Comprehensive Hematology & Oncology Review : Metastatic NSCLC

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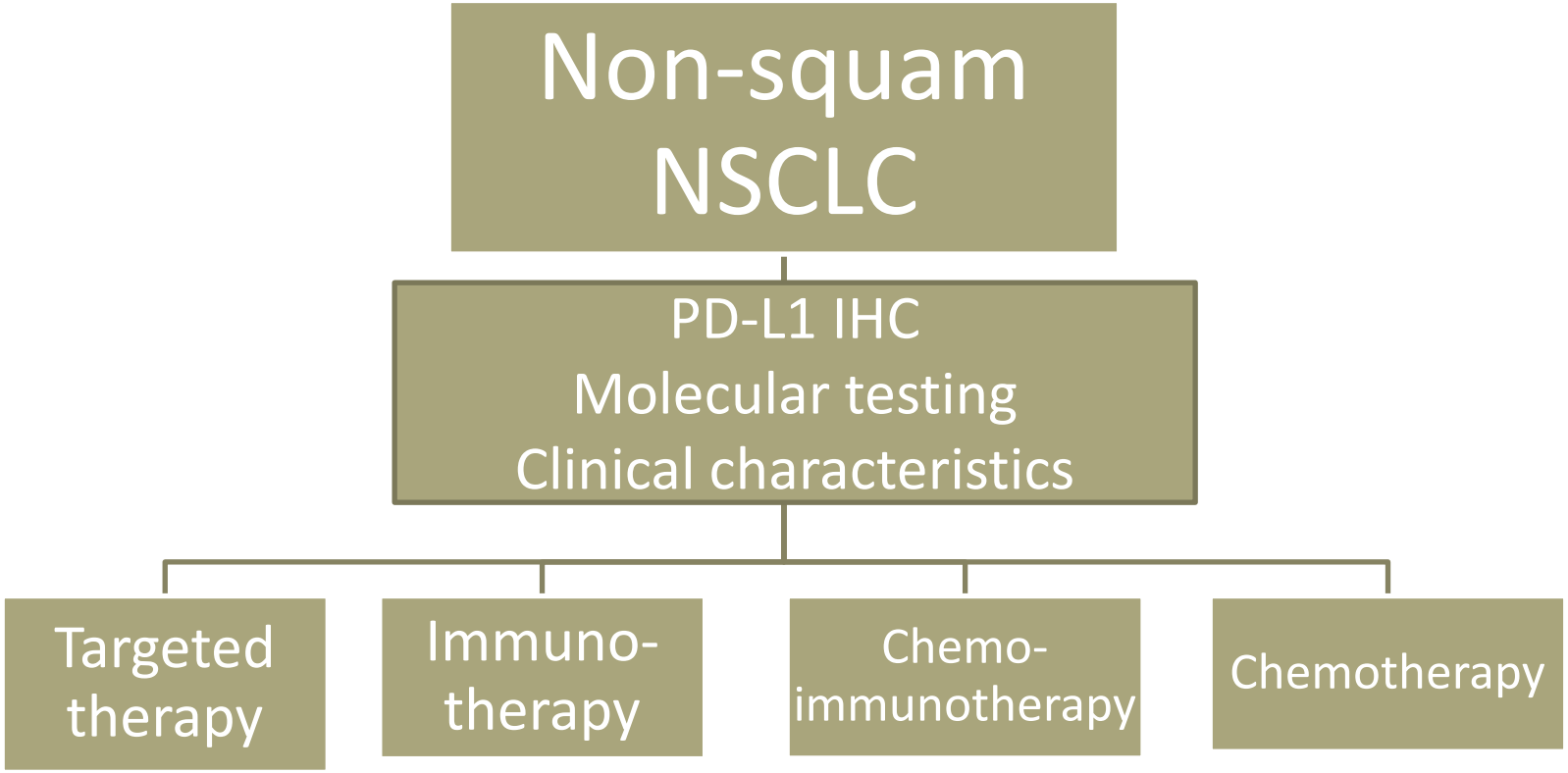
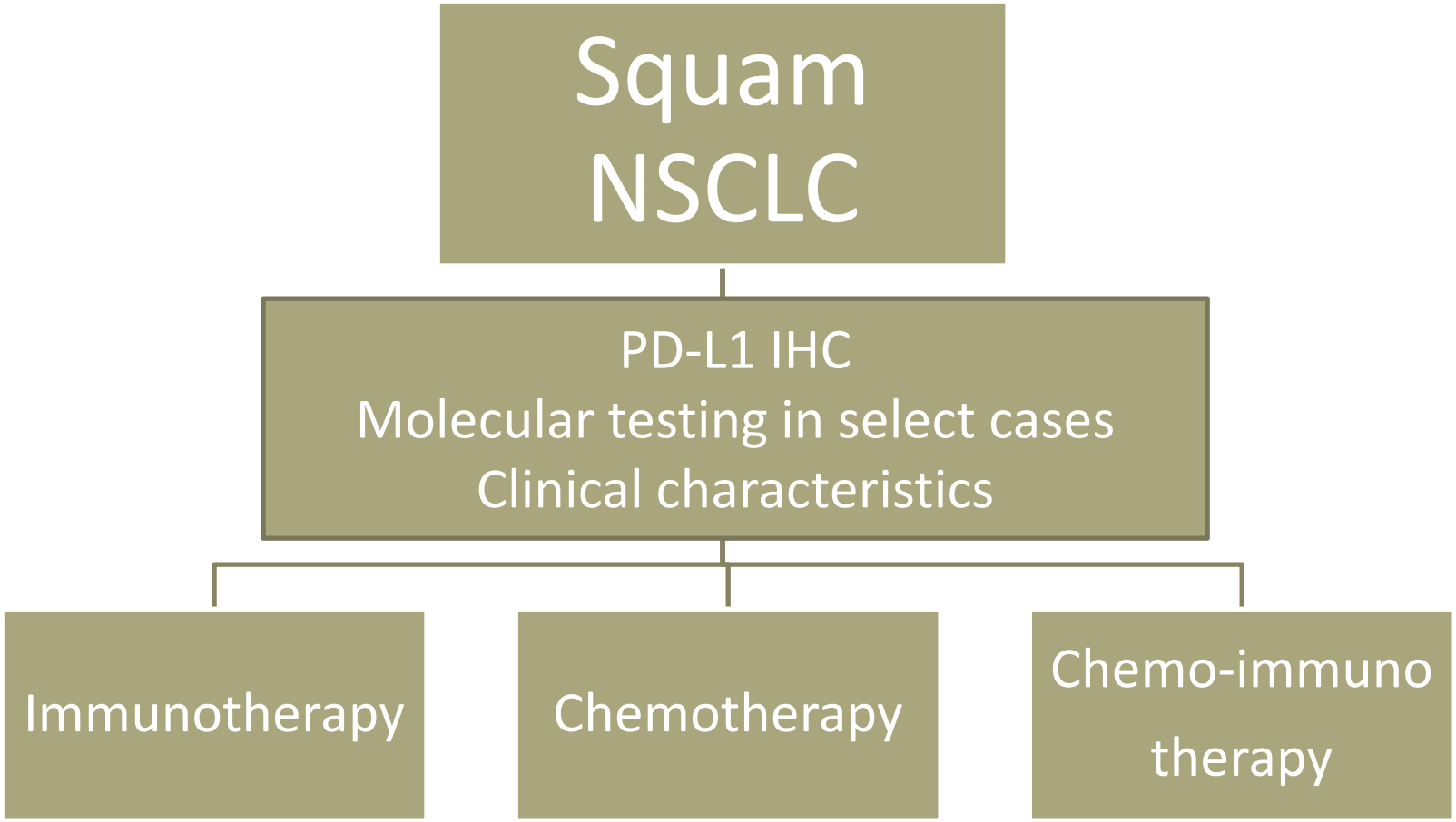
Outline

- Targeted therapy
- Immune checkpoint inhibitor therapy
  - Monotherapy
  - Chemo-immunotherapy
- Chemotherapy


Non-squam NSCLC
PD-L1 IHC
Molecular testing
Clinical characteristics
Targeted therapy
Immuno-therapy
Chemo-immunotherapy
Chemotherapy

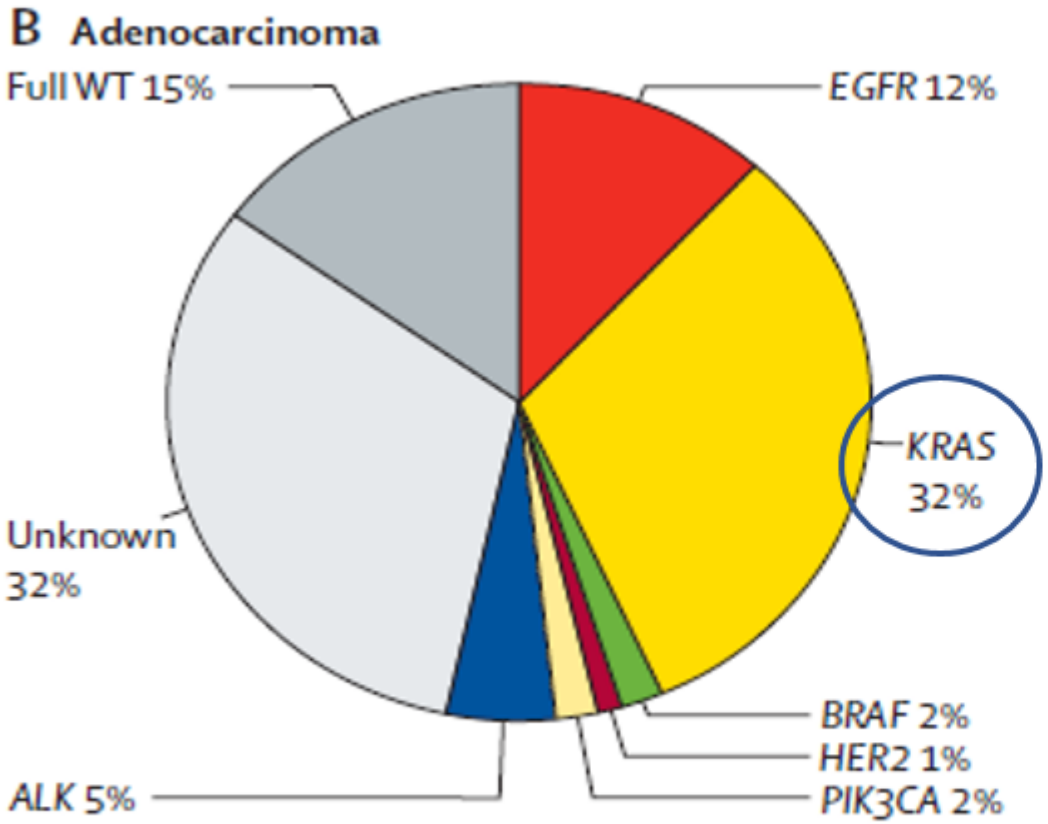

Squam NSCLC
PD-L1 IHC
Molecular testing in select cases
Clinical characteristics
Immunotherapy
Chemotherapy
Chemo-immuno therapy

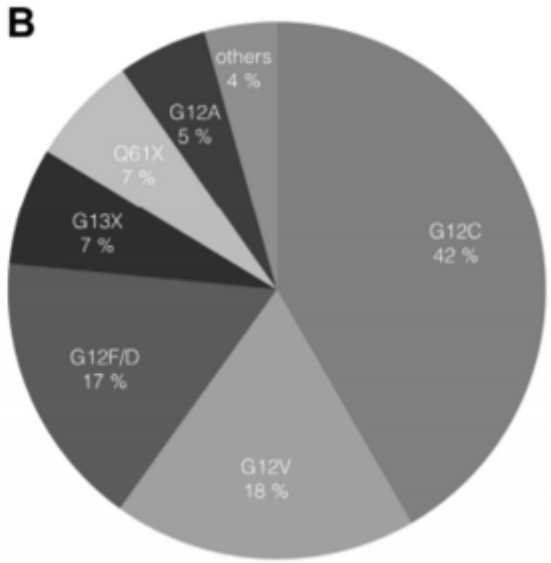
TARGETED THERAPY

Actionable molecular subtypes in lung adenocarcinoma (i.e. available FDA approved drugs in June 2021)

Alteration	Prevalence (estimates)
EGFR mutations, non-exon20 ins	15-20%
EGFR exon 20 ins	2-3%
KRAS G12C	10-13%
ALK rearrangement	3-5%
ROS1 rearrangement	1-2%
BRAF V600E mutation	1-2%
NTRK rearrangement	<1%
MET exon 14 skipping mutation	3-4%
RET rearrangement	1-2%

