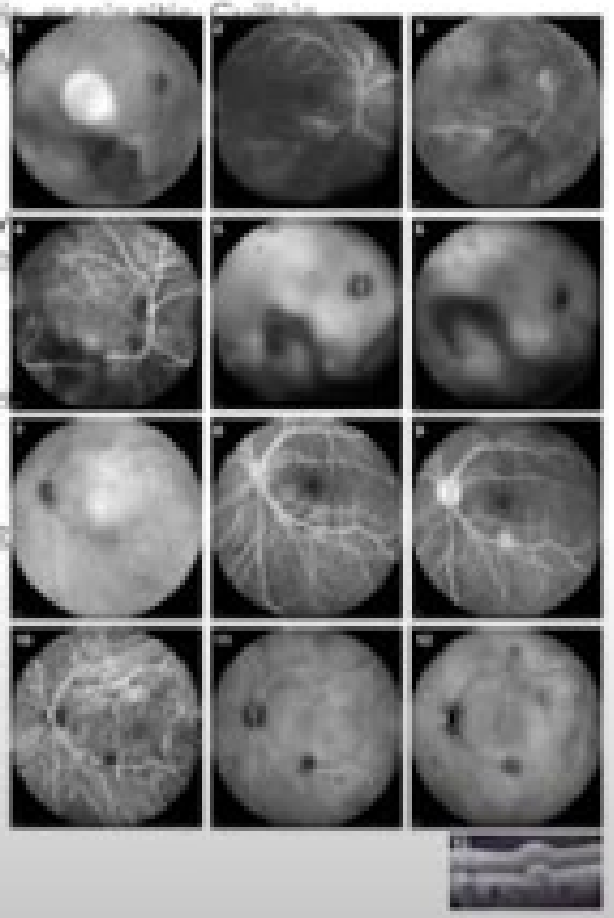
Pulmonary:
Pneumonitis, sarcoidosis

Cardiac:
myocarditis, pe

Digestive:
Diarrhea, colitis, pancreatitis, hepatitis

Renal:
Lupus nephritis, g

Cutaneous:
Rash, erythema, vitiligo, psoriasis, bullous pemphigoid



What do we see ? Rheumatic irAEs

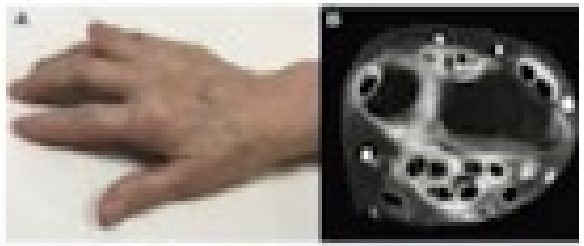
Ophthalmic:
uveitis, conjonctivitis, scleritis

Neurologic:
encephalitis, myelitis, meningitis, Guillain-Barre syndromé, myasthenia, peripheral neuropathy

Endocrine:
hypophysitis, thyroid dysfunction, diabetes mellitus, adrenal insufficiency

Pulmonary:
Pneumonitis, sarcoidosis

Cardiac:
myocarditis, pericarditis, vasculitis

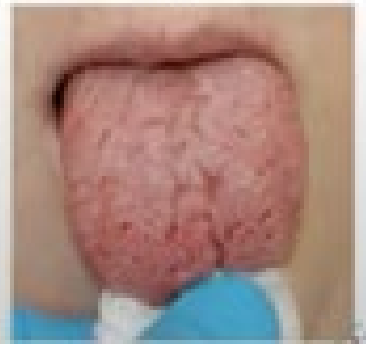


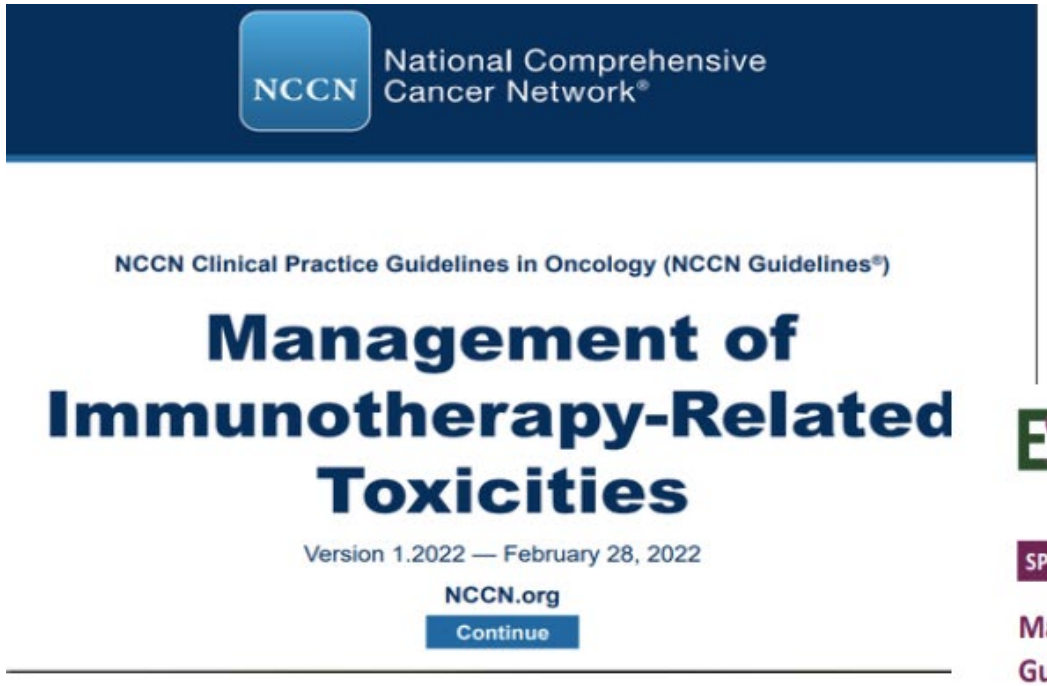
Digestive:
Diarrhea, colitis, pancreatitis, hepatitis

Renal:
Lupus nephritis, glomerulonephritis

Cutaneous:
Rash, erythema, vitiligo, psoriasis, bulous pemphigoid

Rheumatic:
arthralgia, myalgia, arthritis, polymyalgia rheumatica, lupus, systemic sclerosis, sicca syndrome, myositis, vasculitis





ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

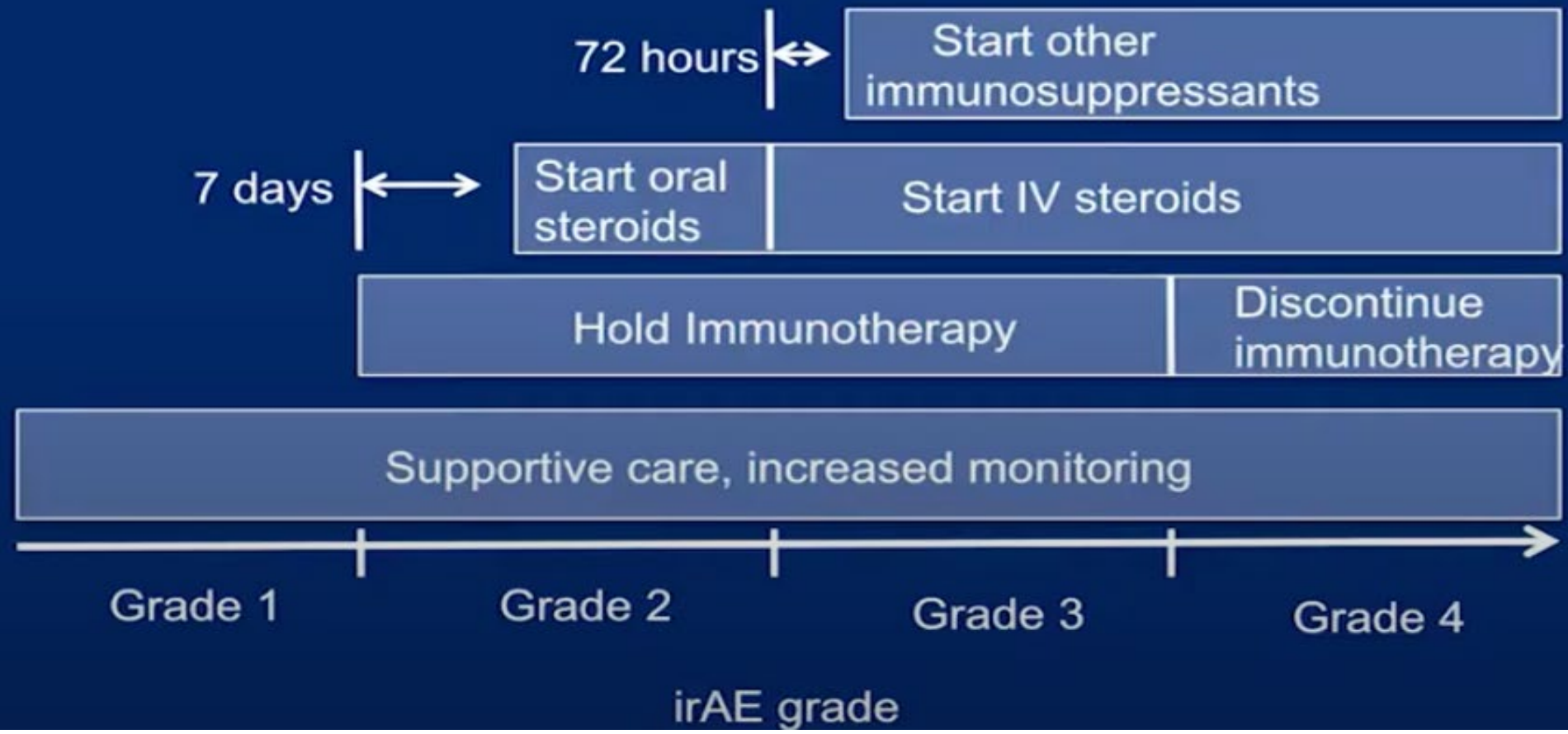
SPECIAL ARTICLE

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

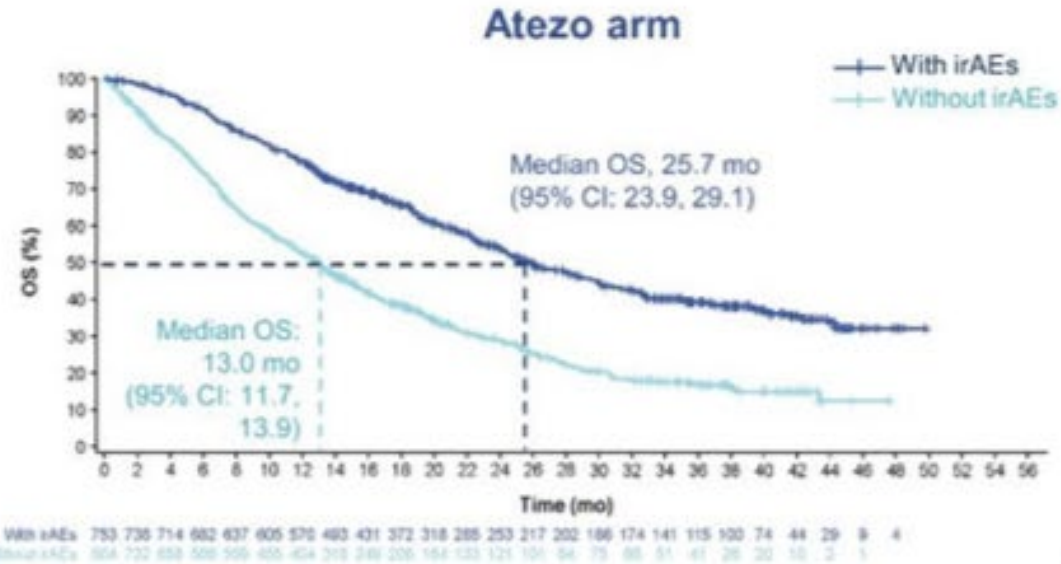
J. Haanen[1†], M. Obeid[2,3,4†], L. Spain[5,6,7], F. Carbonnel[8,9], Y. Wang[10], C. Robert[11,12], A. R. Lyon[13,14], W. Wick[15,16], M. Kostine[17], S. Peters[4], K. Jordan[18,19] & J. Larkin[20], on behalf of the ESMO Guidelines Committee*

