Comprehensive Hematology & Oncology Review : Metastatic NSCLC

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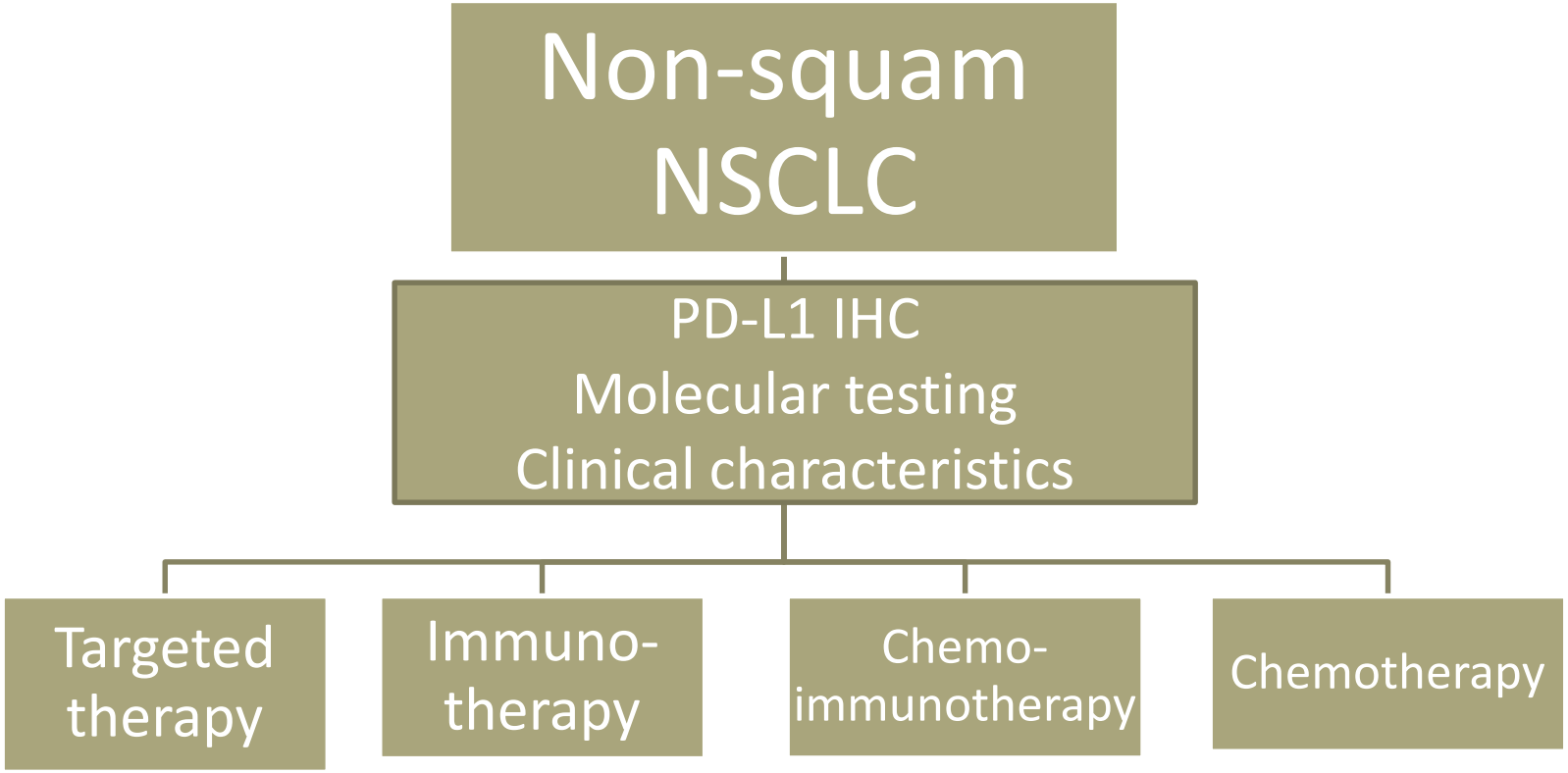