KRAS G12C





KRAS G12C: App 10-13% of all NSCLC

Barlesi et al. Lancet 2016;387:1415-26 Hong et al. NEJM 2020;383:1207 Scheffler et al. JTO 2019; 14(4):606-616

KRAS G12C

- No targeted therapies for KRAS despite decades of investigation in KRAS (lack of an ideal small molecule binding pocket, high GTP affinity)
- New development in G12C
  - Glycine → cysteine mutation favors GTP-bound KRAS (active conformation)
  - Discovery of a "switch-II pocket" at GDP-inactive state near cysteine residue
  - Several G12C inhibitors under investigation: Covalently binds to cysteine and switch-II pocket → maintains in the inactive GDP-bound conformation

Hong et al NEJM 2020;383:1207 Nagasaka et al. Cancer Treatment Reviews 84 (2020) 101974

The NEW ENGLAND JOURNAL of MEDICINE

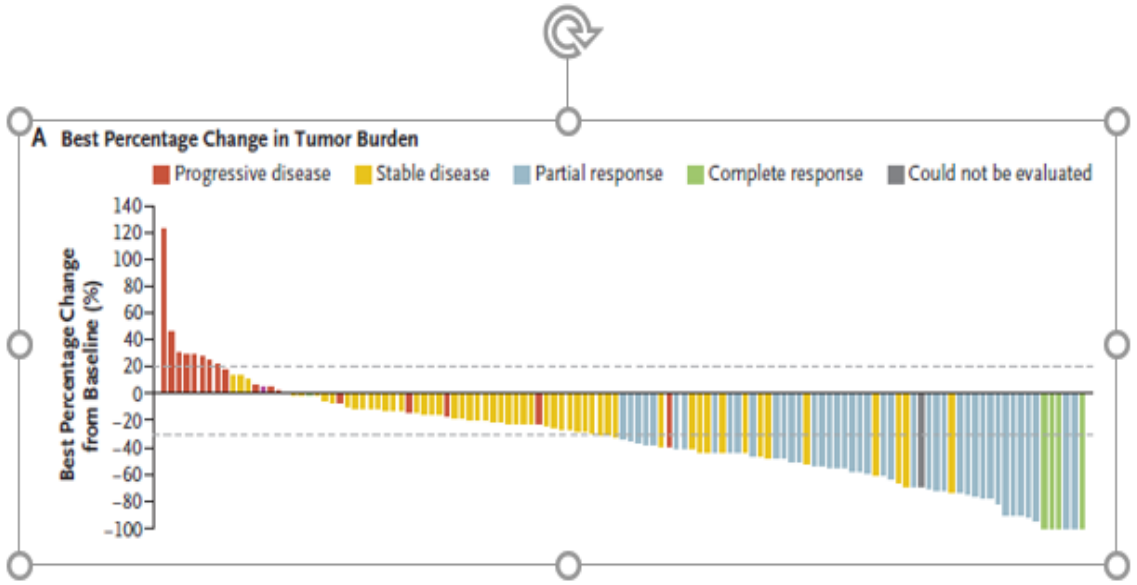
ORIGINAL ARTICLE

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

Table 2. Tumor Response to Sotorasib Therapy According to Independent Central Review.*

Variable	Patients (N = 124)
Objective response — % (95% CI)†	37.1 (28.6–46.2)
Disease control — % (95% CI)‡	80.6 (72.6–87.2)
Best response — no. (%)	
Complete response	4 (3.2)
Partial response	42 (33.9)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
Could not be evaluated	2 (1.6)
Missing scan	2 (1.6)
Median duration of objective response (95% CI) — mo§	11.1 (6.9–NE)

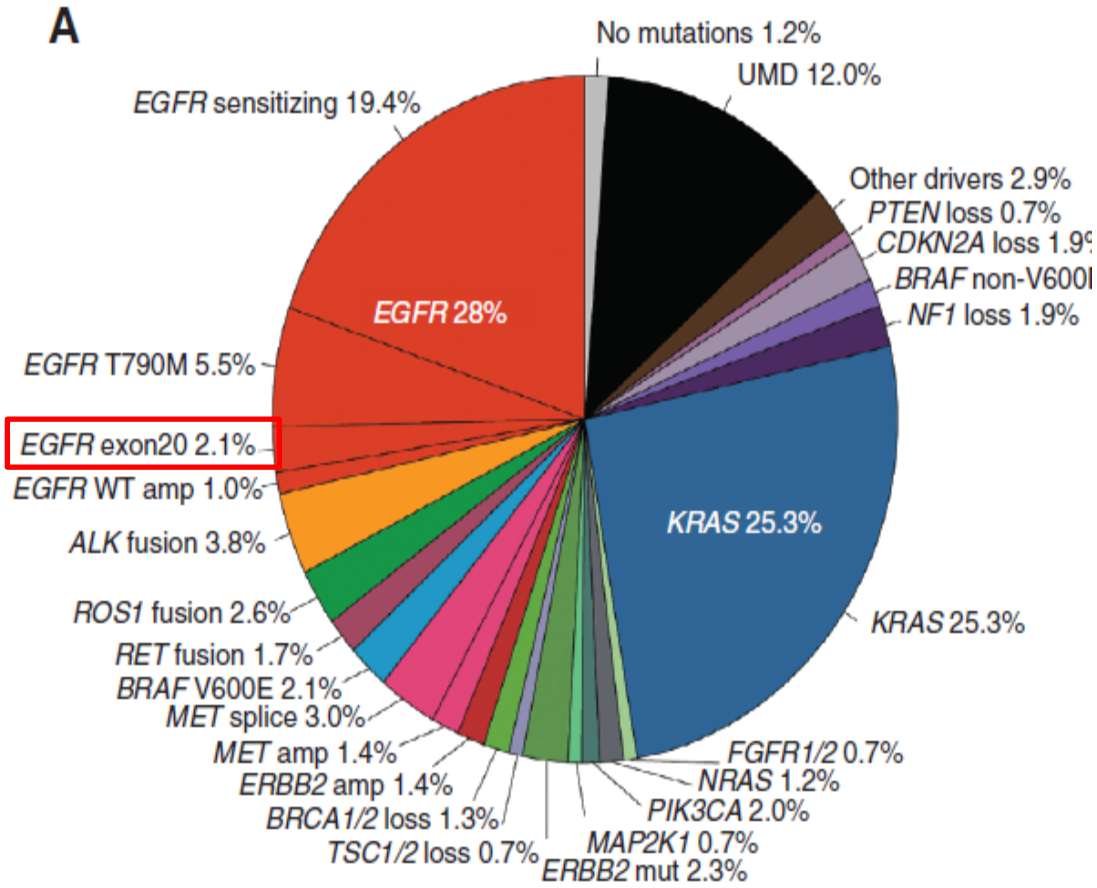


Skoulidis et al. NEJM June 2021

KRAS G12C

- Several G12C inhibitors in development
  - Adagrasib / MRTX849 (n=79): RR 45%, DCR 96% (Janne *et al*. LBA-03. EORTC-NCI-AACR, Oct 2020)
- Combinations are being evaluated: MEK inhibitor, immune checkpoint inhibitor, SHP2 inhibitor, chemotherapy, etc
- What about non-G12C? Various approaches being evaluated (select):
  - MEK inhibition with SHP2 inhibition (NCT03989115)
  - FASN (Fatty acid synthase) inhibitor, TVB-2640 (NCT03808558)
  - panKRAS inhibitor, BI1701963 (NCT04111458)
  - Cancer vaccines

EGFR exon 20 insertion



Amivantamab FDA approved in May 2021

Bispecific antibody (IV) to EGFR and MET

RR % (95% CI)	mPFS, mos (95% CI)	DOR, mos (95% CI)
40 (29-51)	8.3 (6.5-10.9)	11.1 (6.9-NR)

Toxicities (%)	
Rash	86
Infusion reaction	66
Paronychia	45
Hypoalbuminemia	27
Edema	18

Jordan et al. Cancer Discovery 2017; 7(6):596-609 Sabari et al. WCLC 2021

MET exon14 skipping mutation

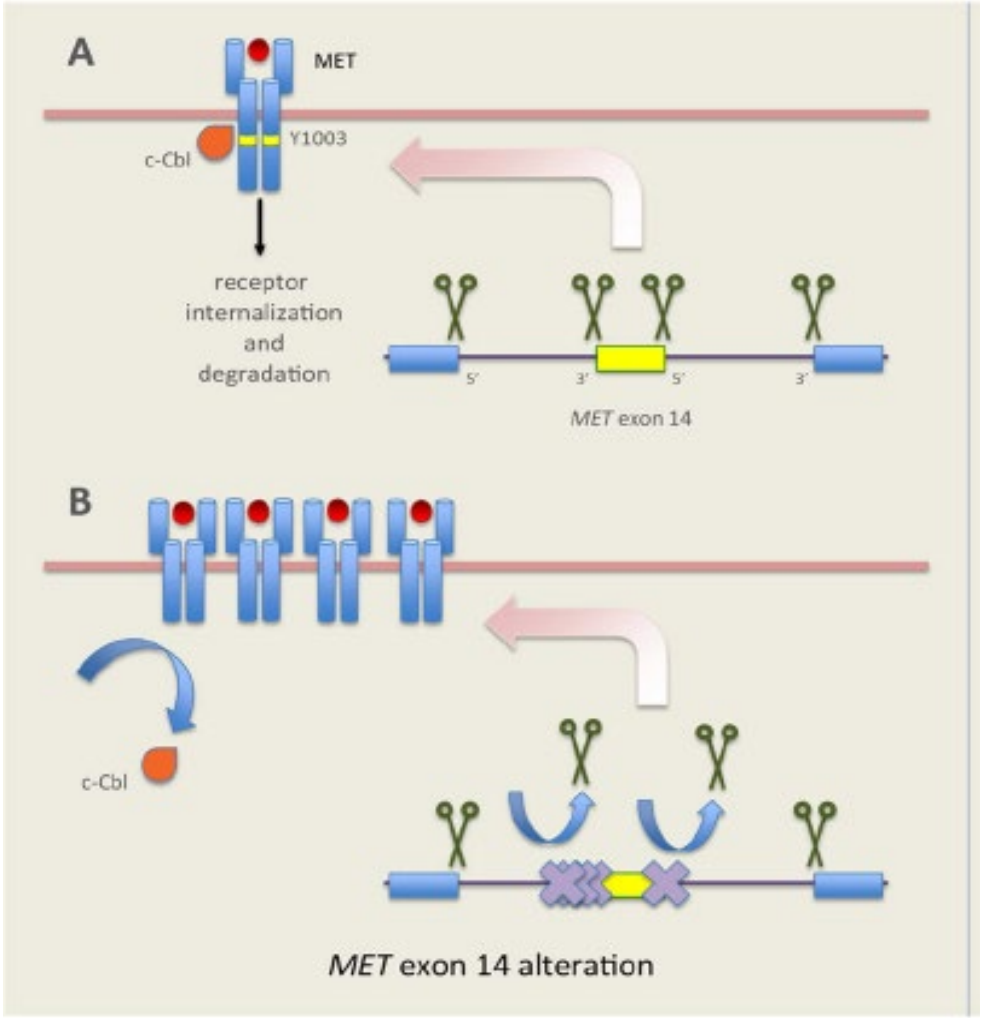
Clinical characteristics

- 3-4% of NSCLC
- Older patients
- Often observed in patients with smoking history
- Present in 20-30% of sarcomatoid histology

Characteristic	*MET* Exon 14 (n = 28)
Median age (range), years	72.5 (59-84)
Sex	
Male	9 (32)
Female	19 (68)
Smoking history, pack-years*	
Never-smoker	10 (36)
≤ 10	3 (11)
> 10	15 (53)
Race	
White, non-Hispanic	28 (100)
Asian	0 (0)
Black	0 (0)
White, Hispanic	0 (0)
Unknown	0 (0)
Histology	
Adenocarcinoma	18 (64)
Pleomorphic with adenocarcinoma component	4 (14)
NSCLC, poorly differentiated	5 (18)
Squamous	0 (0)
Adenosquamous	1 (4)

Drilon et al. JTO 2017; 12(1):15-26
Awad et al. JCO 2016; 34:721-730

MET exon14 skipping mutation



Drilon et al. JTO 2017;12(1): 15-26

- cMET: Transmembrane receptor tyrosine kinase
- Binding to ligand results in receptor activation and cell survival and proliferation
- cMET is degraded when c-Cbl binds to exon 14 region and results in ubiquitination
- In MET exon14 skipping (splice) mutation, there is abnormal splicing resulting in skipping of exon 14 which is the site of c-Cbl binding → less degradation and sustained cMET activation