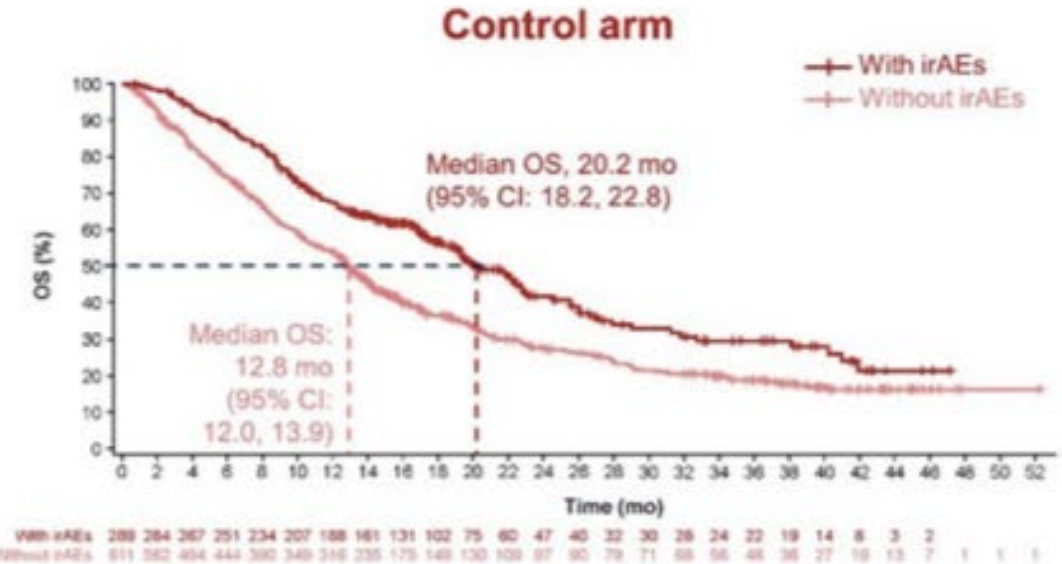
[1]Division of Medical Oncology, Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands; [2]Immunology and Allergy Service, CHUV, Lausanne; [3]Lausanne Center for Immuno-oncology Toxicities (LCIT), CHUV, Lausanne; [4]Department of Oncology, CHUV, Lausanne, Switzerland; [5]Medical Oncology Department, Peter MacCallum Cancer Centre, Melbourne; [6]Department of Medical Oncology, Eastern Health, Melbourne; [7]Monash University Eastern Health Clinical School, Box Hill, Australia; [8]Gastroenterology Department, Assistance Publique-Hôpitaux de Paris, Hôpital Universitaire Bicêtre, Le Kremlin Bicêtre; [9]Université Paris Saclay 11, Le Kremlin-Bicêtre, France; [10]Department of Gastroenterology, Hepatology & Nutrition, The University of Texas MD Anderson Cancer Center, Houston, USA; [11]Department of Medicine, Gustave Roussy Cancer Centre, Villejuif; [12]Paris-Saclay University, Villejuif, France; [13]Cardio-Oncology Service, Royal Brompton Hospital, London; [14]National Heart and Lung Institute, Imperial College London, London, UK; [15]Neurology Clinic and National Centre for Tumour Diseases, University Hospital Heidelberg, Heidelberg; [16]DKTK and Clinical Cooperation Unit NeuroOncology, DKFZ, Heidelberg, Germany; [17]Department of Rheumatology, Hôpital Pellegrin, CHU de Bordeaux, Bordeaux, France; [18]Department of Haematology, Oncology and Palliative Medicine, Ernst von Bergmann Hospital Potsdam, Potsdam; [19]Department of Haematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany; [20]Royal Marsden NHS Foundation Trust, London, UK

Management of immunotherapy side effects



OS by irAE status*†





Time-dependent Cox model:
HR, 0.69 (95% CI: 0.60, 0.78)

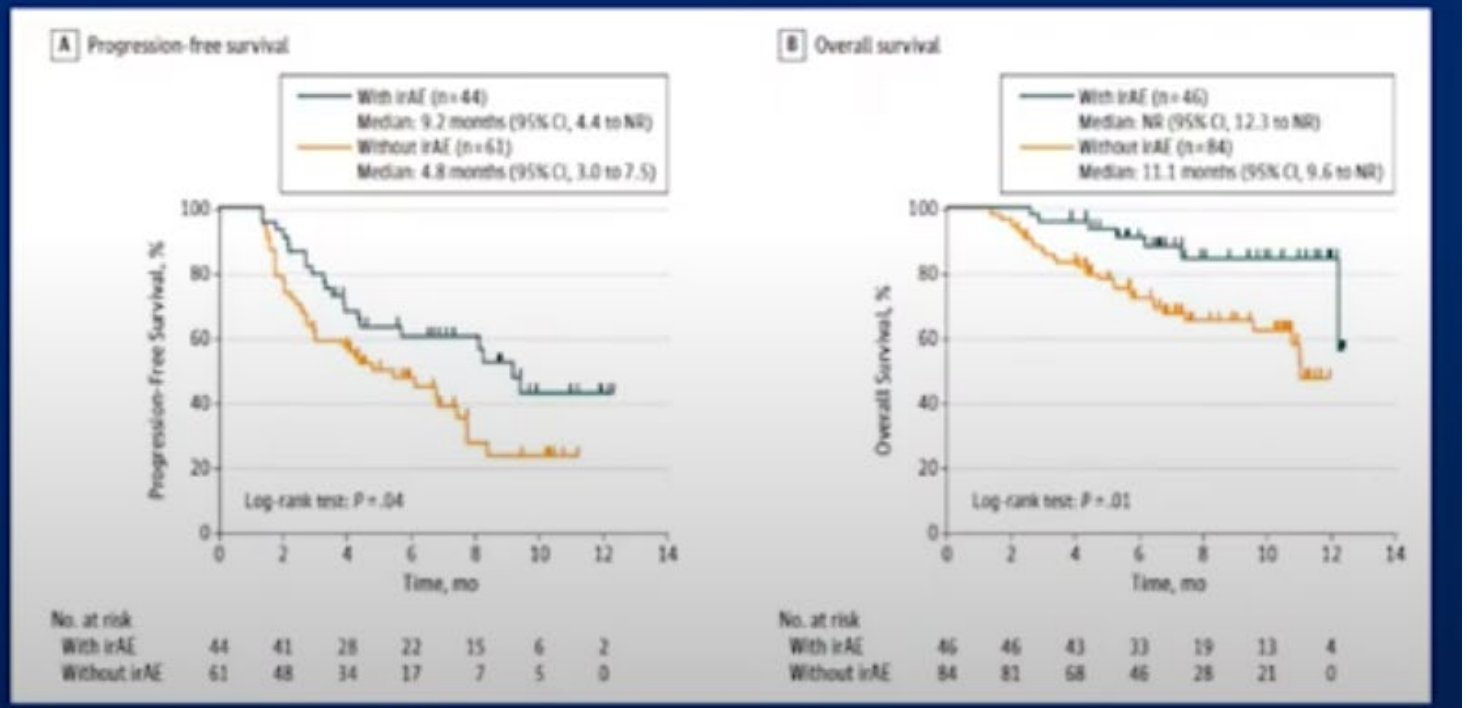
Time-dependent Cox model:
HR, 0.82 (95% CI: 0.68, 0.99)

Patients who experienced irAEs had longer OS than those without irAEs in both the atezo-containing and control arms

*Kaplan-Meier curved are not adjusted for the timing of irAE onset.
†An interaction test of irAE status and treatment arms did not reveal statistical significance (P = .13)
Socinski M, et al. ASCO® 2021. Presentation 9002.

Do patients who develop irAE have better outcomes?

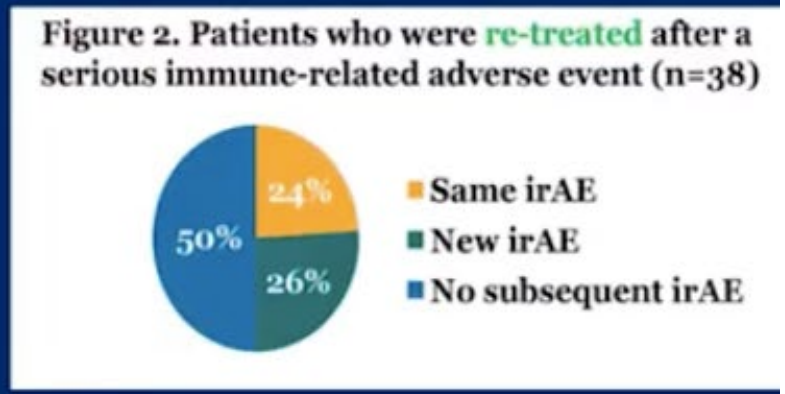
- Several studies in melanoma confirmed improved outcomes if patients developed irAE
- Retrospective analysis of 134 patients with NSCLC from 4 institutions treated with nivolumab



Haratani et al, Jama Oncology 2017

How safe is rechallenge

- 484 patients single institution study, 38 restarted immonotherapy after hold for irAE.
  - If recurrent irAE developed - 84% resolved and improved.
  - two treatment related death
- Two factors are associated with recurrence of the irAE
  - hospitalizations for irAE management
  - irAE within 3month of initiation of immunotherapy.



Santini, ASO 2017, abs 9012

UC San Diego
Moores Cancer Center

AE imunoterapije

1. irAE – može zahvatiti svaki organ
2. irAE – dobar prognostički znak
3. Najčešće u prva 3 meseca – ali moguće i kasnije (čak i nakon obustave ICI)
4. Ako se prepoznaju na vreme – lako se leče (uvek korak ispred AE)
5. Ako se ne prepoznaju i ne leče – moguć fatalni ishod
6. Primena KS ne utiče na efikasnost ICI i OS
7. Spora redukcija doze KS
8. Dobar kontakt sa pacijentom

TNM klasifikacija

	Surgical/Pathological Findings
Primary tumor (T)	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or **bronchoscopy**
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	≤ 3 cm diameter, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus; the uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a
T1mi	Minimally invasive adenocarcinoma
T1a	≤ 1 cm diameter
T1b	> 1 cm but ≤ 2 cm diameter
T1c	> 2 cm but ≤ 3 cm diameter
T2	> 3 cm but ≤ 5 cm diameter or involvement of main bronchus regardless of distance to the carina, but without involving the carina or invasion of visceral pleura or associated with atelectasis or obstructive pneumonitis extending to the hilar region, either involving part of the lung or the entire lung
T2a	> 3 cm but ≤ 4 cm diameter
T2b	> 4 cm but ≤ 5 cm diameter
T3	> 5 cm but ≤ 7 cm or directly invades parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary
T4	> 7 cm or invasion of diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary

	Surgical/Pathological Findings
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral, mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodules in a contralateral node, tumor with pleural nodules, or malignant pleural effusion
M1b	Single extrathoracic metastasis in a single organ and involvement of a single distant (nonregional) node
M1c	Multiple extrathoracic metastases in 1 or several organs

NSCLC Staging

Staging NSCLC[7]