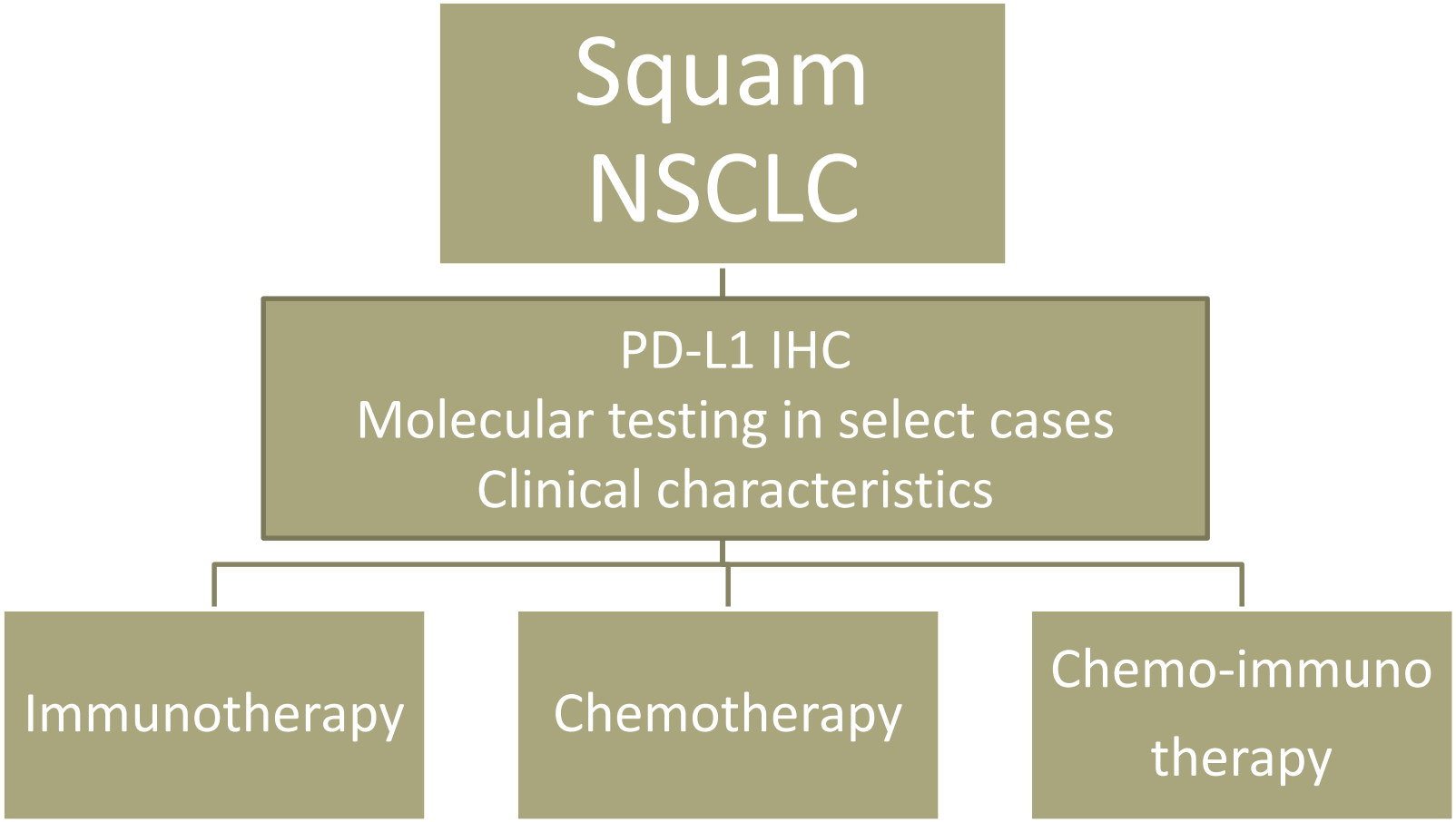
Outline

- 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 Aug 2020)