MET inhibitor: Capmatinib

	Previously treated (n=69)	Treatment naïve (n=28)
ORR % (95% CI)	41 (29-53)	68 (48-84)
DCR % (95% CI)	78 (67-87)	96 (82-100)
DOR months (95% CI)	9.7 (5.6-13)	12.6 (5.6-NE)

ORR, overall response rate;
DCR, disease control rate; DOR, duration of response

Several other MET inhibitors under investigation: e.g. savolitinib

Most common treatment related AEs (≥10%, all grades), n (%)	All Patients N = 334	
	All Grades	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea*	111 (33.2)	6 (1.8)
Increased blood creatinine†	65 (19.5)	0
Vomiting*	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Decreased appetite*	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

Garon et al. CT082 AACR 2020

MET inhibitor: Tepotinib

Patient characteristics (n=99)

Median age: 74 (41-94)

45% never smokers

	Both tx naïve/prev treated
Overall response %	46 (36-57)
Disease control rate %	89
DOR, mos	11 (7.2-NE)
CNS response %	55 (23-83), n=11

Most common treatment related Aes (%)		
	All	Grade 3 / 4
Peripheral edema	63	7
Nausea	26	1
Diarrhea	22	1
Elevated creatinine	18	1
Hypoalbuminemia	16	2
Amylase increase	11	2
Lipase	9	3

Paik et al. NEJM 2020; 383(1):931-943

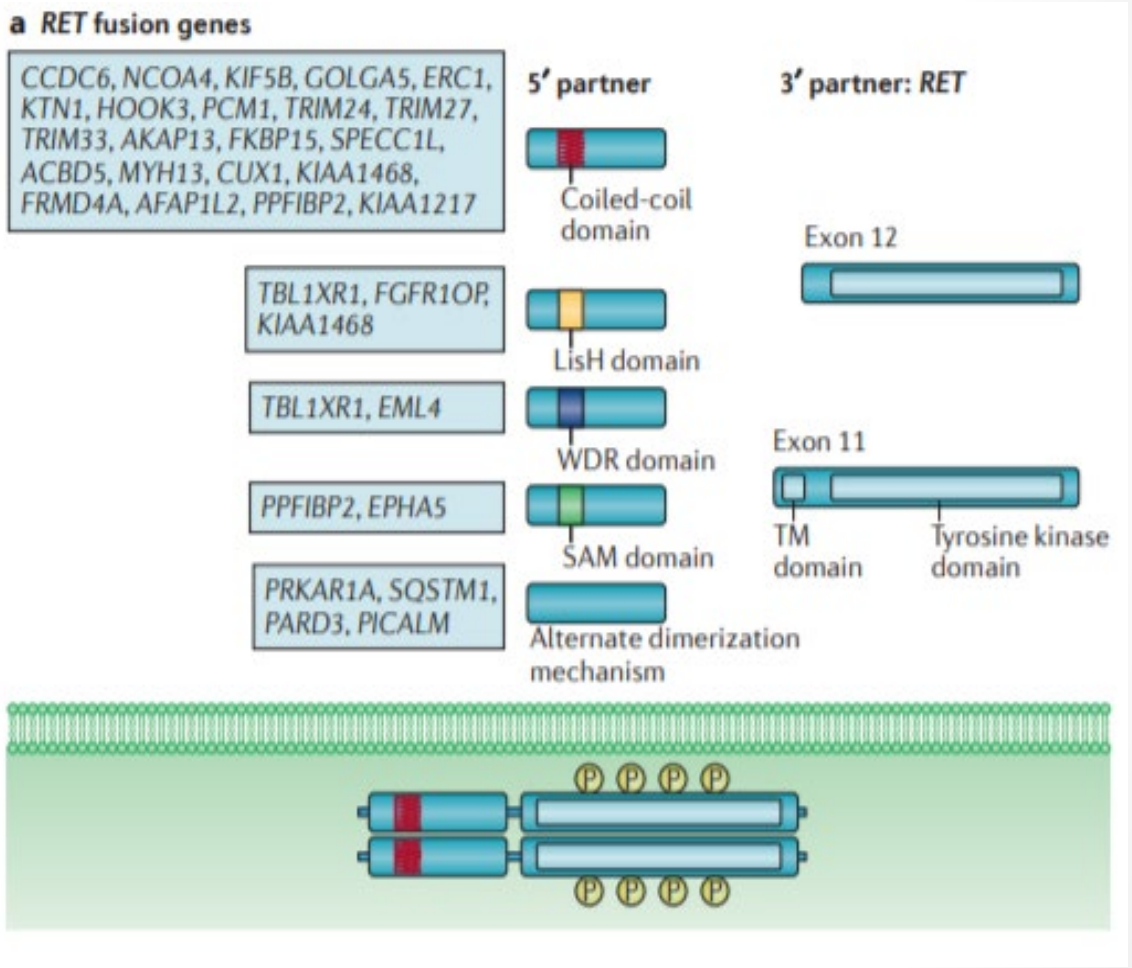
RET rearrangement

Clinical characteristics

- 1-2% of all NSCLC
- Mostly seen in never / minimal smokers

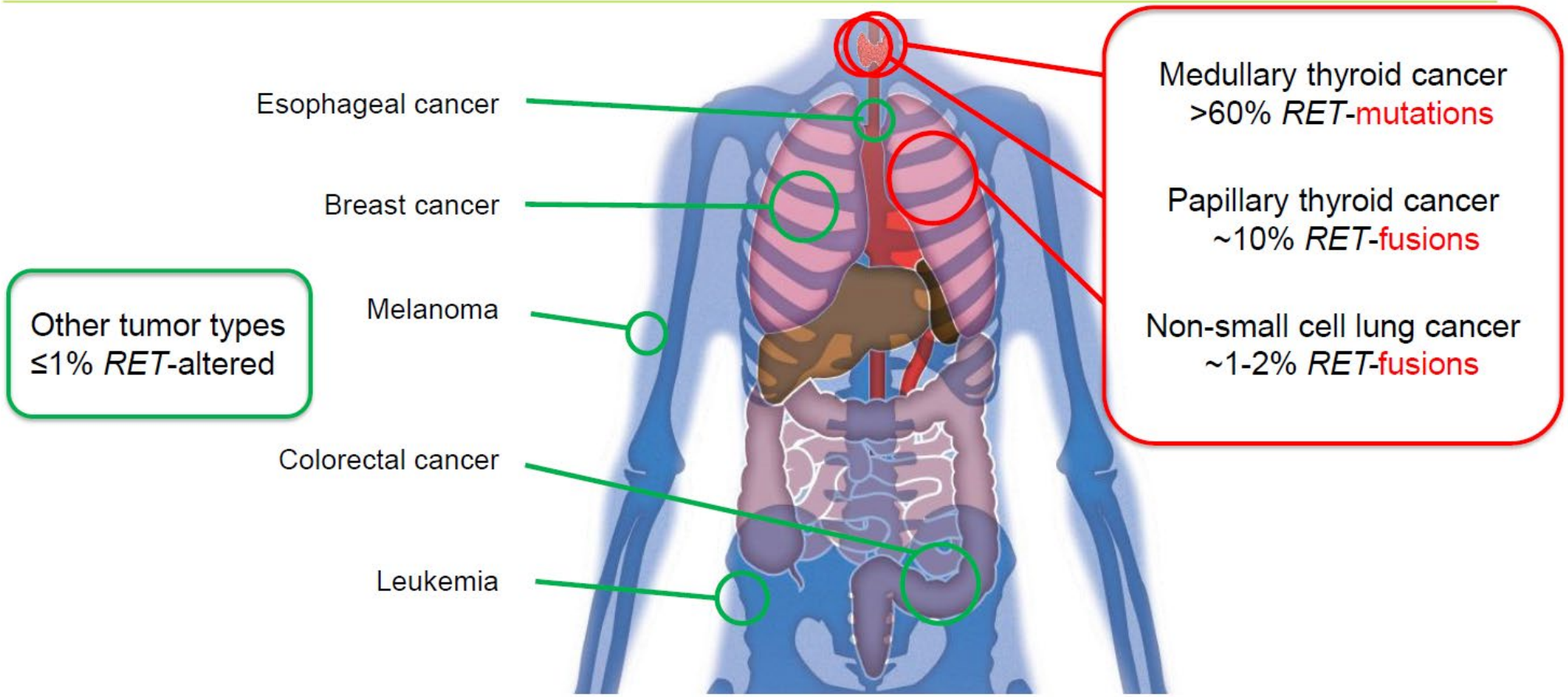
Mechanism of action

Receptor protein fuses with partner protein, inducing dimerization and activation



Drilon et al. Nat Rev Clin Onc 2018; 15:151

RET is a rare driver of multiple, diverse tumor types[1,2]



1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67 2.Kato S, et al. *Clin Cancer Res* 2017;23:1988-1997.

Subbiah et al. AACR 2018

Selective RET inhibitors

	Selpercatinib	Pralsetinib
Dose, frequency	Oral BID: >50kg 160mg, <50kg 120mg	Oral daily, 400mg
Never smoker % (in trials)	72	62
Median age (in trials)	61 (23-86)	60 (28-87)
RR %, treatment naive	85 (70-94), n=34	66 (46-82), n=29
RR %, previously treated	64 (54-73), n=105	65 (55-73), n=92
Disease control rate %	93	90
Progressive disease as best response %	4	4
Duration of response, mos	17.5 (12-NR) in prev treated	NR (11.3-NR) overall
CNS RR %	91 (59-100), n=11	56, n=9
Adverse events, ≥grade 3	Hypertension (14%) Transaminitis (12-14%) Lymphopenia (6%)	Hypertension (10%) Neutropenia (10%) Anemia (8%)
Drug discontinuation rate %	2	4

Drilon et al. NEJM 2020; 383(9):813-824 Gainor et al. ASCO 2020. Abs 9515

EGFR mutation+ NSCLC

- 10-15% NSCLC
- More common in never smoker, Asians, women
- Most common mutations: Exon 19 deletion and exon 21 L858R

FDA approved EGFR TKIs		
1st generation	2nd generation	3rd generation
Erlotinib (+/- ramucirumab)	Afatinib	Osimertinib
Gefitinib	Dacomitinib	

General principles

- TKI treatment is superior to platinum doublet in the first line setting
- Efficacy of 1st and 2nd gen TKIs are similar, although PFS with dacomitinib higher
- Using a 2nd gen TKI after a 1st gen TKI is not effective
- 50-60% of patients develop T790M resistance mutation after 1st and 2nd gen TKIs

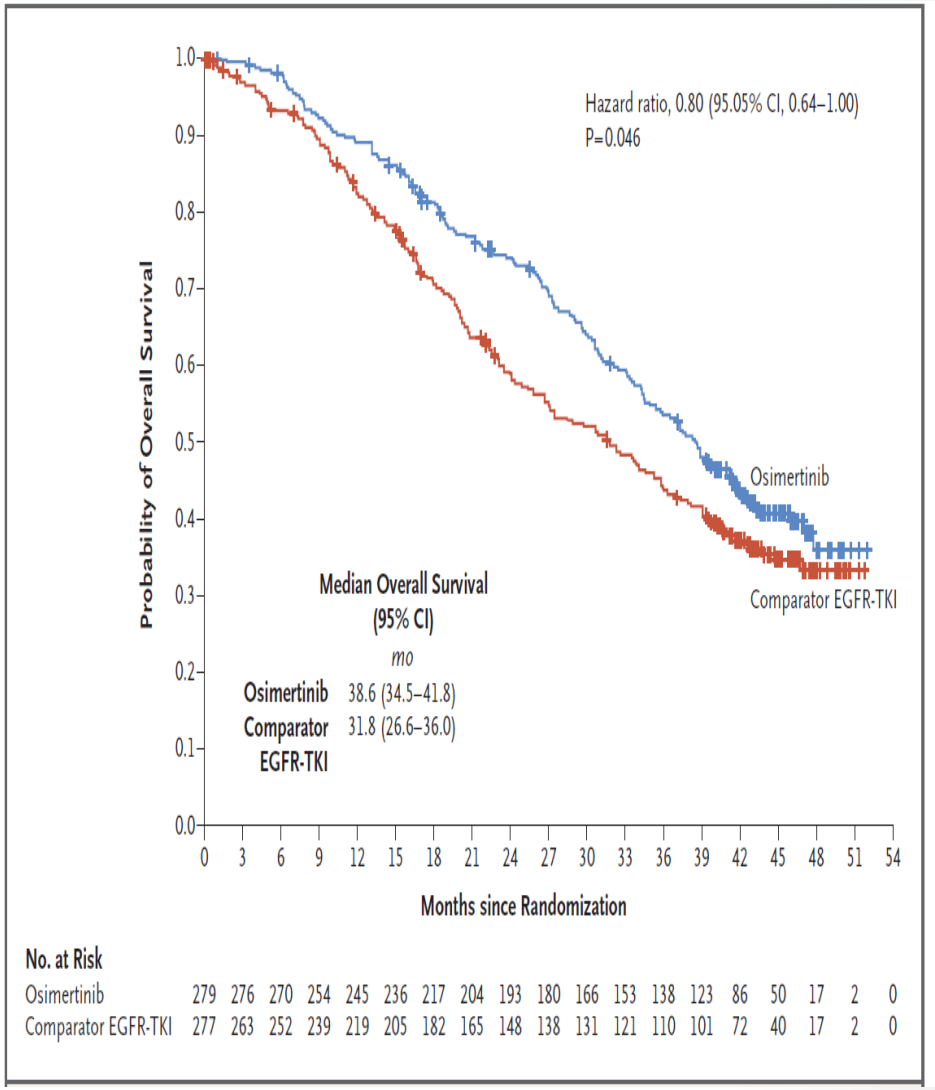
→ Only active FDA approved drug that is active against T790M is osimertinib