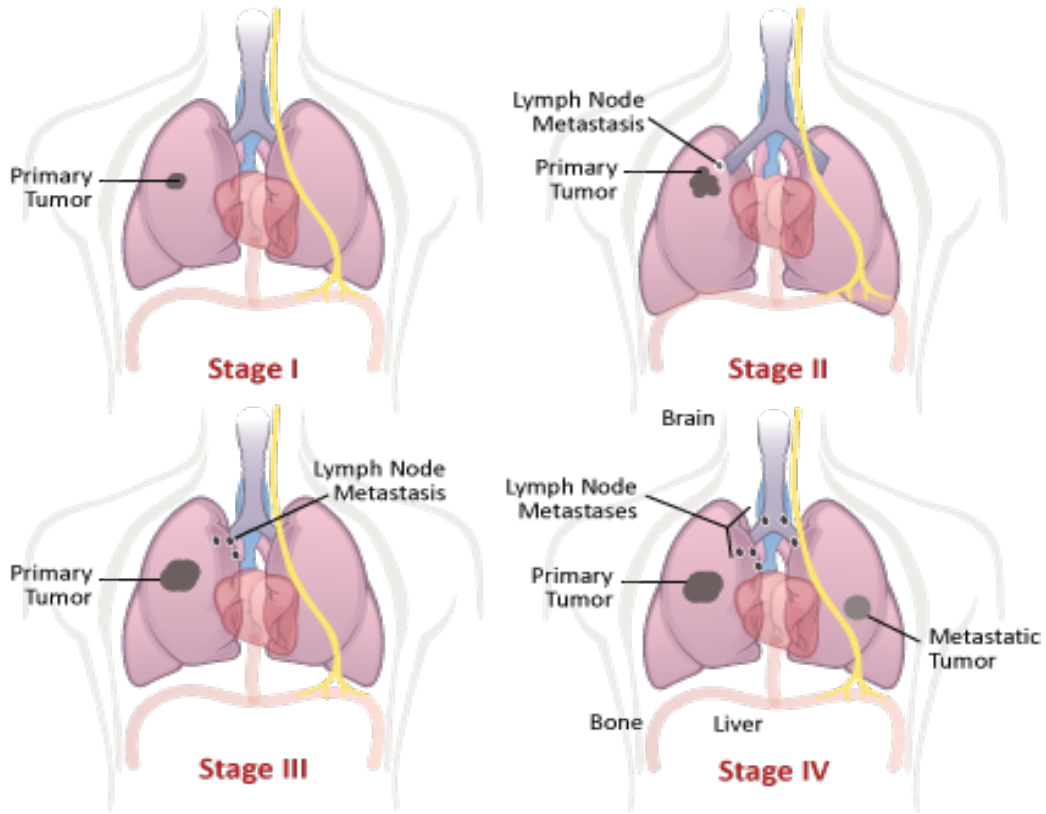


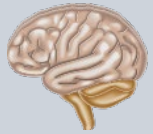
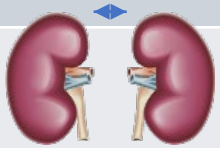
Image adapted from: Free to Breathe. http://www.freetobreathe.org/images/uploads/2014_Living_With_A_Diagnosis_of_Lung_Cancer_Web.pdf.

Anatomic Stage and Prognostic Group[6]

Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1mi, T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3			
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a, T1b, T1c	N1	M0
	T2a, T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a, T1b, T1c	N2	M0
	T2a, T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a, T1b, T1c	N3	M0
	T2a, T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a, M1b
Stage IVB	Any T	Any N	M1c

Metastatic NSCLC

- The most frequent sites for NSCLC metastases include the brain, liver, bone, and adrenal glands[8,9]
  - Metastases may involve single or multiple organs

Organ Involvement	Characteristics
	▪ The incidence of **brain** metastases is increasing, with 30%-50% of patients developing brain metastases during the course of the disease[1,10] – Patients with brain metastases have a poor prognosis
	▪ **Liver** metastases are rare in patients with newly diagnosed disease; however, the incidence increases in later stages[9] – Autopsy studies have found evidence of liver metastases in > 50% of patients
	▪ **Bone** metastases are observed in 30%-40% of patients and are associated with pain[8,11] – Skeletal-related events—including pathological fractures, requirement for surgery or radiation, spinal cord compression, and malignant hypercalcemia—have been reported
	▪ Metastases to the **adrenal glands** have been found in 33%-40% of patients in autopsy studies[1,9]

Prognostic Factors in NSCLC[1,14-17]

- Prognostic factors are clinical or biological characteristics that indicate the likely disease outcome independent of the treatment received[1,14,15]

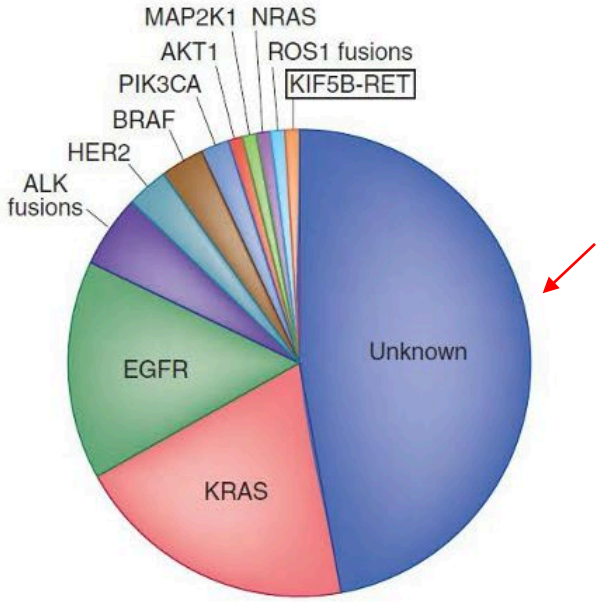
Prognostic Factor	Description
Disease stage at diagnosis	Advanced or metastatic disease (IIIB or IV) at diagnosis is associated with very poor outcomes
Lymph node status	Patients with N1 lymph nodes have a better prognosis than those with N2 or N3 lymph nodes
Performance status (PS)	Patients with a good PS have a more favorable prognosis than those with a poor PS
Weight loss	Weight loss of ≥ 5% predicts decreased survival
Nonsquamous histology	Squamous cell histology is associated with poorer outcomes
***KRAS* mutation**	Absence of *KRAS* mutations indicates a favorable prognosis

Predictive Factors in NSCLC[1,16-18]

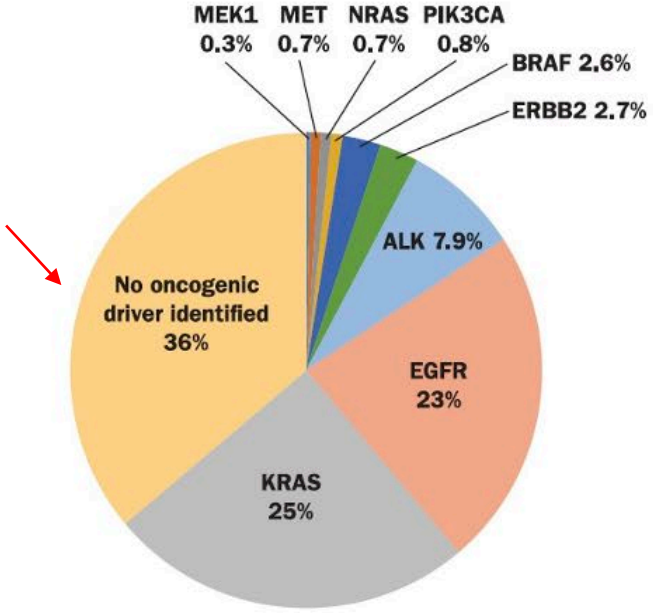
- Predictive factors indicate outcomes following treatment[1,15]

Predictive Factors	Description
Sensitizing *EGFR* mutation	*EGFR* mutations, such as exon 19 deletion, predict response to EGFR-targeting agents
***ALK* rearrangements**	*ALK* rearrangement predicts response to ALK inhibitors
***ROS1* rearrangements**	*ROS1* rearrangement predicts response to the first-generation ALK inhibitor crizotinib
PD-L1 expression	PD-L1 expression levels ≥ 50% predict response to first-line ICI

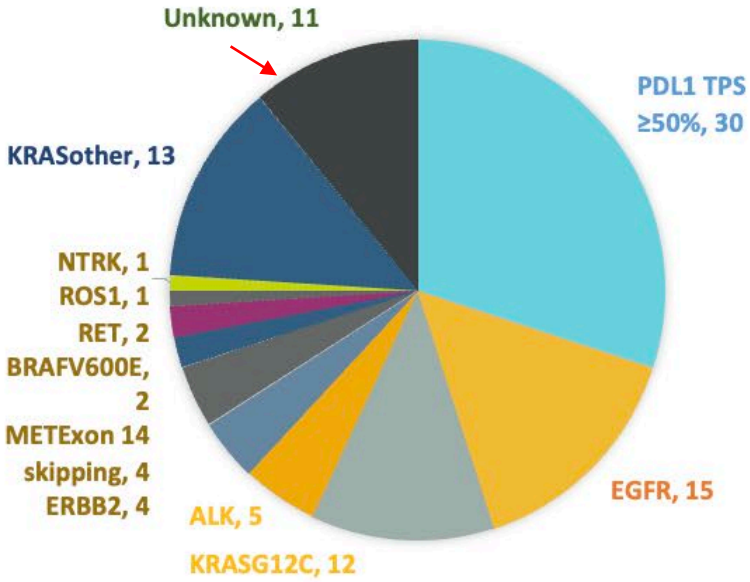
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand 1.



Pao and Hutchinson 'Chipping away at the lung cancer genome'
Nature Medicine. March 2012



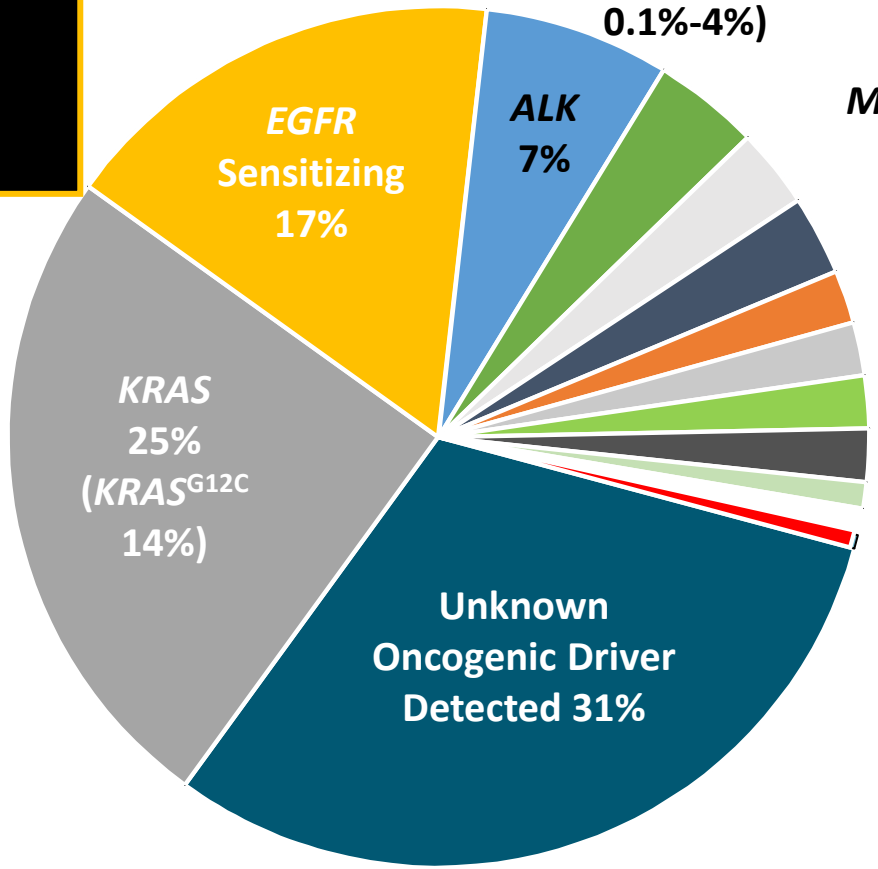
Sholl et al. Lung Cancer Mutation Consortium J Thorac Oncol. May 2015



2021: biomarkers with FDA-approved drugs

~50% of Patients With Adv Nonsq NSCLC Have a Driver Mutation Targetable With an FDA-Approved Agent or on a Clinical Trial

Updated



ALK:
Alectinib
Crizotinib
Ceritinib
Lorlatinib
Brigatinib
Ensartinib

EGFR Sensitizing:
Osimertinib
Gefitinib
Erlotinib
Afatinib
Dacomitinib

EGFR Other 4% (EGFRex20ins 0.1%-4%)