Alteration	Prevalence (estimates)
EGFR mutations (non-exon 20 insertion)	15-20%
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%

MET exon14 skipping mutation

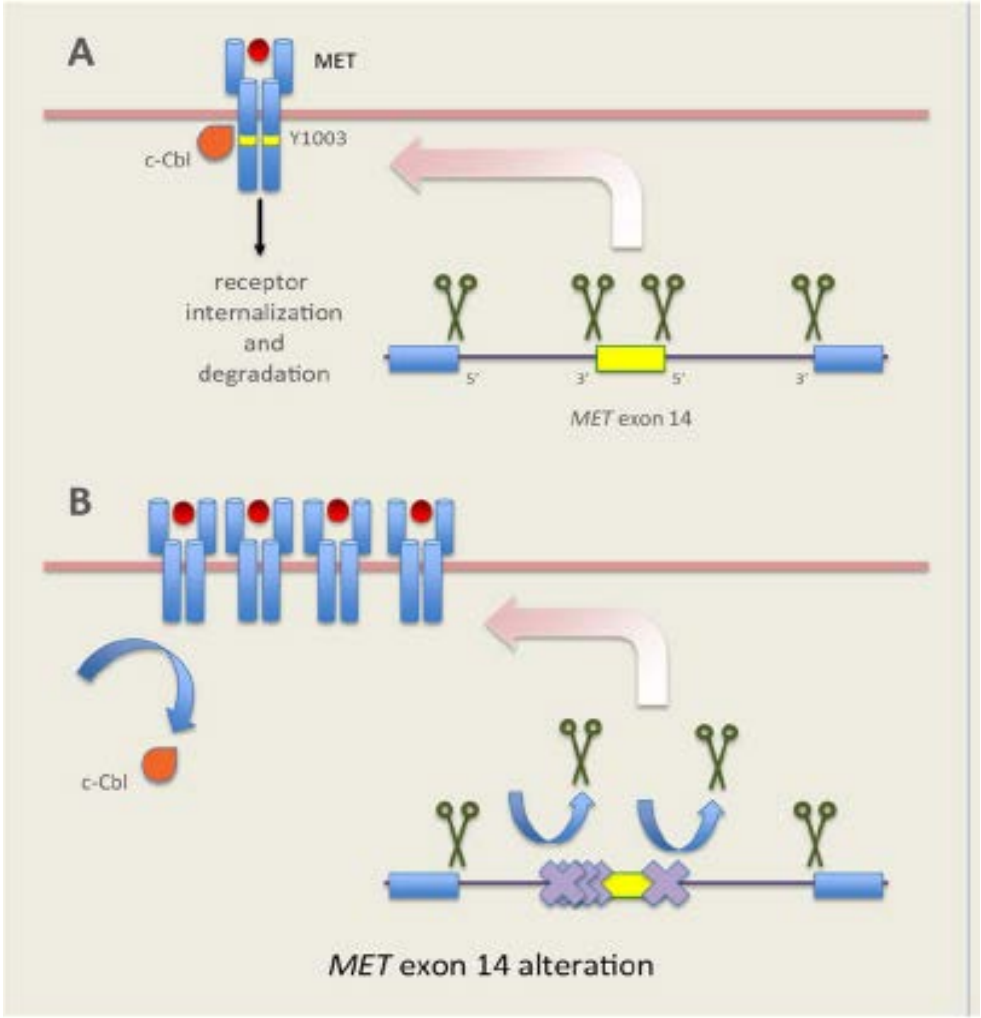
Clinical characteristics

- 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

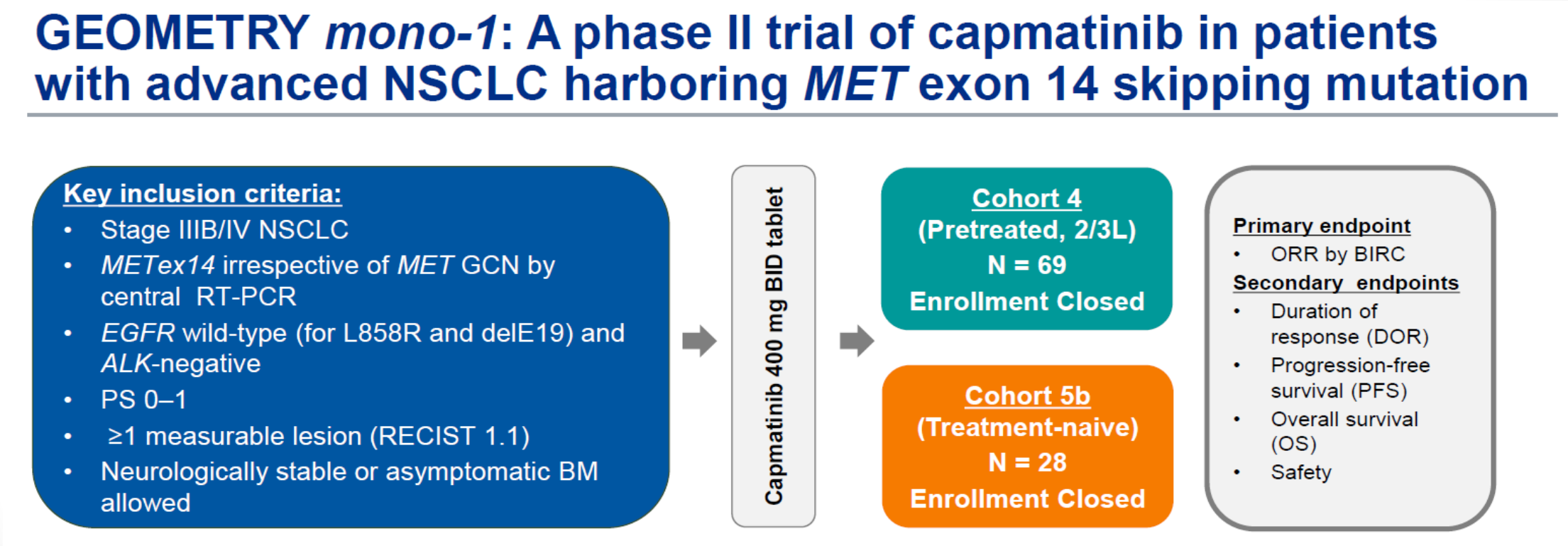


Drilon et al. JTO 2017;12(1): 15-26

- 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 exon14 skipping mutation

Capmatinib: First FDA approved MET inhibitor for MET exon14 mutation



Garon et al. Abs CT082 AACR 2020

MET exon14 skipping mutation - capmatinib

	Previously treated (n=69)	Treatment naïve (n=28)
ORR % (95% CI)	40.6 (28.9-53.1)	67.9 (47.6-84.1)
DCR % (95% CI)	78.3 (66.7-87.3)	96.4 (81.7-99.9)
DOR months (95% CI)	9.72 (5.55-12.98)	11.14 (5.55-NE)

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

Several other MET inhibitors under investigation: e.g. tepotinib, savolitinib, etc