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Overall Survival with Osimertinib in Untreated, *EGFR*-Mutated Advanced NSCLC

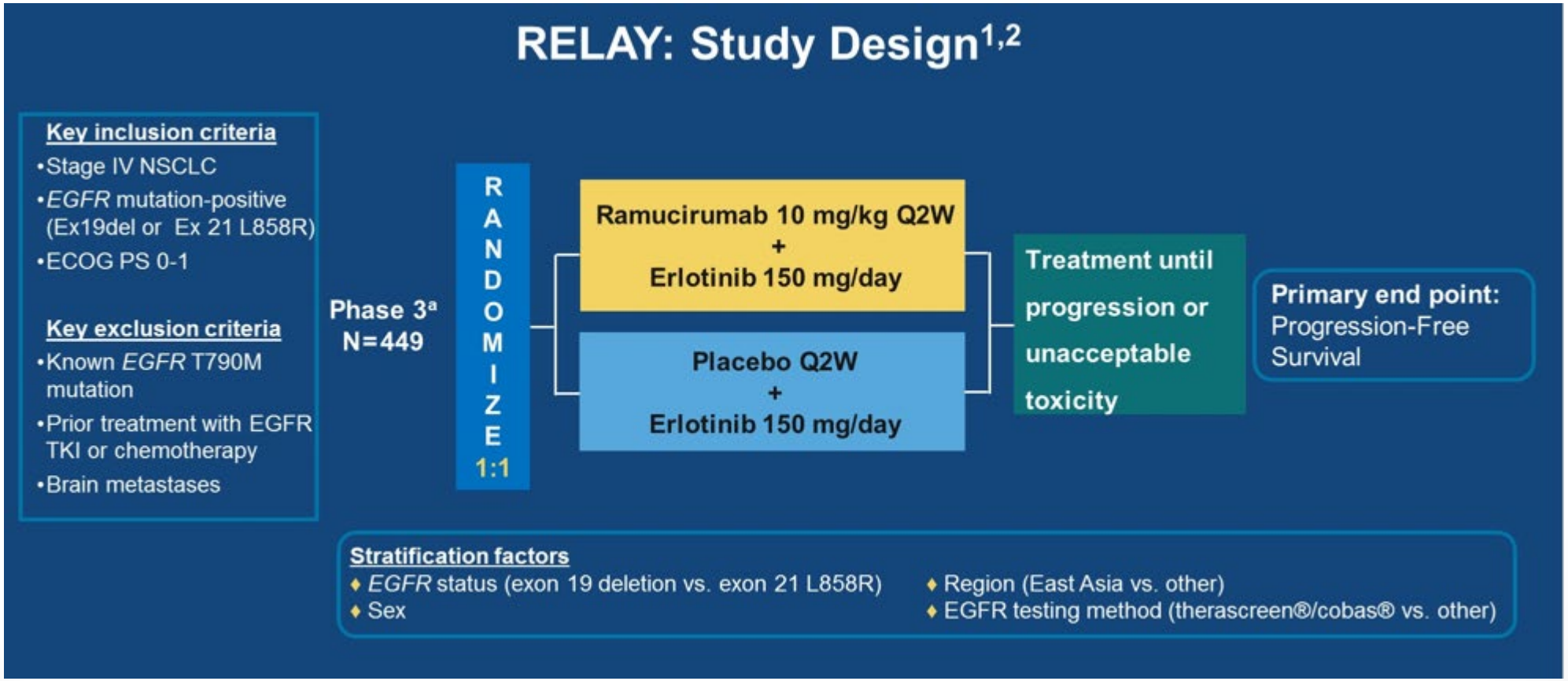
S.S. Ramalingam, J. Vansteenkiste, D. Planchard, B.C. Cho, J.E. Gray, Y. Ohe, C. Zhou, T. Reungwetwattana, Y. Cheng, B. Chewaskulyong, R. Shah, M. Cobo, K.H. Lee, P. Cheema, M. Tiseo, T. John, M.-C. Lin, F. Imamura, T. Kurata, A. Todd, R. Hodge, M. Saggese, Y. Rukazenkov, and J.-C. Soria, for the FLAURA Investigators*



Ramalingam *et al*. NEJM 2020; 382(1);41-50

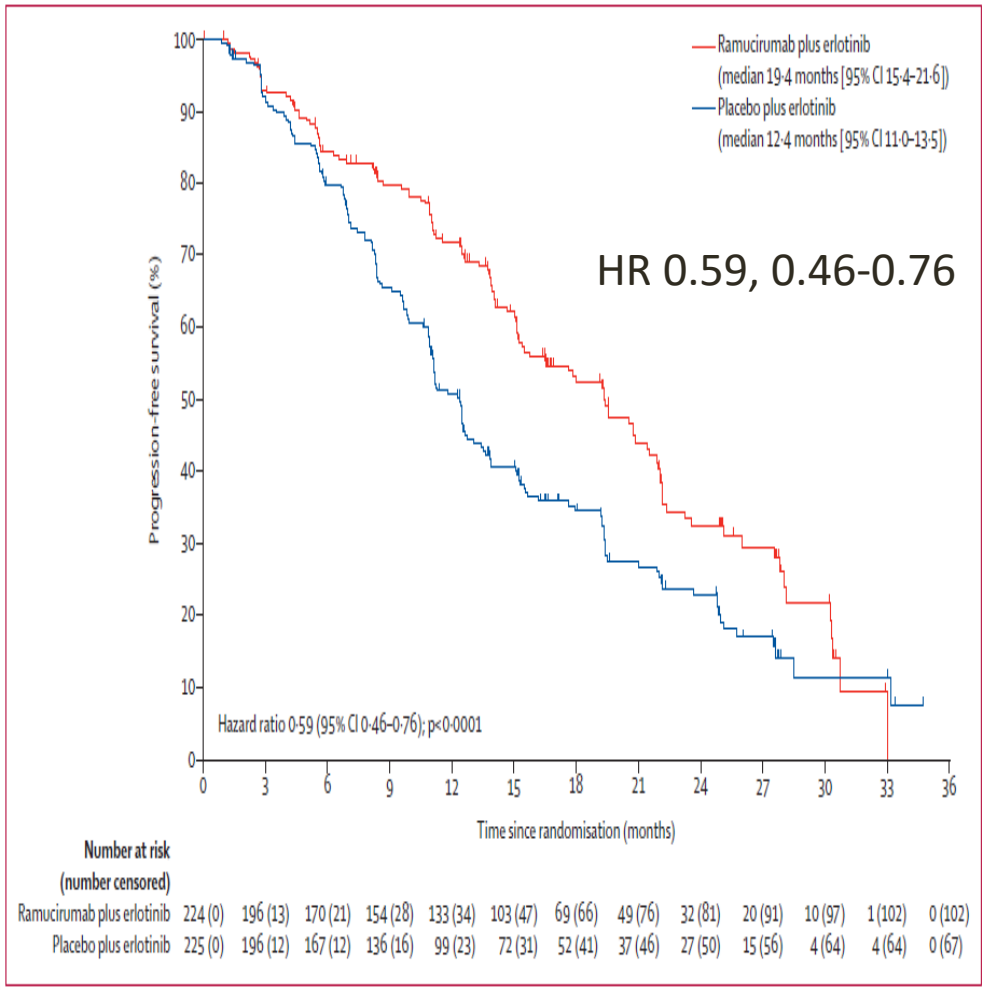
Erlotinib + ramucirumab

Erlotinib and ramucirumab FDA approved in May 2020



Nakagawa *et al.* RELAY. Lancet Oncol 2019;20:1655-1669

Erlotinib + ramucirumab



	Ram + E	Placebo + E
PFS (mos)	19.4 (15.4-21.6)	12.4 (11-13.5)
ORR %	76 (71-82)	75 (69-80)
DCR %	95 (92-98)	96 (93-98)
DOR (mos)	18 (13.9-19.8)	11.1 (9.7-12.3)

- Overall survival data immature
- There is a similar trial with bevacizumab which showed similar PFS benefit but no OS benefit (NEJ026, Maemondo et al. Abs 9506. ASCO 2020)

Nakagawa *et al.* RELAY. Lancet Oncol 2019;20:1655-1669

EGFR summary

- First line options:
  - Osimertinib upfront (has become the preferred approach in US)
  - Erlotinib +/- ramucirumab (no CNS met), afatinib, dacomitinib, gefitinib → osimertinib if T790M+ (about 50%)
- EGFR exon 20 insertion generally NOT sensitive to the above TKIs (trials ongoing with exon 20 targeting TKIs)
- Post-osimertinib:
  - Most of these patients will need chemo
  - Consider trial participation (Emerging resistance mechanisms: MET amplification, HER2 amplification, C797X mutation, etc)

ALK rearranged NSCLC

FDA approved ALK inhibitors		
1st generation	2nd generation	3rd generation
Crizotinib	Alectinib	Lorlatinib
	Ceritinib	
	Brigatinib	

General principles

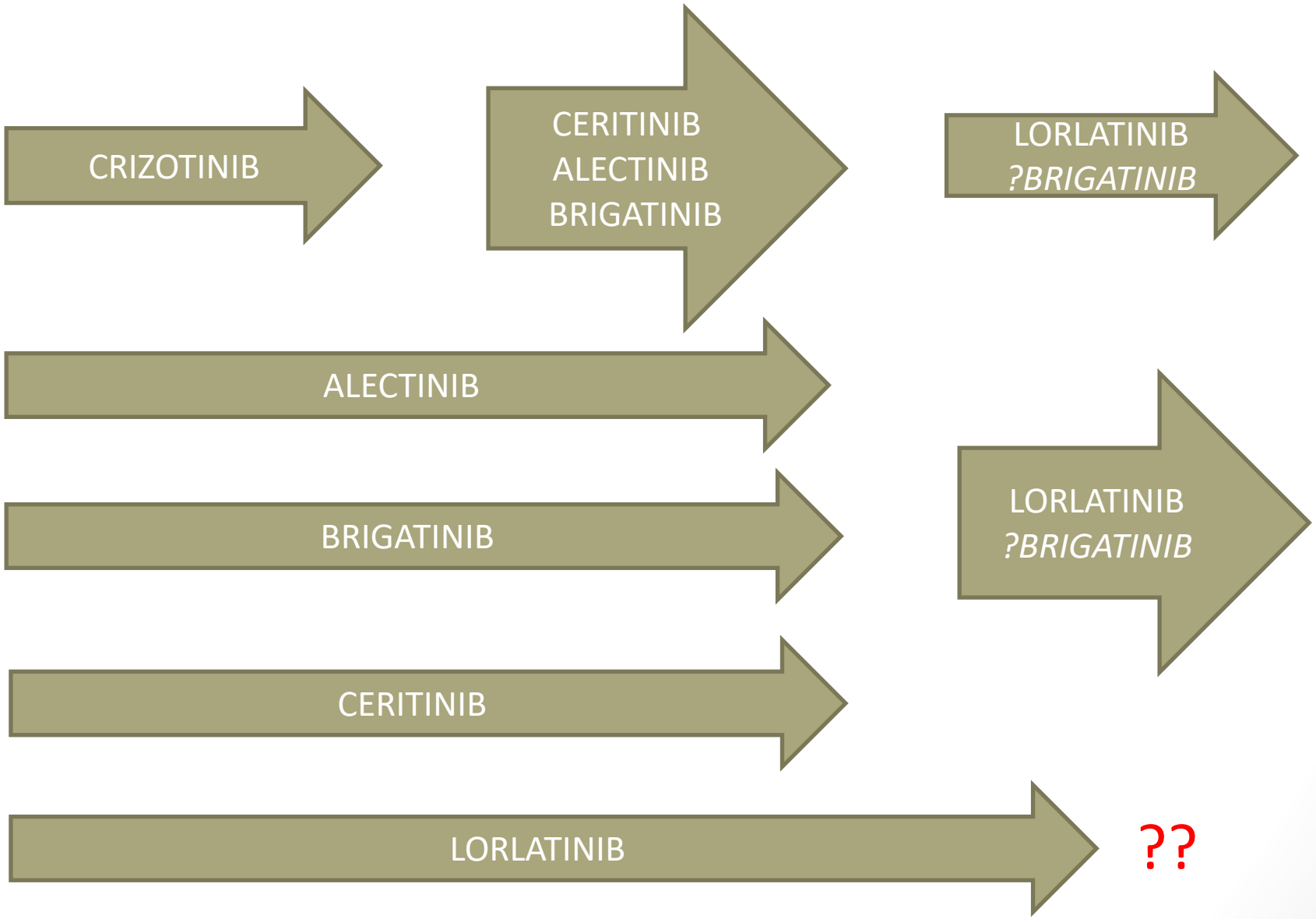
- Second generation TKIs are active after crizotinib but unclear if active after another 2nd gen TKI (although there is some data for brigatinib after alectinib)
- Lorlatinib active after crizotinib and modestly active after second generation TKIs
- All of the above TKIs are approved as first line therapy