MET 3%

>1 Mutation 3%

HER2 2%

ROS1 2%

BRAF 2%

RET 2%

NTRK1 1%

PIK3CA 1%

MEK1 <1%

KRASG12C:
Sotorasib†
Adagrasib

EGFRex20ins:
Amivantamab*
Mobocertinib*

METex14:
Capmatinib
Tepotinib

HER2:
T-DXd†
Poziotinib

ROS1:
Crizotinib
Entrectinib

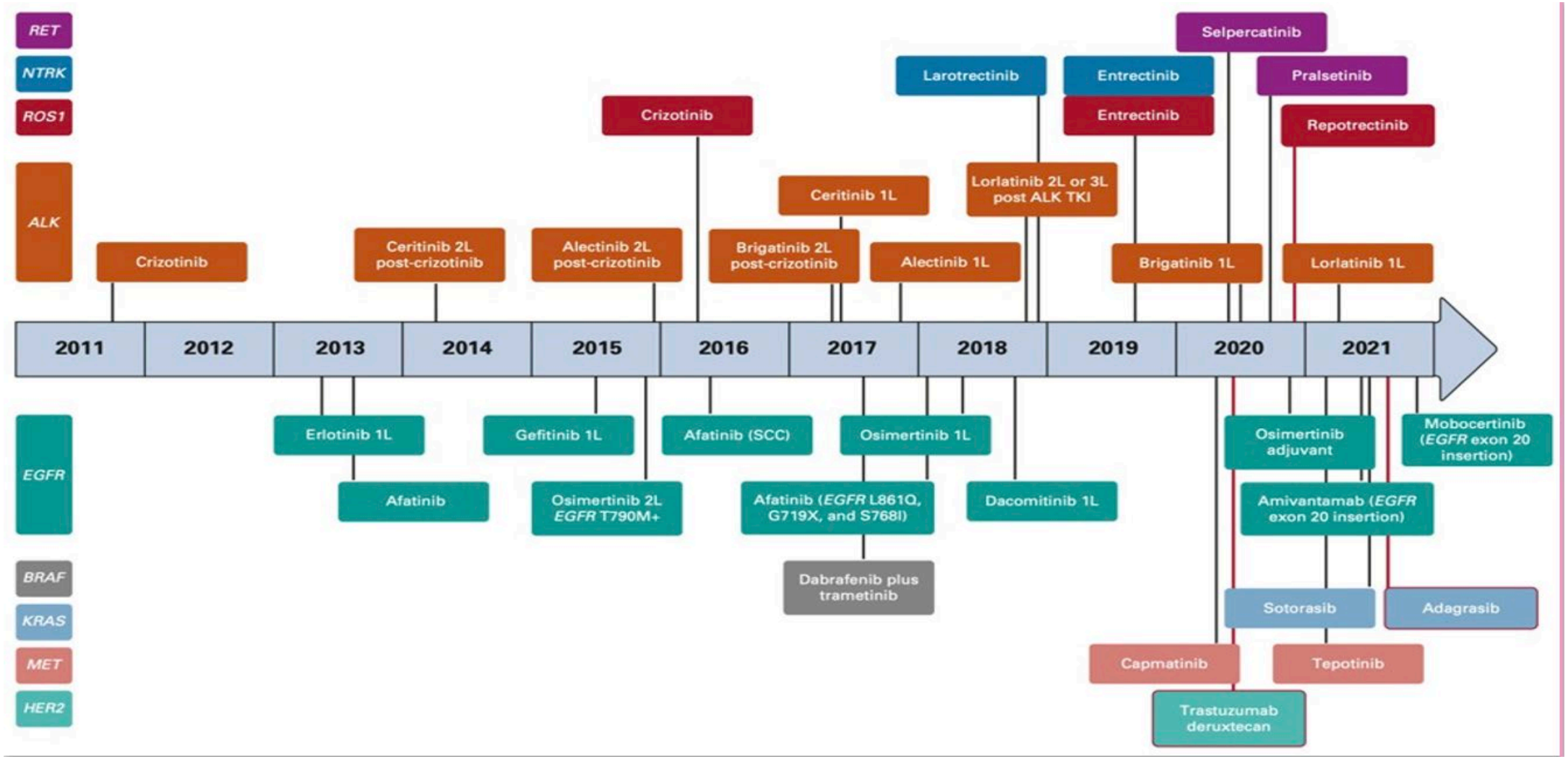
BRAF V600E:
Dabrafenib‡

RET fusion:
Selpercatinib
Pralsetinib

NTRK fusion:
Entrectinib
Larotrectinib

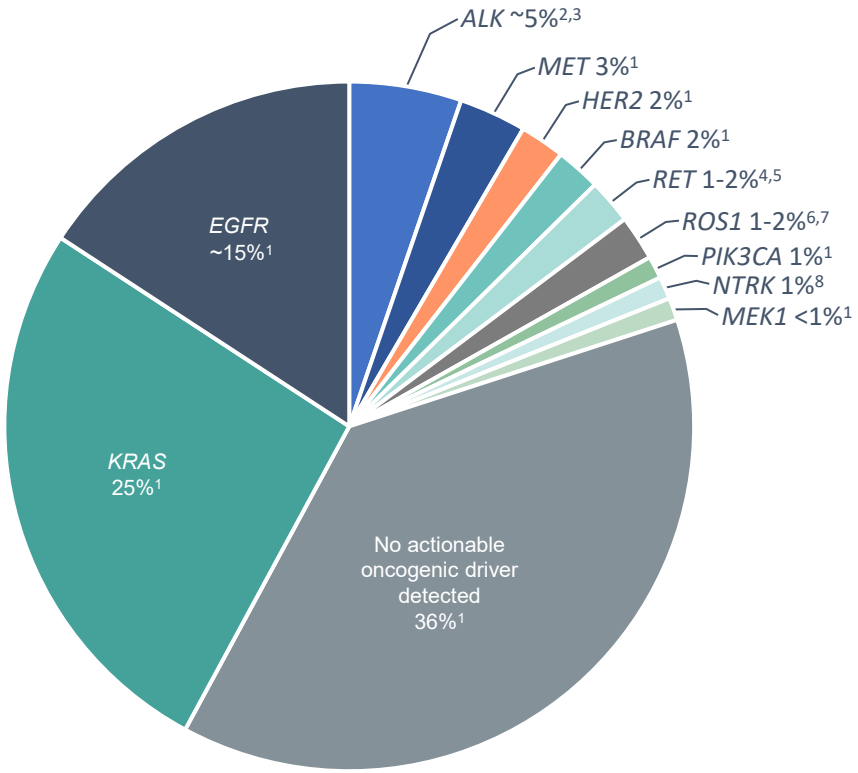
Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613. Burnett. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.

*Approved after PD on plt-based CT. †Approved after ≥1 prior systemic tx.
‡Approved with trametinib (MEK inhibitor) for *BRAF* V600E mutation.


RET
NTRK
ROS1
ALK
EGFR
BRAF
KRAS
MET
HER2
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
Crizotinib
Crizotinib
Ceritinib 2L post-crizotinib
Alectinib 2L post-crizotinib
Brigatinib 2L post-crizotinib
Ceritinib 1L
Alectinib 1L
Larotrectinib
Lorlatinib 2L or 3L post ALK TKI
Selpercatinib
Entrectinib
Entrectinib
Pralsetinib
Repotrectinib
Brigatinib 1L
Lorlatinib 1L
Erlotinib 1L
Afatinib
Gefitinib 1L
Osimertinib 2L EGFR T790M+
Afatinib (SCC)
Osimertinib 1L
Afatinib (EGFR L861Q, G719X, and S768I)
Dabrafenib plus trametinib
Dacomitinib 1L
Osimertinib adjuvant
Mobocertinib (EGFR exon 20 insertion)
Amivantamab (EGFR exon 20 insertion)
Sotorasib
Adagrasib
Capmatinib
Tepotinib
Trastuzumab deruxtecan

NSCLC: Informacije na molekularnom nivou i napredak u dijagnostici promenili su kliničku praksu

„Targetabilne“ alteracije u karcinomu pluća



Approved drugs*

Investigational drugs†

Lečenje na osnovu genomskog profilisanja

EGFR (23 / 6 + 17)

- Afatinib
- Dacomitinib▼
- Erlotinib (± anti-VEGF / VEGFR)
- Gefitinib
- Necitumumab▼[10]
- Osimertinib▼
- Amivantamab[11]
- Abivertinib[12]
- Olafertinib[13]
- Icotinib[14]
- Lazertinib[15]
- Mobocertinib[16]
- Nazartinib[17]
- Neratinib▼[18]
- Olaparib + durvalumab▼[19]
- Olmutinib[20]
- Avitinib[21]
- Pirotinib[21]
- Nimotuzumab[21]
- Poziotinib[22]
- Tarloxotinib[23]
- Patritumab deruxtecan[24]
- Zorifertinib[25]

ALK (9 / 5 + 4)

- Alectinib▼
- Brigatinib▼
- Ceritinib▼
- Crizotinib
- Lorlatinib▼
- Cobimetinib + alectinib▼[30]
- Ensartinib[31]
- Repotrectinib[32]
- TQ-B3139[33]

BRAF (7 / 5 + 2)

- Binimetinib▼[26]
- Cobimetinib[28]
- Encorafenib▼[41]
- Dabrafenib (+ trametinib)
- Vemurafenib
- Ulixertinib[27]
- Selumetinib[29]

RET (9 / 2 + 7)

- Pralsetinib
- Selpercatinib▼
- Alectinib▼[47]
- Apatinib[10]
- Cabozantinib▼
- Lenvatinib▼[10]
- Ponatinib▼[10]
- TPX-0046[48]
- Vandetanib▼

KRAS (9)

- Adagrasib[34]
- Binimetinib▼[26]
- Binimetinib▼+ palbociclib▼[35]
- Erlotinib + tivantinib[36]
- JDQ443 (+ TNO155)[37]
- Selumetinib[29]
- Sotorasib[38]
- Trametinib[39]
- VS-6766 (+ defactinib)[40]

HER2 (12 / 4 + 8)

- Neratinib▼[42]
- Pertuzumab + trastuzumab▼[43]
- Trastuzumab emtansine[10] / deruxtecan▼[44]
- Afatinib[10]
- Dacomitinib▼[10]
- Lapatinib[29]
- Mobocertinib[16]
- Poziotinib[22]
- Pyrotinib maleate[21]
- Tarloxotinib[23]
- TAS0728[45]

MET (11 / 2 + 9)

- Capmatinib[49]
- Tepotinib[50]
- Bozitinib[51]
- Cabozantinib▼[52]
- Crizotinib
- Ensartinib[21]
- Glesatinib[53]
- Glumetinib[54]
- Merestinib[55]
- Savolitinib (+ osimertinib▼)[56]
- Sym015[57]

PIK3CA (4 / 1 + 3)

- Alpelisib▼[26]
- Copanlisib[27]
- Ipatasertib[28]
- MK-2206[29]

MEK1 (3)

- Cobimetinib[10]
- Trametinib[10]
- Selumetinib[10]

NTRK (7 / 2 + 5)

- Entrectinib▼
- Larotrectinib▼
- Cabozantinib▼[10]
- Taletrectinib[10]
- Ensartinib[21]
- Repotrectinib[32]
- Selitrectinib[46]

ROS1 (8 / 2 + 6)

- Crizotinib
- Entrectinib▼
- Cabozantinib▼[10]
- Ceritinib▼
- Ensartinib[21]
- Lorlatinib▼
- Repotrectinib[32]
- Taletrectinib[58]

…nove ciljane terapijske opcije kod pacijenata sa prisutnim genomskim alteracijama

All drugs listed are included in NSCLC NCCN Guidelines unless otherwise indicated. **Some non-investigational drugs are only approved for use in specific indications in Europe and / or USA and / or Japan. Some therapies listed target specific variants of the indicated gene.**