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

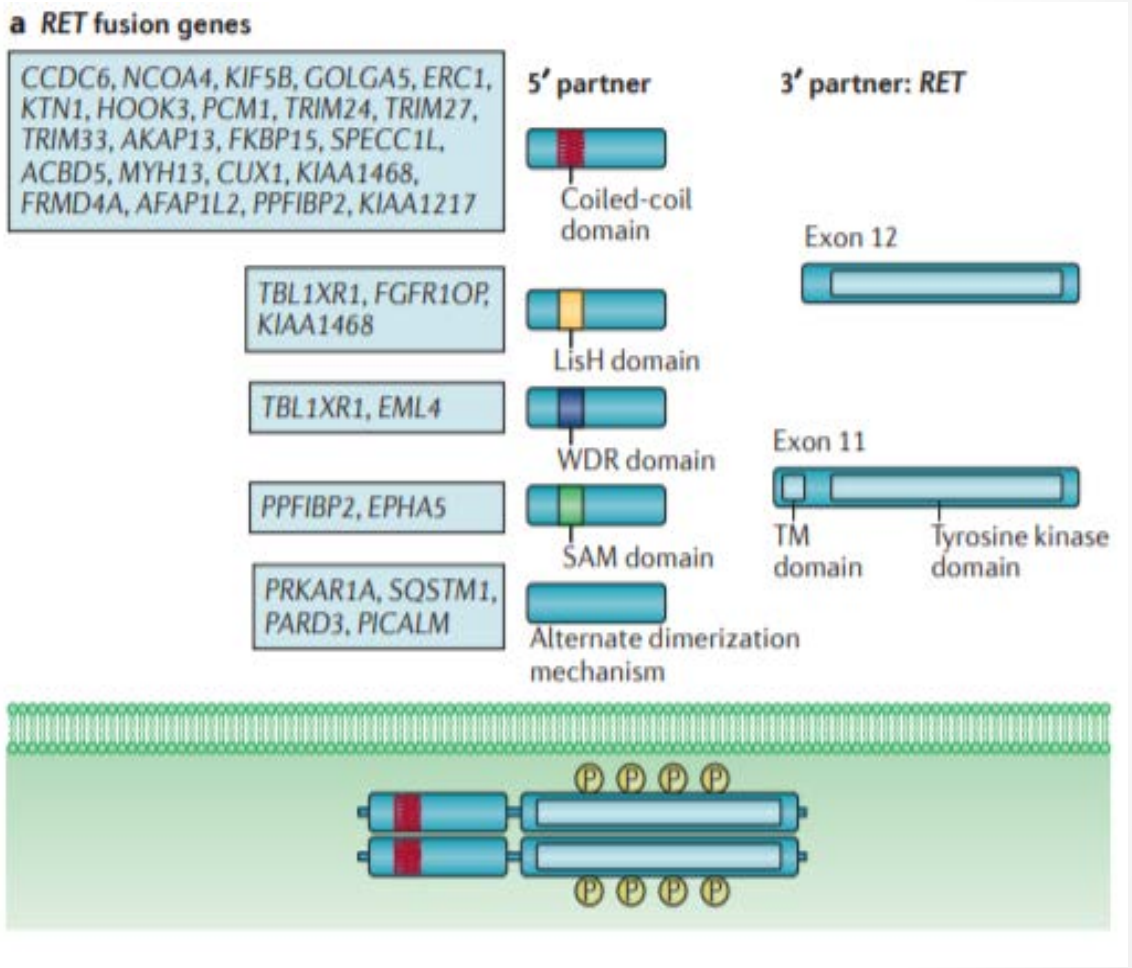
RET rearrangement

Clinical characteristics

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

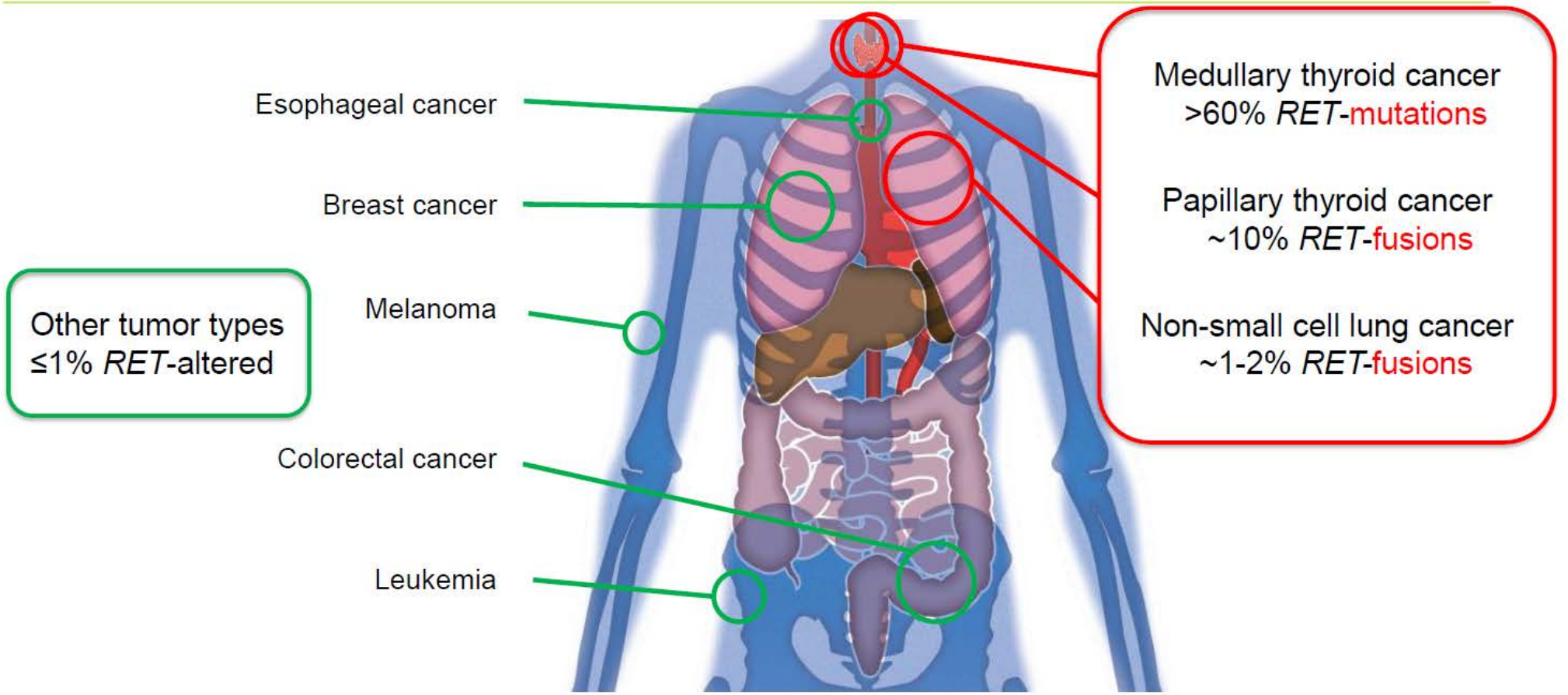
Mechanism of action

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

RET rearrangement: Selpercatinib

Selpercatinib:

FDA approved in May 2020 for RET rearranged NSCLC / iodine refractory thyroid cancer and RET mutant medullary thyroid cancer

<u>LIBRETTO-001, phase 2 trial</u>
(n=253 NSCLC)

- ORR 68% (58-76)
- DOR 20.3 mos (13.8-24)
- PFS 18.4 mos (12.9-24.9)

Treatment emergent adverse events (mostly gr1-2)	
Dry mouth	32%
Diarrhea	31%
Hypertension	29%
Transaminitis	26-28%
Fatigue	24%
Constipation	22%
Headaches	20%
Nausea	19%
Peripheral edema	19%
Increased creatinine	18%

Drilon et al. WCLC 2019

Selective RET inhibitors

	selpercatinib[1]	pralsetinib[2]
ORR in naïve	85% (69-95)	71% (NA)
ORR in chemo-pretreated	68% (58-76)	60% (42-76)
PFS	18.4	NR
DoR	20.3	NR
Intracranial activity	91 (59-100)%	78 (NA)%
Safety (G3%)*		
HTN	14%	13%
Transaminitis	6-7%	3%
Anemia, Neutropenia	NA	7%, 13%
Drug discontinuation rate	1.7%	7%
Activity against MTC RET mutations	Yes	Yes
Tumor agnostic RET fusion activity	Yes	Yes