ALK first line therapy

Drug	Progression free survival (median, mos)
Crizotinib (1)	10.9
Ceritinib (2)	16.6
Alectinib (3,4)	~ 35
Brigatinib (5,6)	~24-29
Lorlatinib (7)	Not reached

(1) Solomon *et al*. NEJM 2014; 371: 2167-2177
(2) Soria *et al*. Lancet 2017;389:917-29
(3) Peters *et al*. NEJM 2017. DOI: 10.1056/NEJMoa1704795
(4) Camidge *et al*. JTO 2019; 14(7): 1233-1243
(5) Camidge *et al*. DOI: 10.1056/NEJMoa191071
(6) Camidge et al. Doi.org/10.1200/JCO.20.00505
(7) Shaw et al. Doi.org/10.1056/NEJMoa2027187

ALK therapy: Optimal sequence?



Toxicities

CRIZOTINIB	CERITINIB	ALECTINIB	BRIGATINIB	LORLATINIB
Diarrhea	Diarrhea	Myalgia	Diarrhea	Increased cholesterol / triglyceride
Nausea	Nausea	Constipation	HTN	Peripheral edema / neuropathy
Visual changes	Abdominal cramps	Peripheral edema / Weight gain	Early pulmonary toxicity (uncommon)	Cognitive changes (usually mild)

ROS1 rearranged NSCLC

- First line options: Crizotinib, Entrectinib, (Ceritinib – off label)
  - Entrectinib and ceritinib not active in crizotinib pre-treated (different from ALK in which ceritinib is active after crizotinib)
- Lorlatinib active after crizotinib but not FDA approved (ORR 26.5, 12.9-44.4; median PFS 8.5mos)

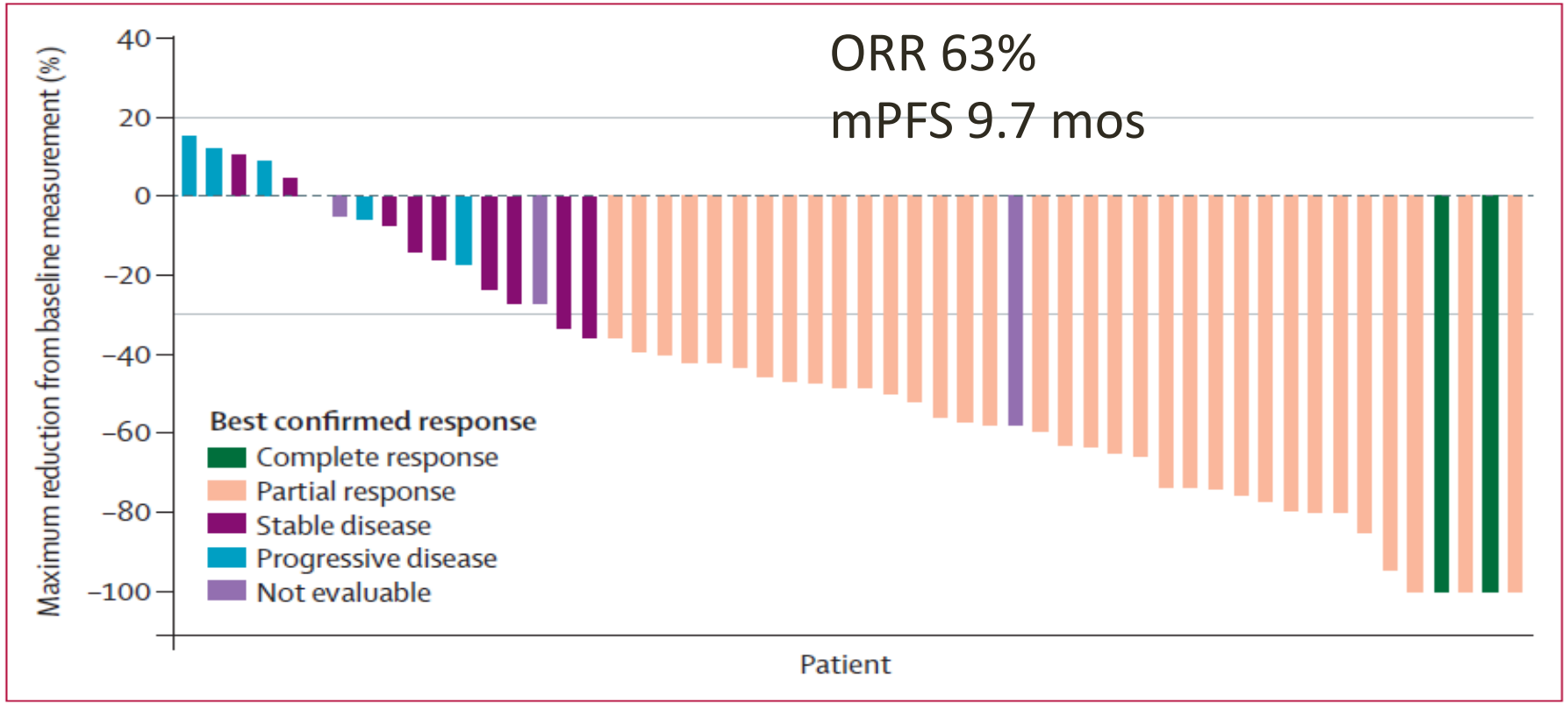
	RR, %	PFS, mos	CNS RR
Crizotinib (n=50)	72 (58-84)	19.2 (14.4-NR)	N/A
Entrectinib (n=53)	77.4 (64-88)	19.0 (12.2-36.6)	79% (n=19)

Shaw et al. NEJM 2014; 371: 1963
Doebele et al. OA02.01 WCLC 2018
Ou et al. WCLC 2018
Dziadziusko et al. JCO 2021

BRAF V600E

- Occur in 1-4% of NSCLC
- Present regardless of smoking history
- Dabrafenib (BRAFi) + trametinib (MEKi) – only approved regimen

  (Planchard *et al*. Lancet Oncol 2016; 17: 984-993)



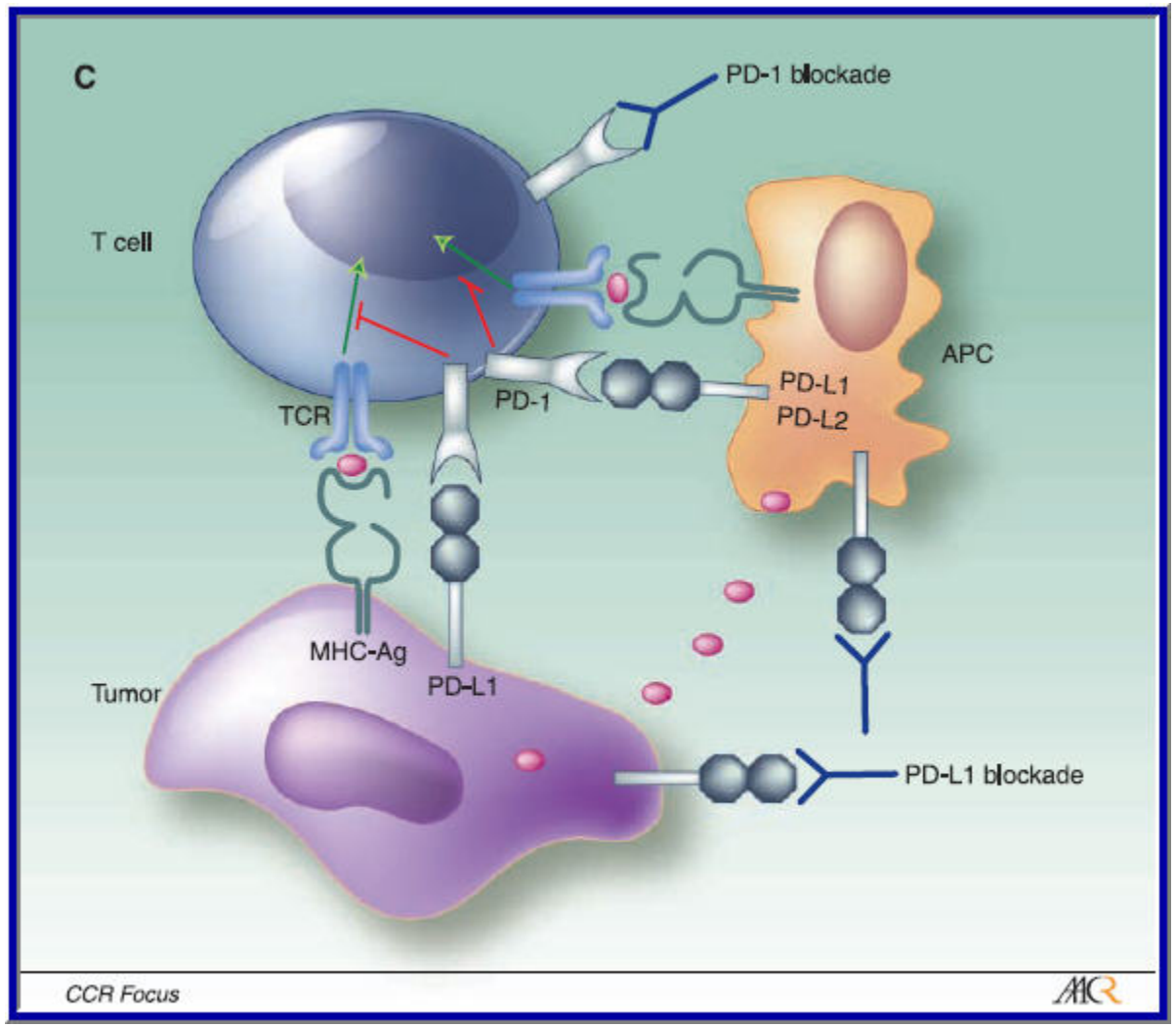
NTRK rearrangement

- NTRK+ NSCLC is rare (<1%), although not clearly characterized
  - DNA based next-generation sequencing is often used but likely limited sensitivity
  - Limited data on clinical characteristics but seen more commonly in light smokers but also observed in patients with smoking history
- Two FDA approved drugs (for all solid tumor with NTRK fusion without resistance mutations):
  - **Larotrectinib** (ORR 80%, 95% CI 61-85; PFS not reached. Drilon *et al*. NEJM 2018)
  - **Entrectinib** (ORR 57%, 95% CI 43-71; PFS 11.2 mos, 95% CI 8.0-14.9. Demetri *et al* ESMO 2018)

Targets with FDA approved drugs (as of June 2021)								
EGFR (non-exon20 ins)	**EGFR (exon20 ins)**	**ALK fusion**	**ROS1 fusion**	**BRAF V600E**	**NTRK fusion**	**MET exon14**	**RET fusion**	**KRAS G12C**
Erlotinib Gefinitb Afatinib Dacomitinib Osimertinib	Amivanta-mab (May 2021)	Crizotinib Alectinib Ceritinib Brigatinib Lorlatinib	Crizotinib Entrectinib	Dabrafenib + trametinib	Larotrectinib Entrectinib	Capmatinib Tepotinib	Selpercatinib Pralsetinib	Sotorasib (May 2021)