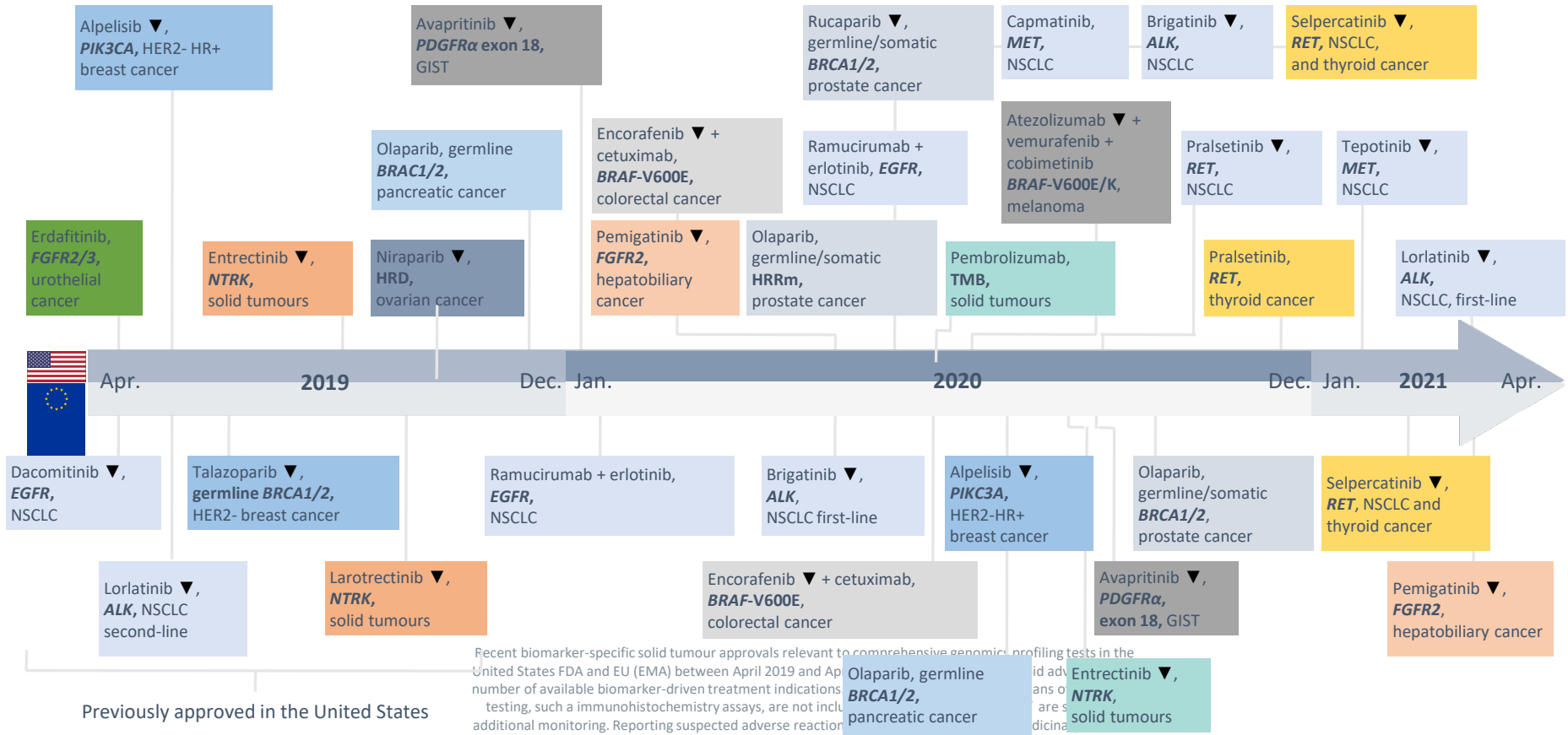
* Some drugs are approved for cancer types other than lung cancer with alterations in the indicated gene with clinical trials investigating efficacy in lung cancer.

† Some drugs are investigational and not approved in any indication.

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective local office [see slide notes for full listing].

A full list of references can be found in the slide notes.

Značajan broj novih ciljanih i nekoliko tumor-agnostik terapija je odobreno od strane FDA i EMA u poslednje 3 godine

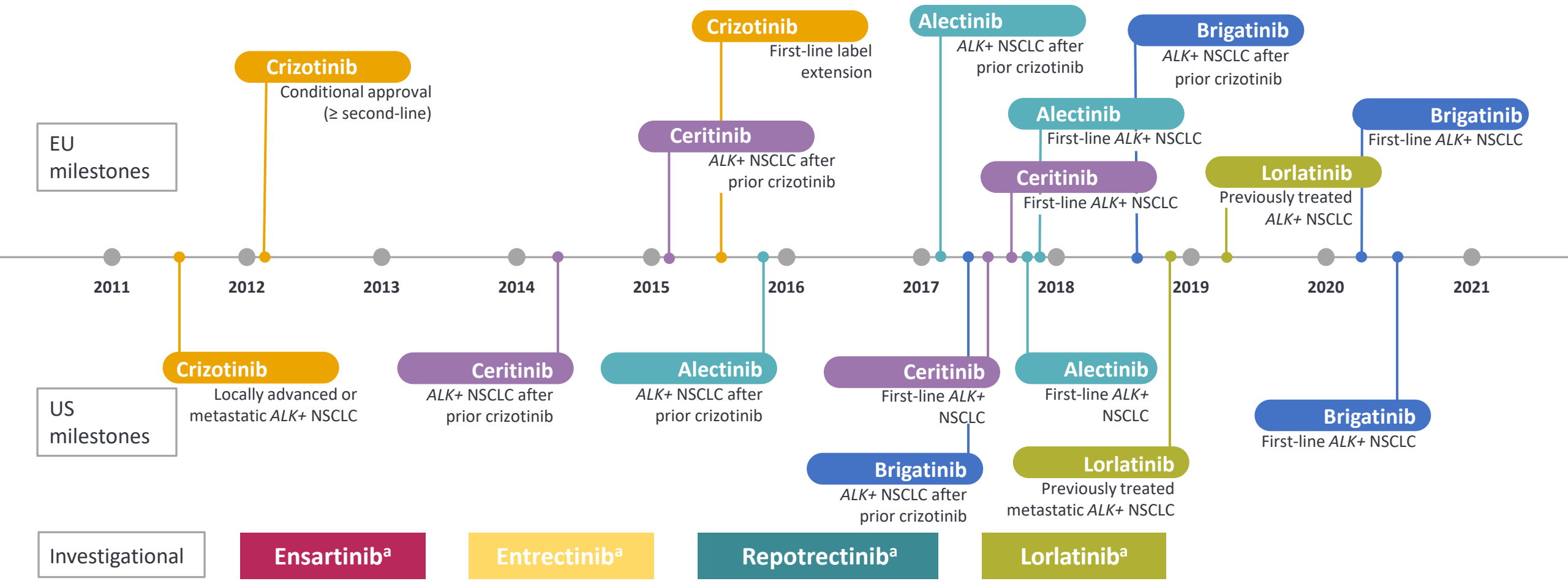


Recent biomarker-specific solid tumour approvals relevant to comprehensive genomic profiling tests in the United States FDA and EU (EMA) between April 2019 and Ap id adv number of available biomarker-driven treatment indications ans o testing, such a immunohistochemistry assays, are not inclu are s additional monitoring. Reporting suspected adverse reaction dicina important. Adverse events should be reported to your respective local office. Bayer AG: Larotrectinib; Blueprint Medicines (Netherlands) B.V.: Avapritinib; Clovis Oncology UK Limited: Rucaparib; Eli Lilly Nederland B.V.: selpercatinib; GlaxoSmithKline (Ireland) Limited: Niraparib; Incyte Biosciences Distribution B.V.: Pemigatinib; Merck Europe B.V.: Tepotinib; Novartis Europharm Limited: Alpelisib; Pierre Fabre Medicament: Encorafenib; Pfizer Europe MA EEIG: Dacomitinib, Lorlatinib, Talazoparib; Roche Registration GmbH: Atezolizumab, Entrectinib, Pralsetinib; Takeda Pharma A/S: Brigatinib.

GIST: gastrointestinal stromal tumour; HR: hormone receptor; HRD: homologous recombination repair deficiency; HRRm: homologous recombination repair gene mutated; PDGFRα: platelet-derived growth factor alpha; TMB: tumour mutational burden.

Mateo, J., et al. (2022) *Nature Medicine* 28: 658-65.

ALK inhibitor development

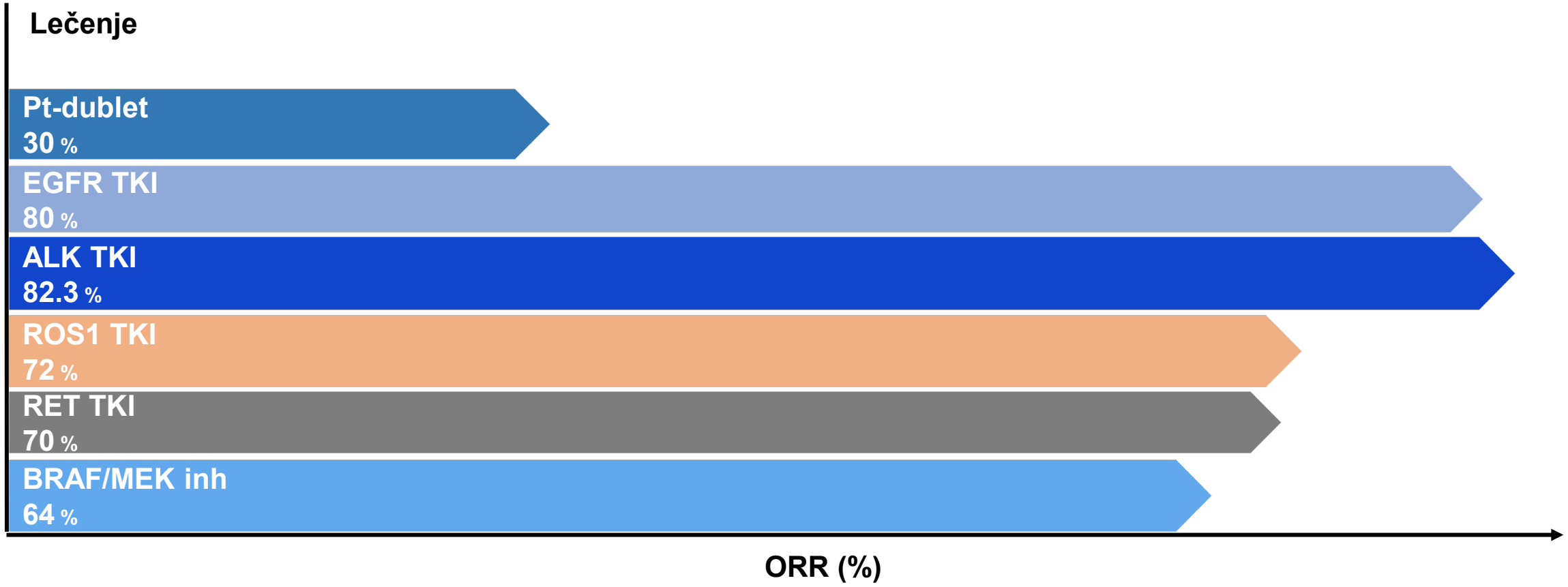


All approved products' information can be found in the associated Summary of Product Characteristics.
ALK, Anaplastic lymphoma kinase; NSCLC, Non-small cell lung cancer

[a]Investigational compound in identified treatment setting – currently not labelled for this indication in the EU.

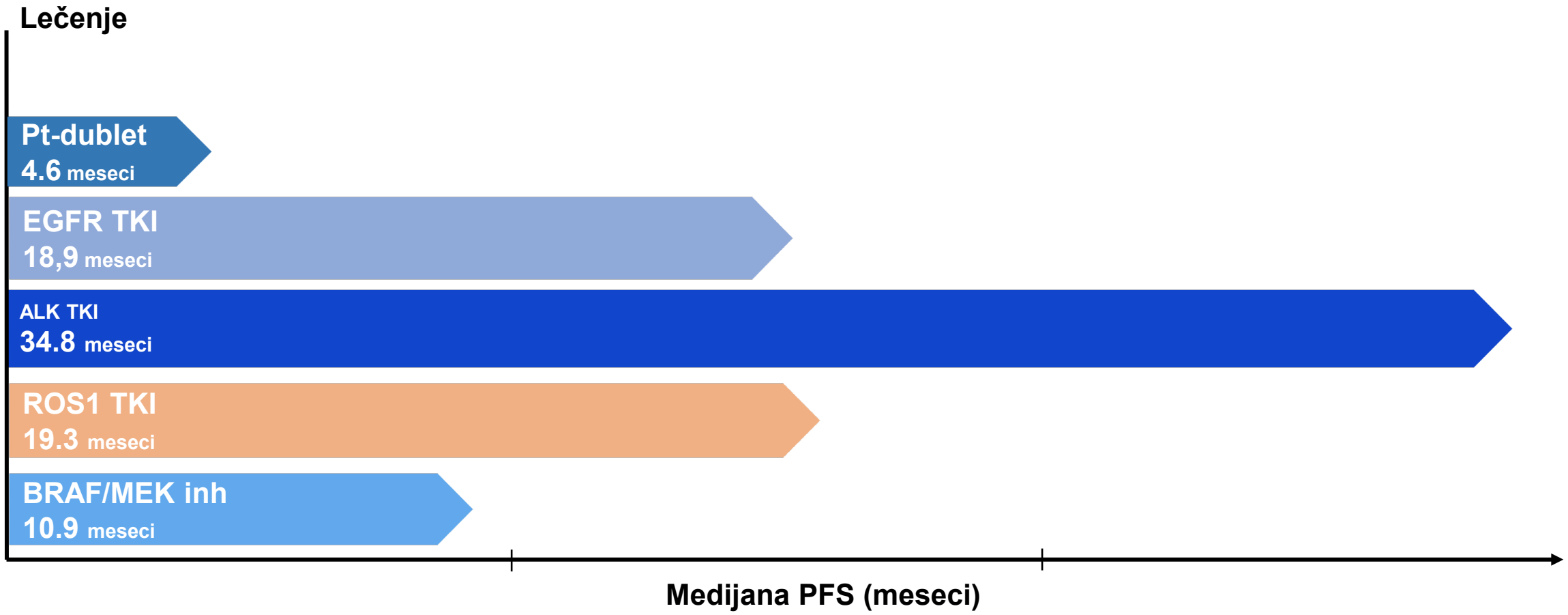
For detailed information about an individual medicinal product, please read the last approved Summary of Product Characteristics www.ema.europa.eu or at the website of your national authority. Please note that all medicinal products mentioned may not be authorized/available in all countries.

Ukupan terapijski odgovor (ORR) za hemioterapiju i ciljane terapijske opcije odobrene u prvoj liniji lečenja uznapredovalog NSCLC



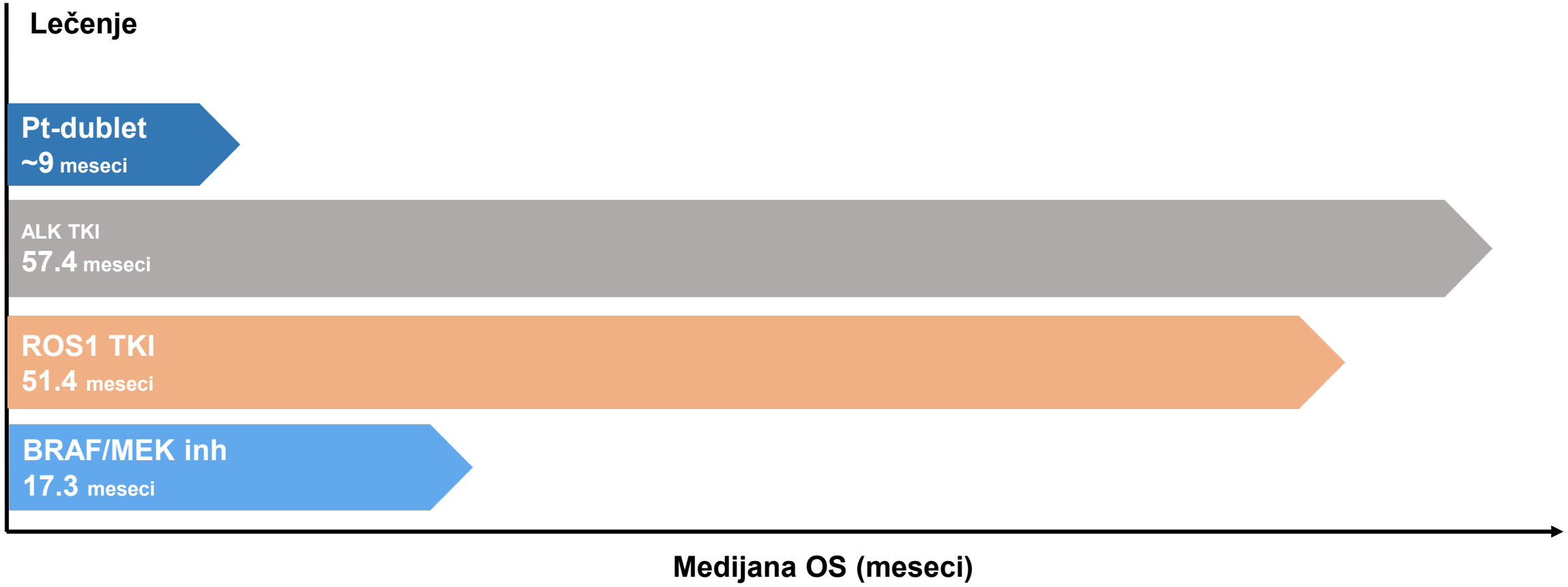
Scagliotti et al. JCO 2002; Soria et al. NEJM 2018; Camidge, et al. J Thorac Oncol 2019; Mok, et al. Ann Oncol 2020; Shaw et al. Ann Oncol 2019; Gainor, J.F., et al. Lancet 2021; Planchard et al. J Thorac Oncol 2021

Preživljavanje bez progresije bolesti (PFS) za hemioterapiju i ciljane terapijske opcije odobrene u prvoj liniji lečenja uznapredovalog NSCLC



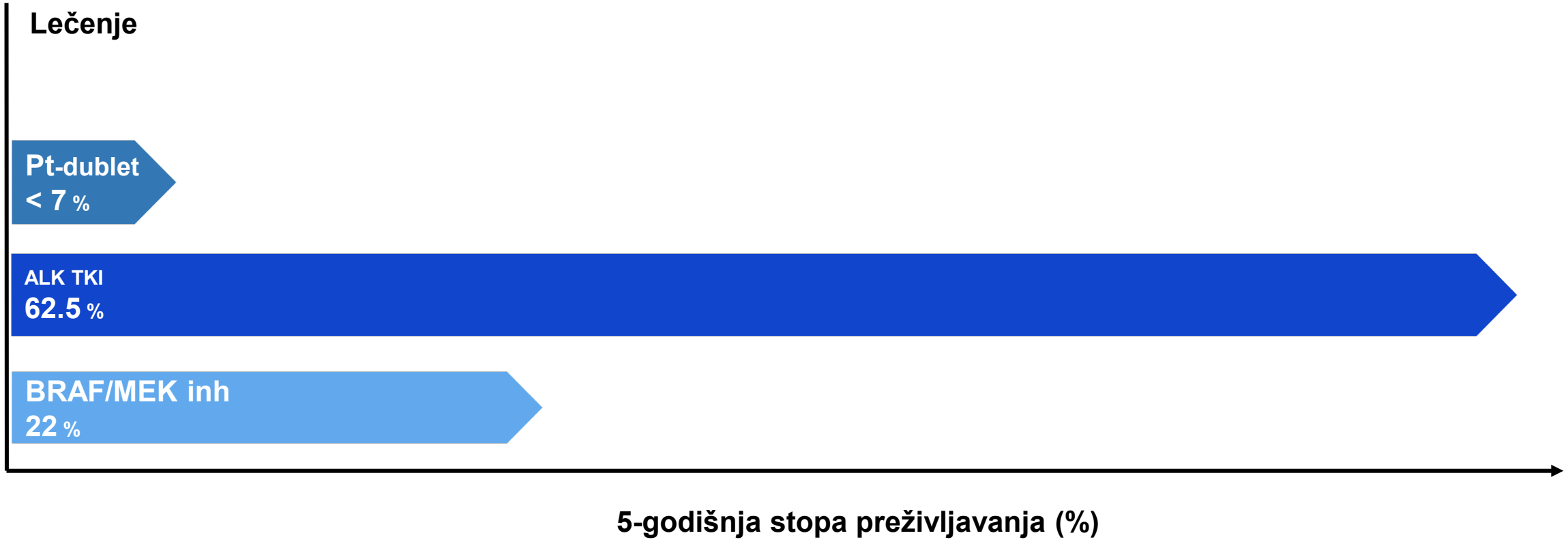
Scagliotti et al. JCO 2002; Soria et al. NEJM 2018; Camidge, et al. J Thorac Oncol 2019; Mok, et al. Ann Oncol 2020; Shaw et al. Ann Oncol 2019; Gainor, J.F., et al. Lancet 2021; Planchard et al. J Thorac Oncol 2021

Ukupno preživljavanje (OS) za hemioterapiju i ciljane terapijske opcije odobrene u prvoj liniji lečenja uznapredovalog NSCLC



Scagliotti et al. JCO 2002.; Mok, et al. Ann Oncol 2020; Shaw et al. Ann Oncol 2019; Planchard et al. J Thorac Oncol 2021

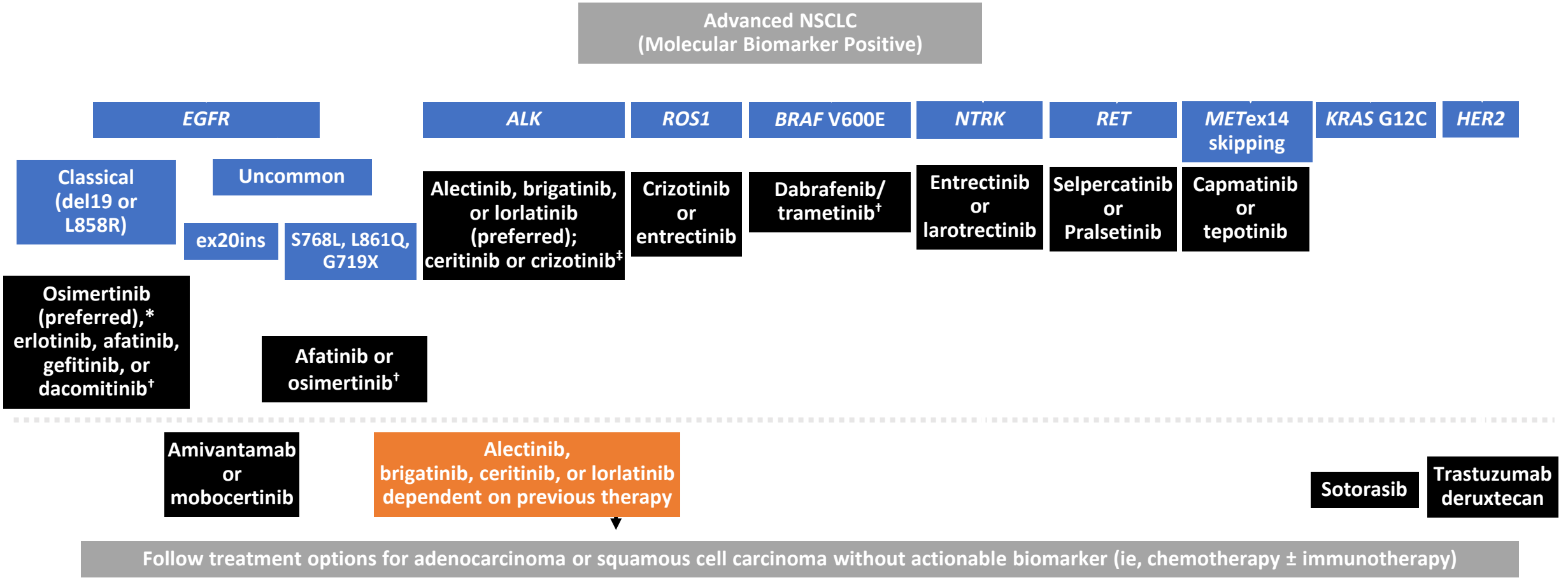
5-ogodišnja stopa preživljavanja za hemioterapiju i ciljane terapijske opcije odobrene u prvoj liniji lečenja uznapredovalog NSCLC