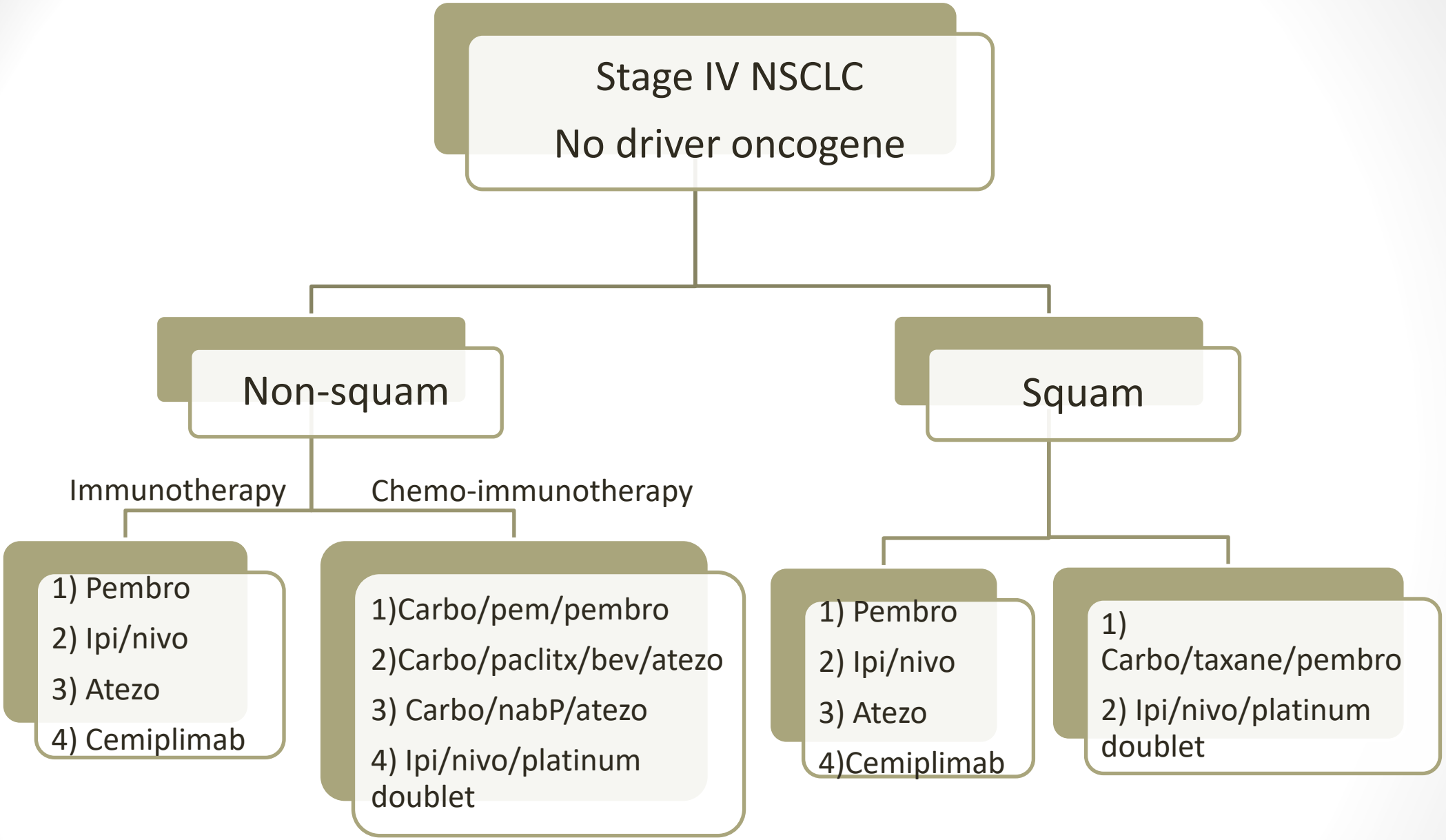
Investigational (select)			
EGFR (exon20 ins)	**HER2**	**KRAS**	**MET amplification**
Poziotinib TAK788 (mobocertinib)	Trastuzumab deruxtecan Trastuzumab emtansine Poziotinib TAK788	MRTX849 Many others	Tepotinib Capmatinib Sym015 Savolitinib

Immune checkpoint inhibitors (ICIs)



FDA approved ICIs in metastatic NSCLC

	Type of drug	First-line	Later line (post chemo)
Pembrolizumab	Anti-PD1	Monotx: ≥1% PD-L1 (IHC 22C3) With chemo: No PD-L1 requirement	≥1% PD-L1
Nivolumab	Anti-PD1	In combination with ipilimumab in ≥1% PD-L1 (IHC 28-8) With ipi and chemo: No PD-L1 requirement	No PD-L1 requirement
Atezolizumab	Anti-PD-L1	Monotx: Tumor PDL1 ≥50%, immune PD-L1 ≥10% (IHC SP142) With chemo: no PD-L1 requirement	No PD-L1 requirement
Cemiplimab	Anti-PD1	Monotx: Tumor PD-L1 >50% (IHC 22C3)	N/A
Ipilimumab	Anti-CTLA4	In combination with nivolumab in ≥1% PD-L1 (IHC 28-8)	N/A


Stage IV NSCLC
No driver oncogene
Non-squam
Squam
Immunotherapy
Chemo-immunotherapy
1) Pembro
2) Ipi/nivo
3) Atezo
4) Cemiplimab
1)Carbo/pem/pembro
2)Carbo/paclitx/bev/atezo
3) Carbo/nabP/atezo
4) Ipi/nivo/platinum doublet
1) Pembro
2) Ipi/nivo
3) Atezo
4)Cemiplimab
1) Carbo/taxane/pembro
2) Ipi/nivo/platinum doublet

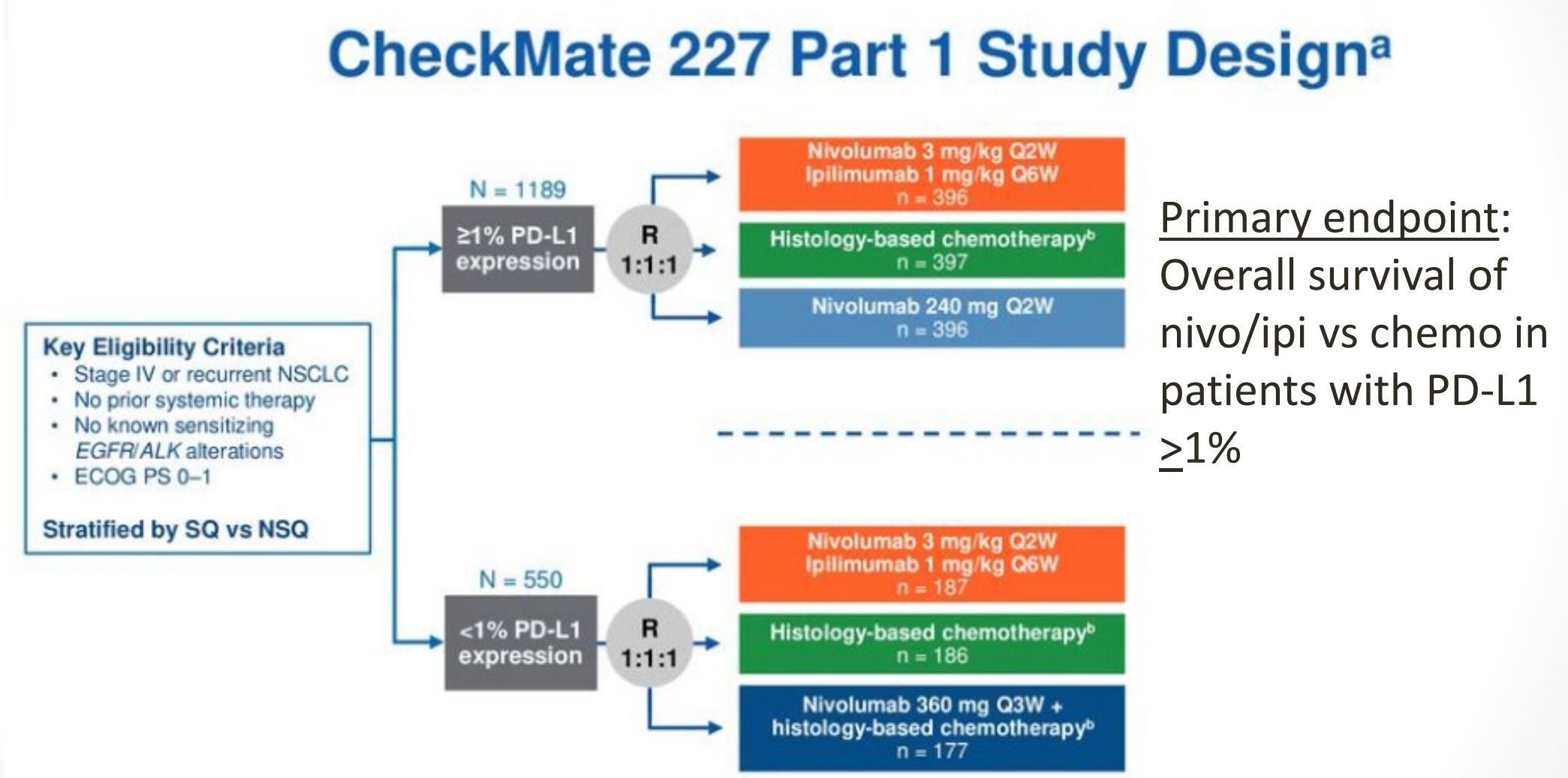
Anti-PD(L)-1 vs platinum doublet chemo

	PD-L1 (Assay)	ORR (%)	PFS (months)	OS (months)
Pembrolizumab (KN24)	≥50% (22C3)	44.8 vs 27.8	10.3 vs 6.0	30 vs 13 (HR 0.63, 0.47-0.86)
Pembrolizumab (KN42)	≥1% (22C3)	27 vs 27	5.4 vs 6.5	16.7 vs 12.1 (HR 0.81,0.71-0.93)
Atezolizumab	≥50% TC or ≥10% IC (SP142)	38.3 vs 28.6	8.1 vs 5.0	20 vs 13 (HR 0.59, 0.40-0.89)
Cemiplimab	≥ 50% (22C3)	37 v 21	6.2 v 5.6	NR vs 14 (HR 0.57,0.42-0.77)

TC, tumor cells IC, immune cells

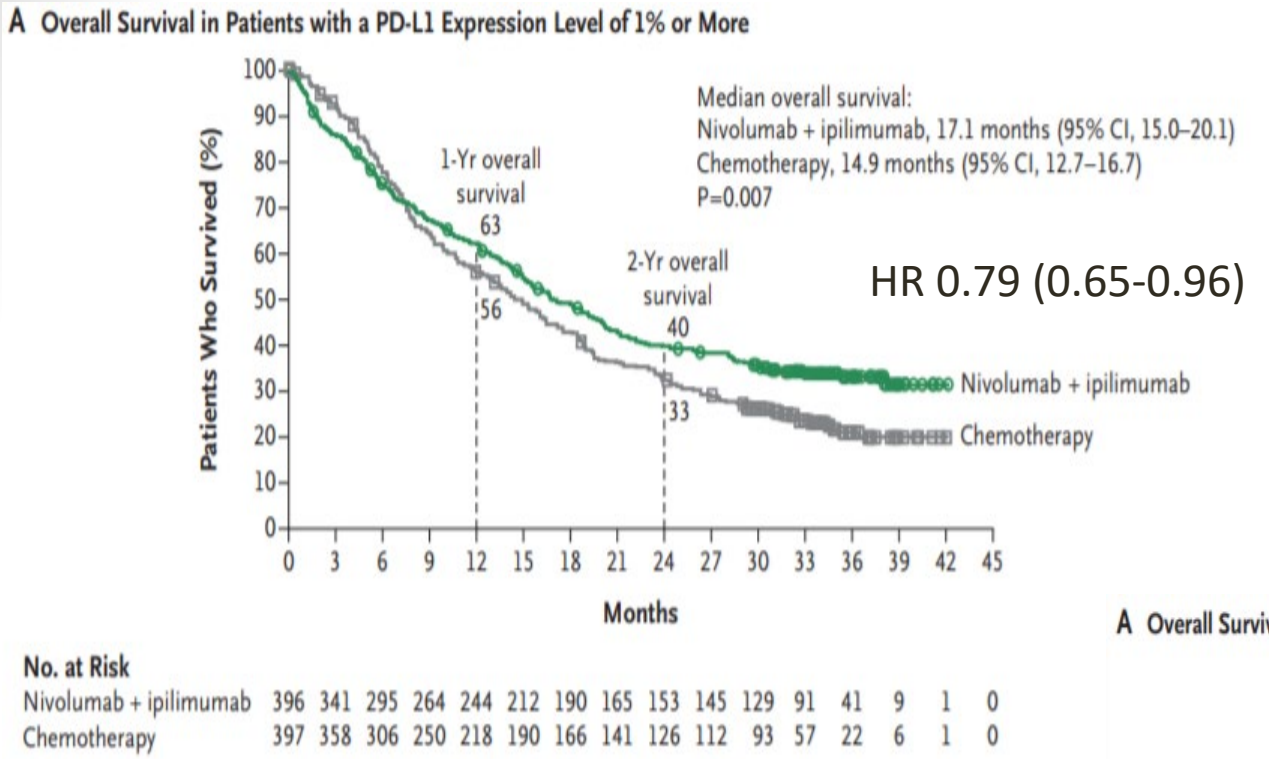
Sezer et al Lancet 2021;397:592-604 Herbst et al NEJM 383:1328-39 Reck et al. NEJM DOI:10.1056/NEJMoa1606775
Mok et al. Lancet 2019;393:1819-30