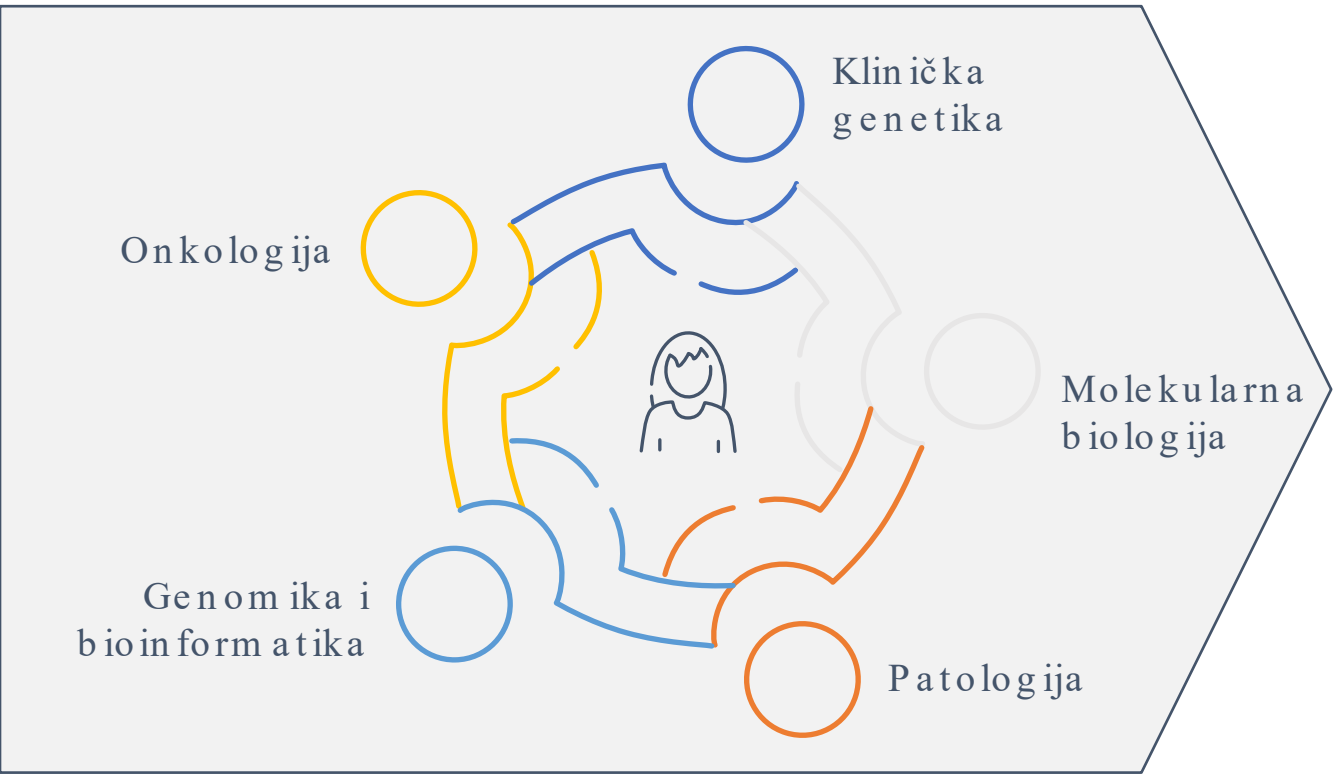
Howlader N et al. SEER Cancer Statistics Review, 1975–2017 ; Camidge, et al. J Thorac Oncol 2019; Mok, et al. Ann Oncol 2020; Planchard et al. J Thorac Oncol 2021

2022 Treatment Paradigm for Molecular Biomarker-Positive Advanced NSCLC

Updated



MTB kao središte za donošenje odluke



Olakšava interpretaciju
kompleksnih molekularnih podataka[1,2]

Predlaže ciljanu terapiju
pacijentima koji mogu imati benefit[1,2,4]

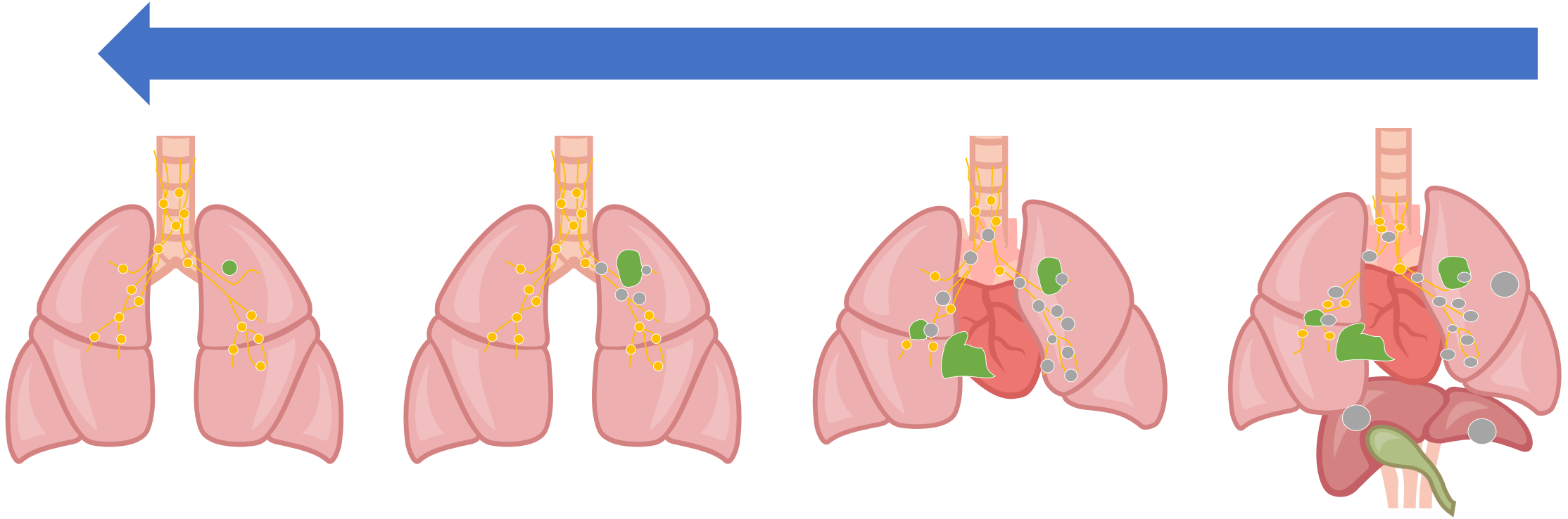
Edukacija
O molekularnim testovima, nalazima i kako su oni povezani sa terapijskim odlukama[1,4]

Praćenje
kliničkih studija i terapija na osnovu molekularnih otisaka, često uz pomoć CGP izveštaja[1,3]

Praćenje kliničkih studija
i upućivanje pacijenata na kliničke studije sa odgovarajućom terapijom[5]

CGP: comprehensive genomic profiling; MTB: molecular tumour board.
1. van der Velden, D.L., et al. (2017) *Ann Oncol* 28:3070-5; 2. Burkard, M.E., et al. (2017) *JCO Precis Oncol* 1:1-10; 3. Knepper, T.C., et al. (2017) *Oncologist* 22:144-51; 4. 2017 ACCC Educational series – Virtual Molecular Tumour Boards. Available at: https://www.accc-cancer.org/resources/pdf/VTB-ACCC-Molecular-Testing-Article.pdf (Accessed November 2019); 5. Basse, C., et al. (2018) *ESMO Open* 3:e000339

Moving Targeted Therapy and Immunotherapy Earlier in Disease Course

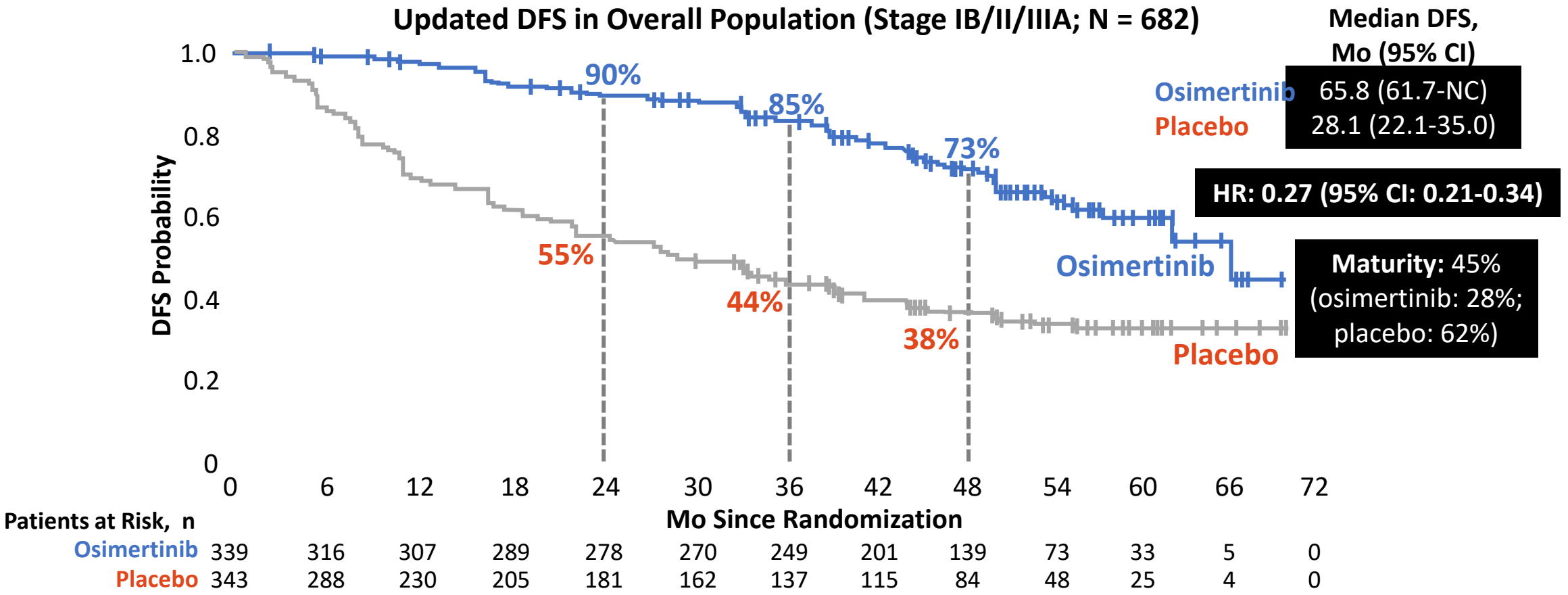


Stage I **Stage II** **Stage III** **Stage IV**

Tumors Nonmetastatic lymph nodes Regional/local metastatic lymph nodes/distant metastases

Phase III ADAURA: Adjuvant Osimertinib for Early-Stage *EGFR*-Mutated NSCLC

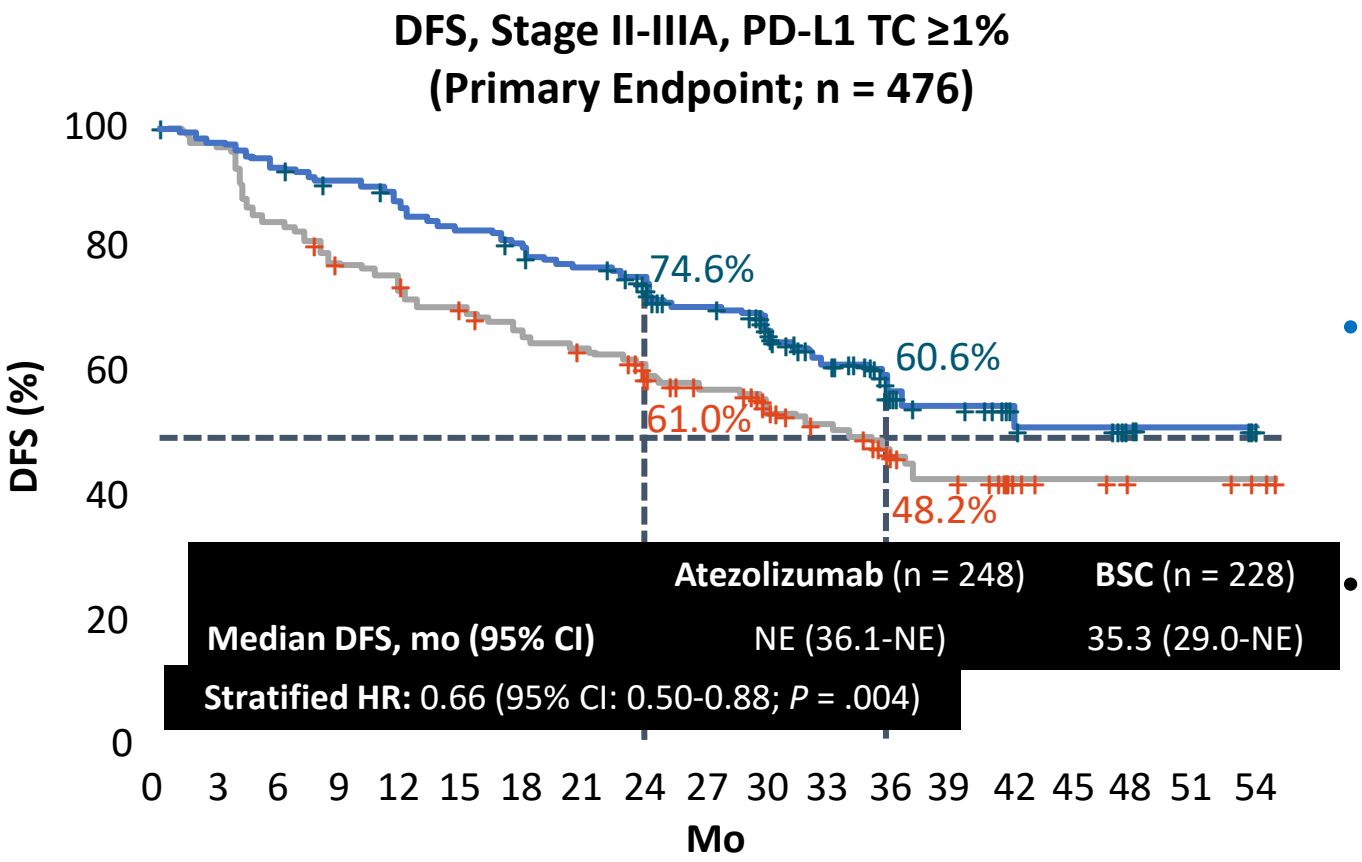
Updated



- FDA approved in December 2020 for adjuvant treatment of adults with stage IB-IIIA *EGFR+* (del19 or L585R) NSCLC following tumor resection ± adjuvant chemotherapy

Tsuboi. ESMO 2022. Abstr LBA47. Osimertinib PI.

Phase III IMpower010: **Adjuvant Atezolizumab vs BSC** in Resected Stage IB-IIIA NSCLC After Adjuvant CT

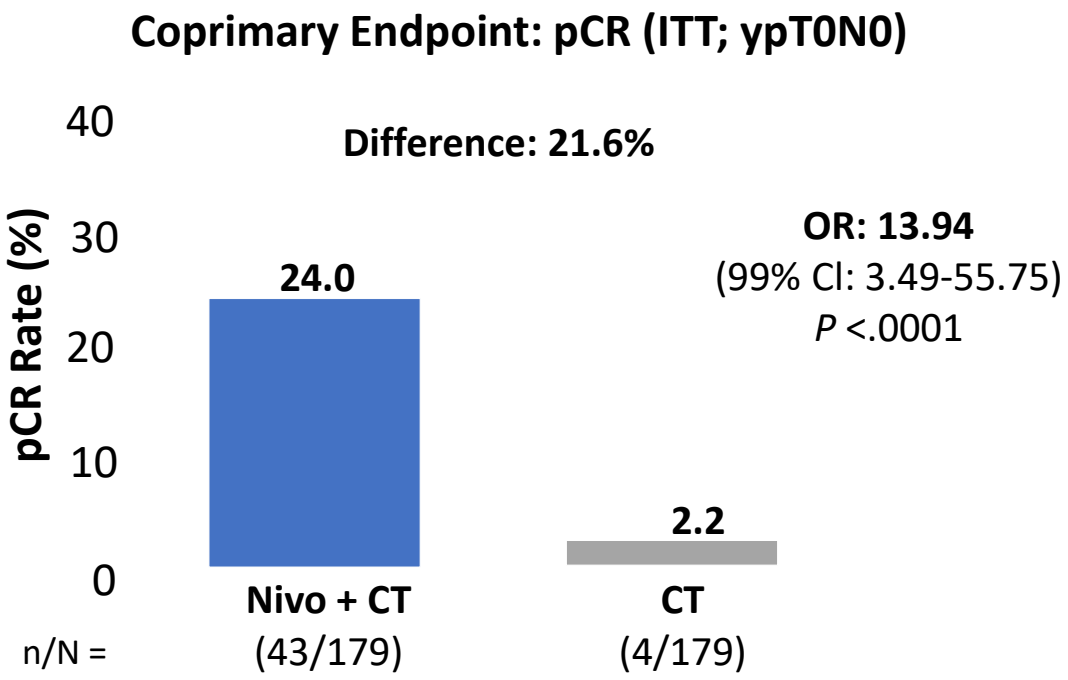


- DFS benefit by PD-L1 status assessed by SP263 IHC: HR (95% CI)
  - **TC ≥50%: 0.43** (0.27-0.68)
  - TC ≥1%: 0.66 (0.49-0.87)
  - TC <1%: 0.97 (0.72-1.31)
- **FDA approved in October 2021 for adj treatment following resection and adj plt-based CT for adults with stage II-IIIA NSCLC, PD-L1 TC ≥1%**
- First pre-specified interim analysis of OS showed trend in favor of atezolizumab in stage II-IIIA with PD-L1 TC ≥1% and ≥50% but not in all randomized stage II-IIIA or ITT populations

Wakelee. ASCO 2021. Abstr 8500. Felip. Lancet. 2021;398;1344. Felip. WCLC 2022. Abstr PL03.09.

Slide credit: clinicaloptions.com

Phase III CheckMate 816: **Neoadjuvant Nivolumab + Platinum CT for Resectable Stage IB-IIIA NSCLC**



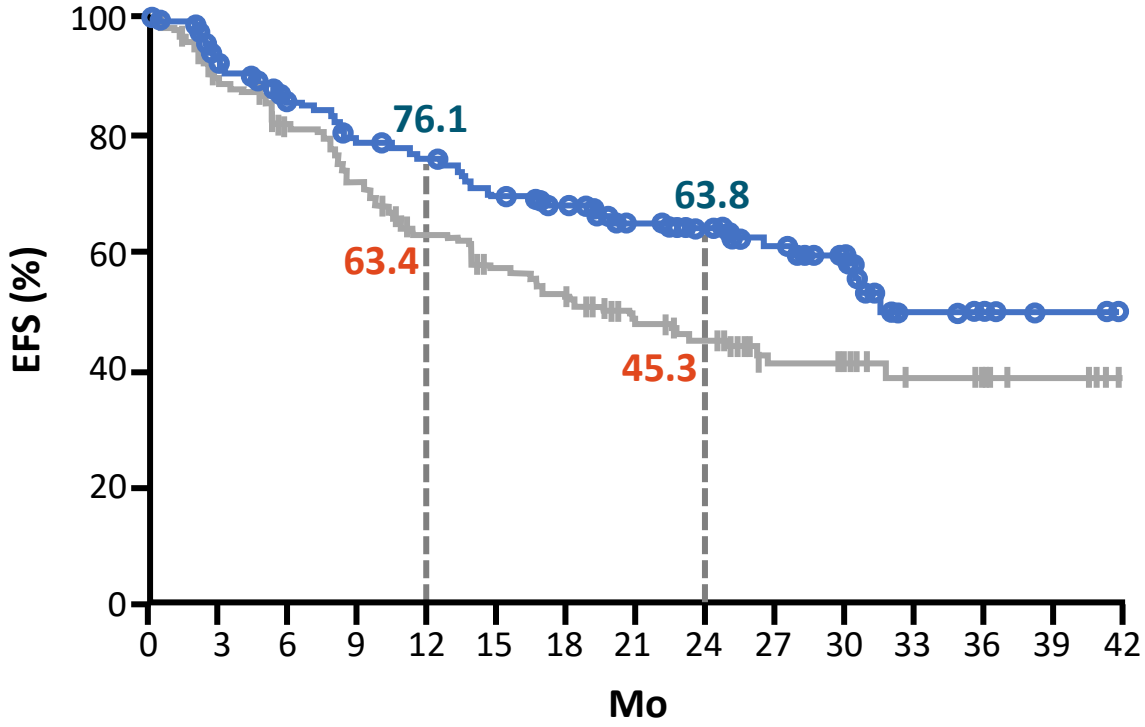
- **FDA approved in March 2022 for adults with resectable NSCLC (tumors ≥4 cm or N+) in combination with platinum doublet CT in the neoadjuvant setting**

Surgery-Related Parameter in All Randomized Patients	Nivolumab + CT (n = 179)	CT (n = 179)
Surgery received/cancelled, %	83.2/15.6	75.4/20.7
Median duration of surgery, min (IQR)	185 (133-260)*	213.5 (150-283)†
Surgery approach, %		
▪ Thoracotomy	59.1‡	63§
▪ Minimally invasive	29.5‡	21.5§
▪ Minimally invasive → open	11.4‡	15.6§
Type of surgery, %#		
Lobectomy	77.2‡	60.7§
Pneumonectomy	16.8‡	25.2§
Complete resection (R0), %	83.2	77.8

*n = 122. †n = 121. ‡n = 149. §n = 135. #Calculated from patients who received definitive surgery. Patients may have had ≥1 surgery type.

Forde. NEJM. 2022;386:1973.

CheckMate 816: Event-Free Survival by BICR (Coprimary Endpoint)



Patients at Risk, n

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

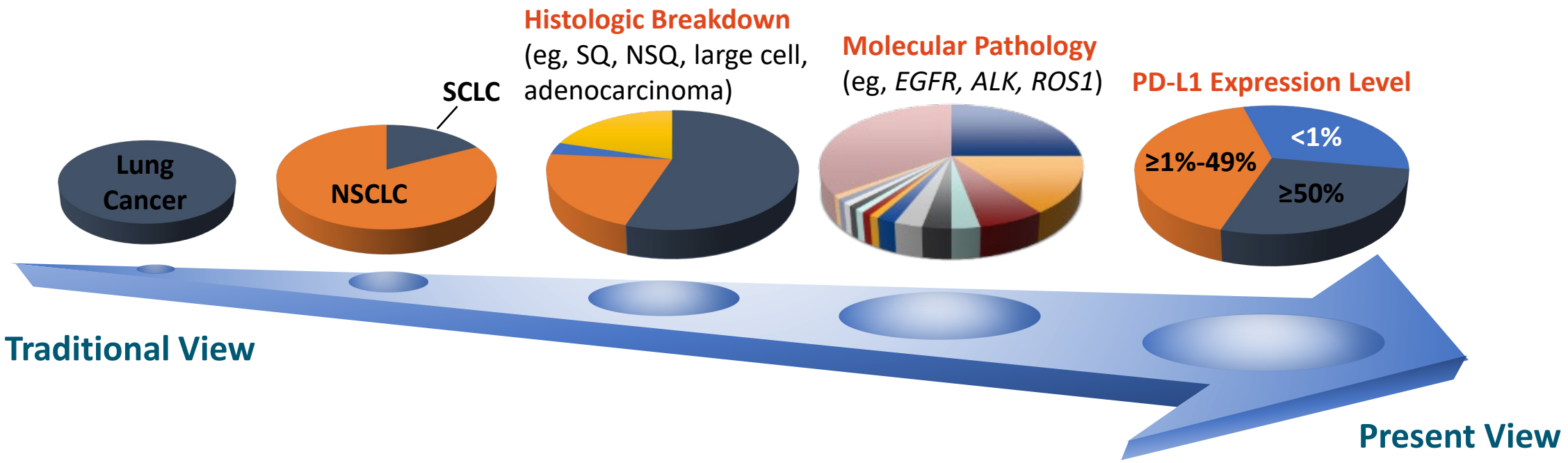
	Patients, n	**Median** EFS, **Mo (95% CI)**
Nivolumab + CT	179	31.6 (30.2-NR)
CT alone	179	20.8 (14.0-26.7)

HR for PD, disease recurrence, or death: 0.63 (97.38% CI: 0.43-0.91; *P*=.005)

Forde. NEJM. 2022;386:1973.

Evolution of Therapy in Lung Cancer

- **Not 1 disease, but many**



Cooper. Pathology. 2011;43:103. Langer. JCO. 2010;28:5311. Galon. Immunity. 2013;39:11.
Pao. Lancet Oncol. 2011;12:175. Krigsfeld. AACR 2017. Abstr CT143.