First line ipilimumab and nivolumab



Primary endpoint: Overall survival of nivo/ipi vs chemo in patients with PD-L1 ≥1%

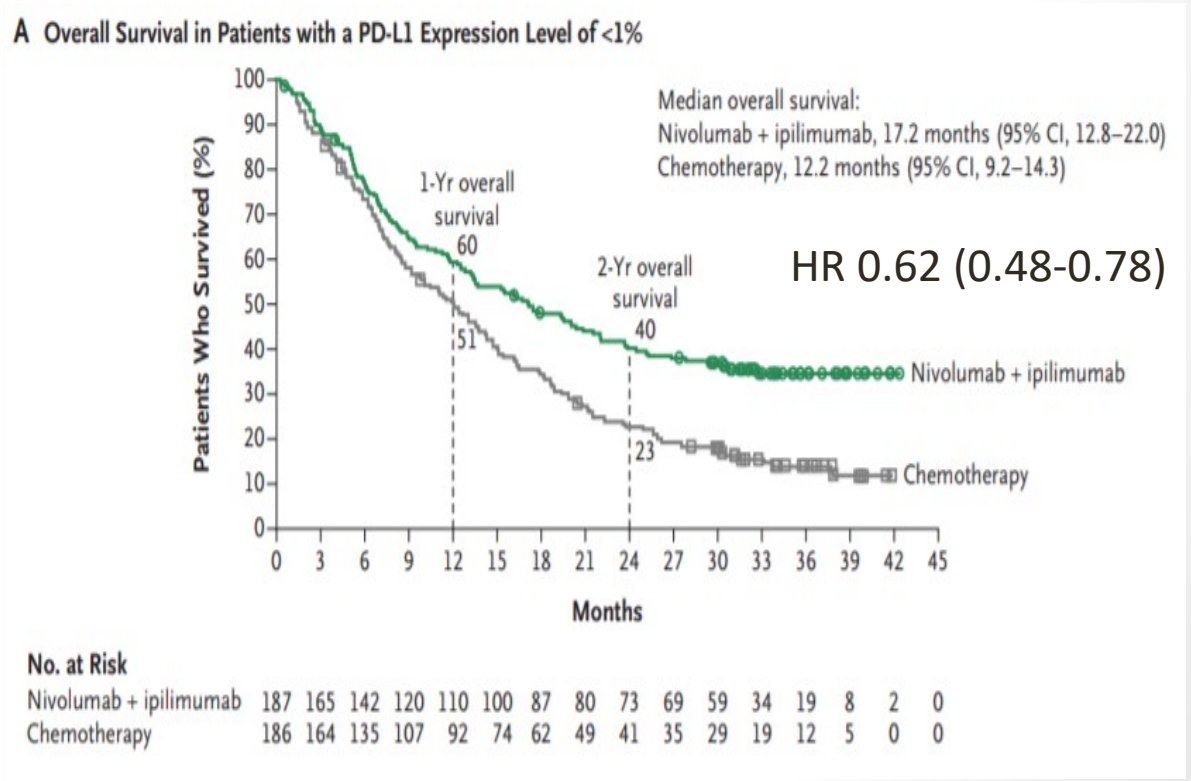
Hellmann et al. NEJM 2019; 381:21



HR 0.79 (0.65-0.96)

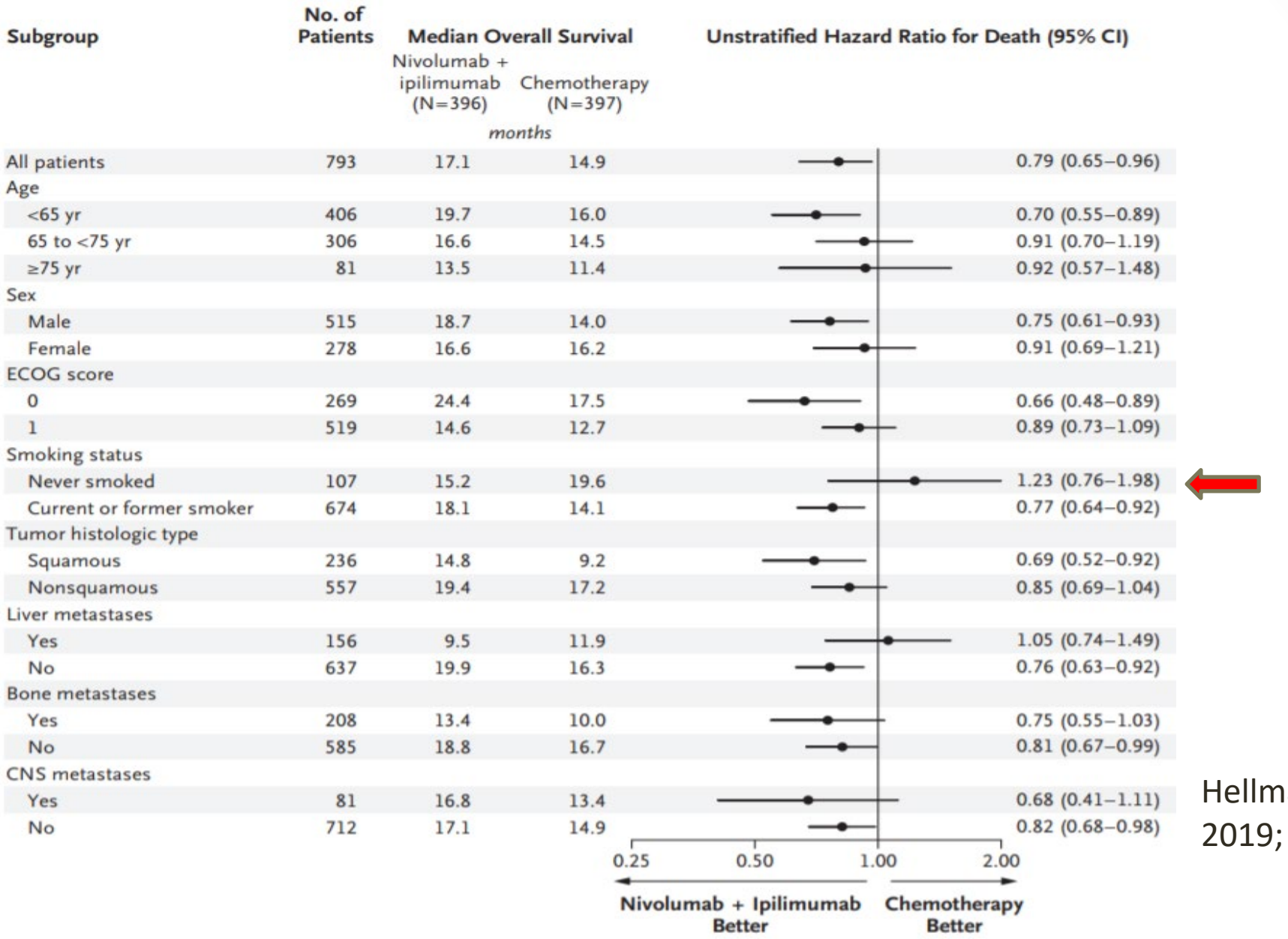
PD-L1 positive

PD-L1 negative



HR 0.62 (0.48-0.78)

Hellmann et al. NEJM 2019; 381:21



Hellmann et al. NEJM 2019; 381:21

FDA approved ipilimumab / nivolumab for NSCLC with PD-L1 >=1% (IHC 28-8) in May 2020

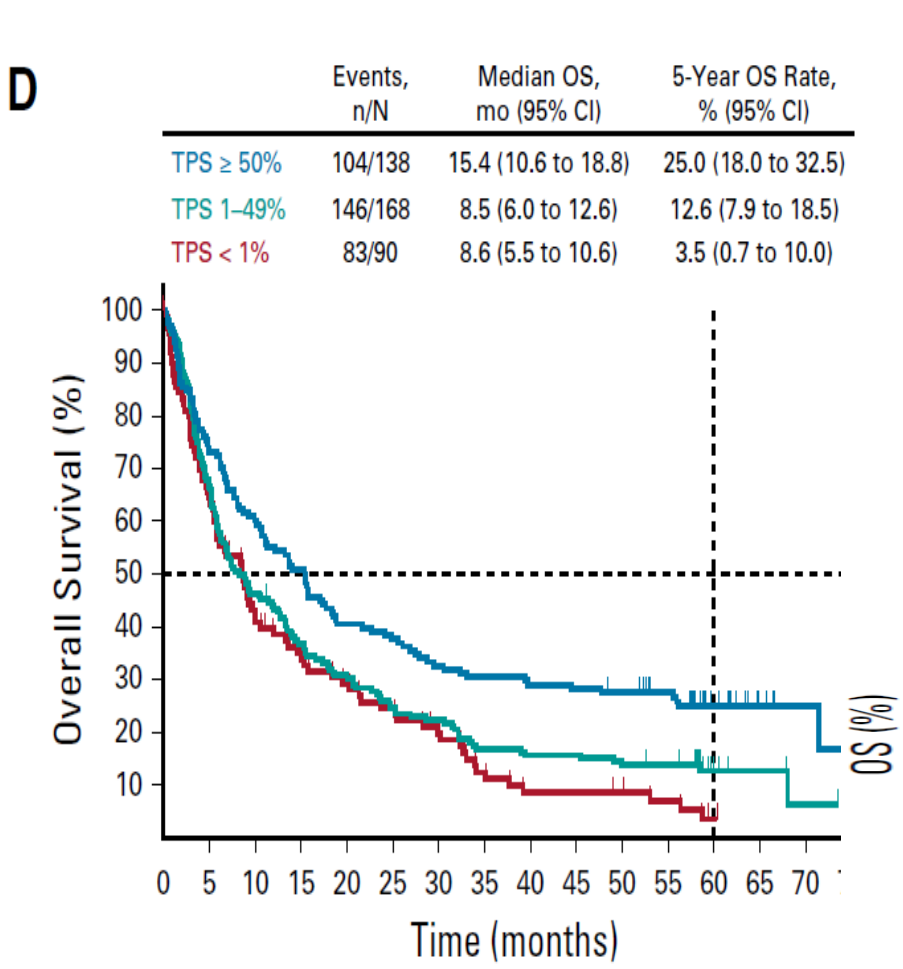
Chemo-immunotherapy

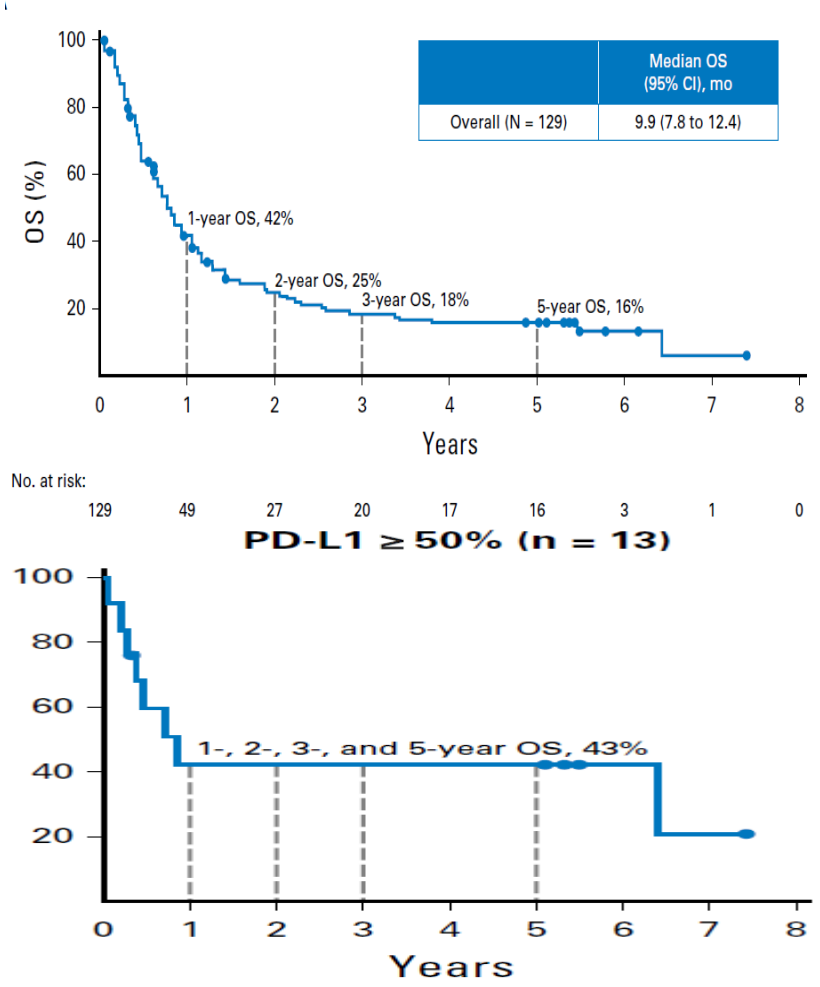
Regimen (ref)	n	ORR (%)	PFS (mos)	OS (mos)
Non-squamous NSCLC				
Carboplatin / pemetrexed +/- pembrolizumab(1,6)	616	47.6 v 18.9	8.8 v 4.9 (HR 0.52,0.43-0.64)	22 vs 10.7 (HR 0.49, 0.38-0.64)
Carbo/paclitax/bevacizumab +/- atezolizumab(2)	692	63.5 v 48	8.3 v 6.8 (HR 0.62, 0.52-0.74)	19.2 v 14.7 (HR 0.78, 0.64-0.96)
Carbo/nabP +/- atezo (3)	724	49.2 v 31.9	7.0 v 5.5 (HR 0.64, 0.54-0.77)	18.6 v 13.9 (HR 0.79, 0.64-0.98)
Both histology				
Platinum chemo +/- ipi/nivo(4)	719	38 v 25	6.7 v 5.0 (HR 0.68, 0.57-0.82)	15.6 v 10.9 (HR 0.66, 0.55-0.80)
Squamous NSCLC				
Carbo/paclitx or nabP +/- pembro(5)	559	57.9 v 38.4	6.4 v 4.8 (HR 0.56, 0.45-0.70)	15.9 v 11.3 (HR 0.64, 0.49-0.85)

nabP, *nab*-paclitaxel

(1)Gandhi NEJM 2018;378:2078 (2)Socinski NEJM 2018;378:2288 (3) West et al LancetOnc 2019; 20:924
(4)Reck ASCO 2020;Abs9501 (5)Paz-Ares NEJM 2018; 379:2040 (6) Gadgeel et al. JCO 2020

We are starting to see long term survivors





Pembrolizumab: Garon et al. JCO 2019
doi:10.1200/JCO.19.01207

Nivolumab: Gettinger et al. JCO 2018
Doi:10.1200/JCO.2017.77.0412

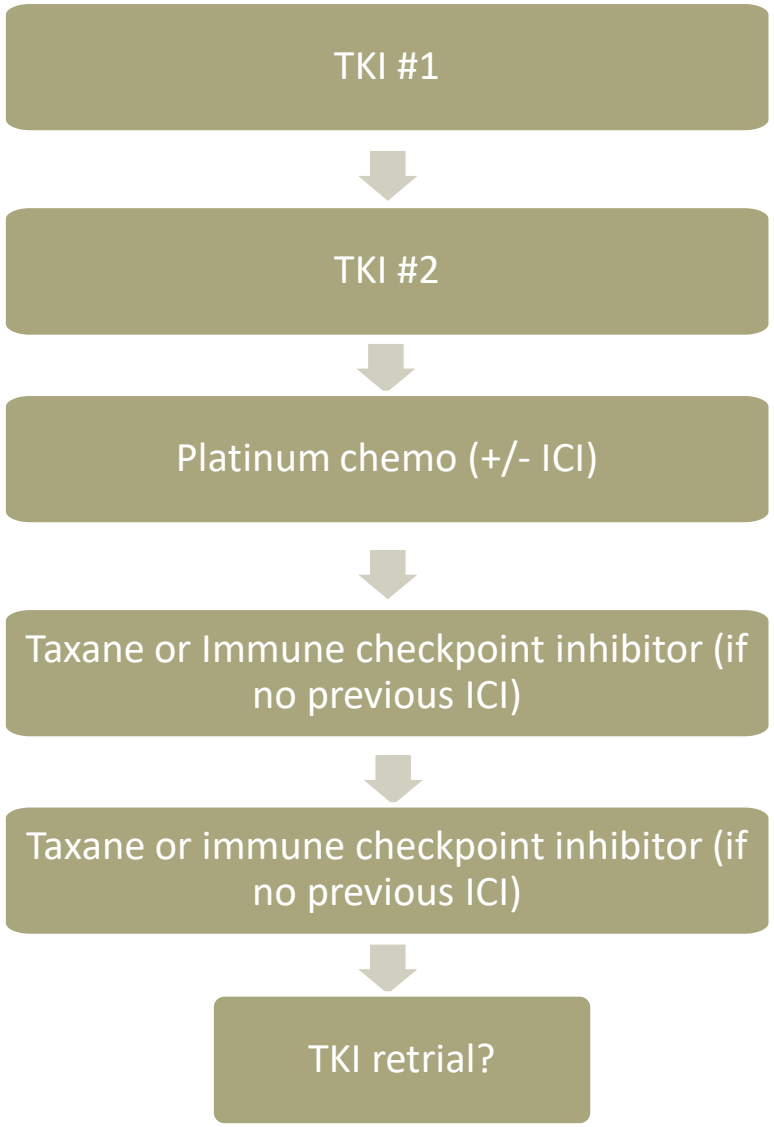
Summary - Immune checkpoint inhibitor

- Pembrolizumab / atezolizumab / cemiplimab monotherapy is a reasonable option for PD-L1 high tumors as first-line therapy (but no head-to-head data vs chemo-immunotherapy)
- In PD-L1 1-49% patients, I prefer chemo-immunotherapy since the benefit of pembro alone does not appear to be significantly better compared to chemo alone (my personal opinion)
- I also prefer chemo-immunotherapy in high PD-L1 patients if high response rate is desired (e.g. symptomatic disease burden) or never smokers
- When to use ipi/nivo? Perhaps in patients intermediate / low or negative PD-L1 expression who want to avoid chemo (but FDA approved only in PD-L1 expressed patients)

Brief overview of chemotherapy (for patients not eligible for immunotherapy first line e.g. active autoimmune disease)

- A few pearls on chemo / anti-angiogenetic therapy
  - Platinum doublet is standard of care in immunotherapy ineligible patients
  - Pemetrexed only approved for non-squamous histology
  - Bevacizumab contraindicated in squamous histology (cases of fatal hemoptysis)
- Squamous cell carcinoma:
  - Platinum + gemcitabine
  - Platinum + taxane **(no bevacizumb)**
  - Cisplatin + gemcitabine + **necitumumab**
- Non-squamous cell carcinoma:
  - Platinum + **pemetrexed** → maintenance pemetrexed
  - Platinum + paclitaxel + bevacizumab → maintenance bevacizumab
- Later line chemo (post-immunotherapy):
  - Docetaxel +/- ramucirumab in **both** histologies (no history of hemoptysis)

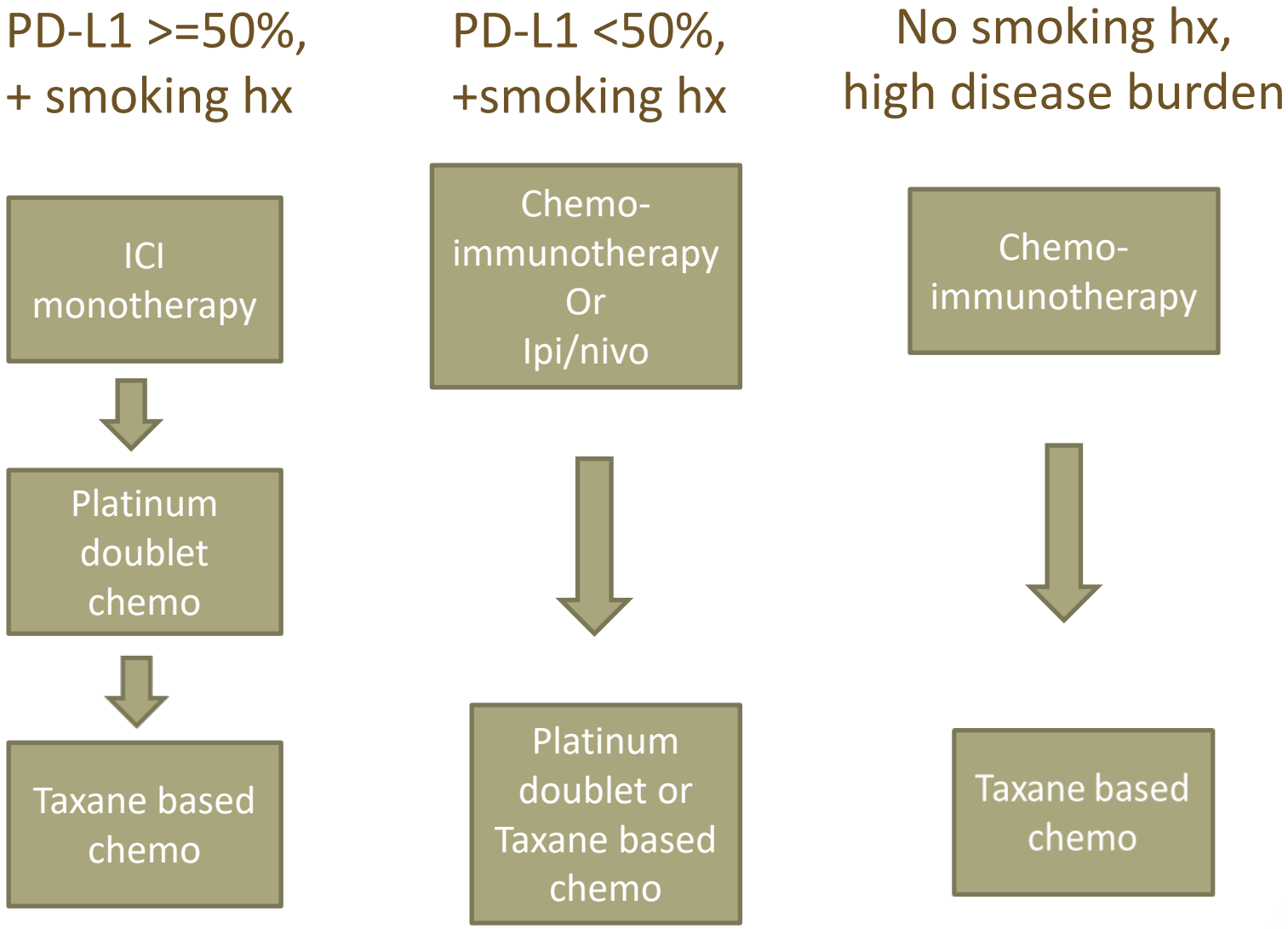
+ Molecular target



Data for frontline TKI:

- Strongest for: EGFR, ALK
- No randomized data but very compelling: ROS1, RET, NTRK, BRAF V600E
- Data not entirely clear but reasonable: MET exon14, EGFR exon20, KRAS G12C

No targetable genetic alteration, good PS (my personal practice)



Stage IV NSCLC – final thoughts

- Complete molecular testing as much as possible
  - All non-squamous histology
  - Squamous histology if light smoking history, small specimen, younger

- Blood based molecular testing is helpful but recognize that has limited sensitivity, especially in patients with low disease burden / intrathoracic only disease → complete tissue testing as much as possible if blood based test is negative

- Oncogene driven NSCLC (especially EGFR, ALK, ROS1, RET): Immune checkpoint inhibitor monotherapy has low activity, even in PDL1 high patients. Exhaust TKI options first before considering immunotherapy based treatments

- Emerging data indicate that the combination of TKI + immunotherapy is associated with high rates of toxicities

- Use of immunotherapy continues to evolve – stay tuned