Doebele. WCLC 2019; Gainor et al. ASCO 2019

EGFR mutation+ NSCLC

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

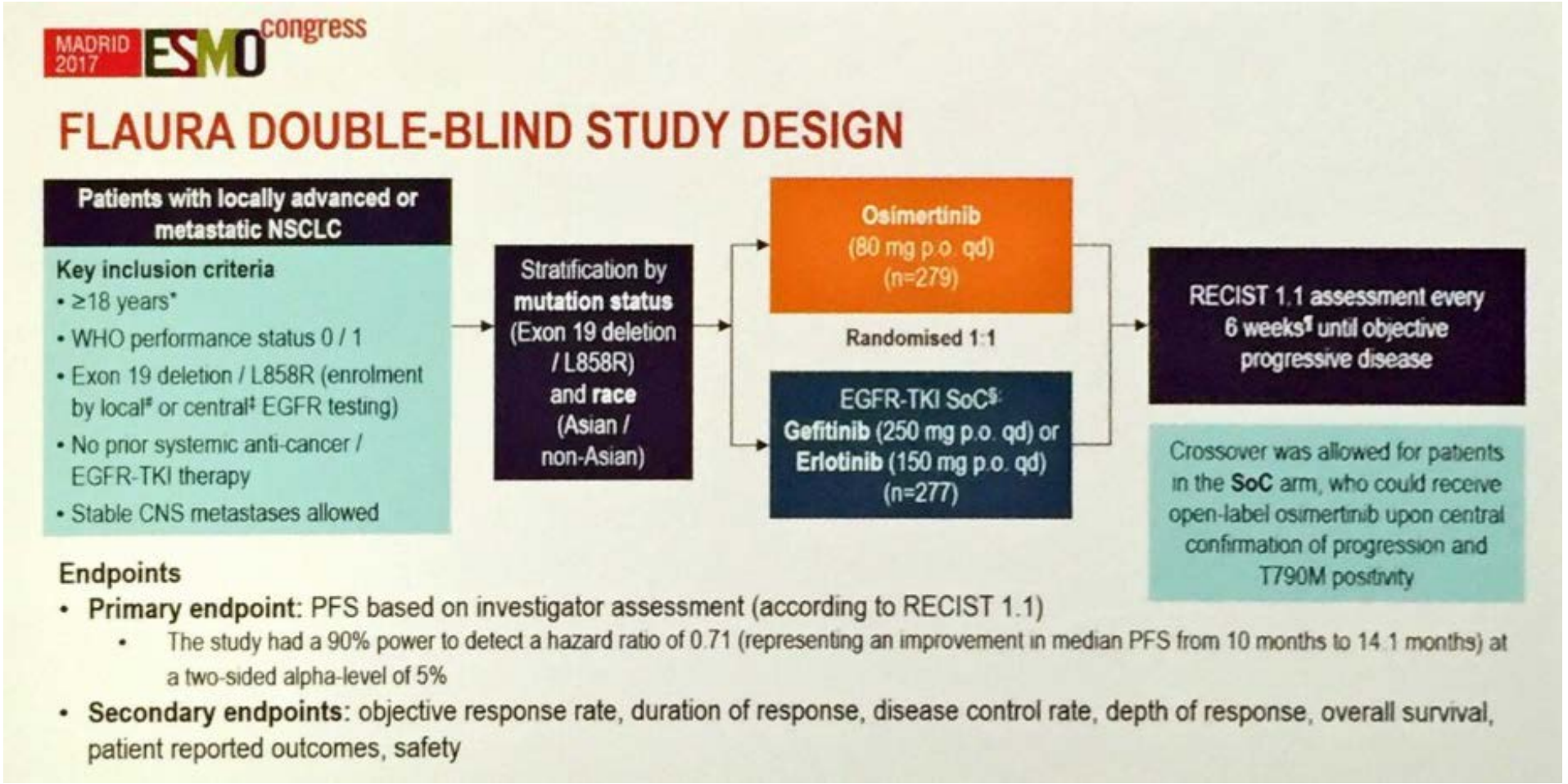
FDA approved EGFR TKIs		
1st generation	2nd generation	3rd generation
Erlotinib (+/- ramucirumab)	Afatinib	Osimertinib
Gefitinib	Dacomitinib	

General principles

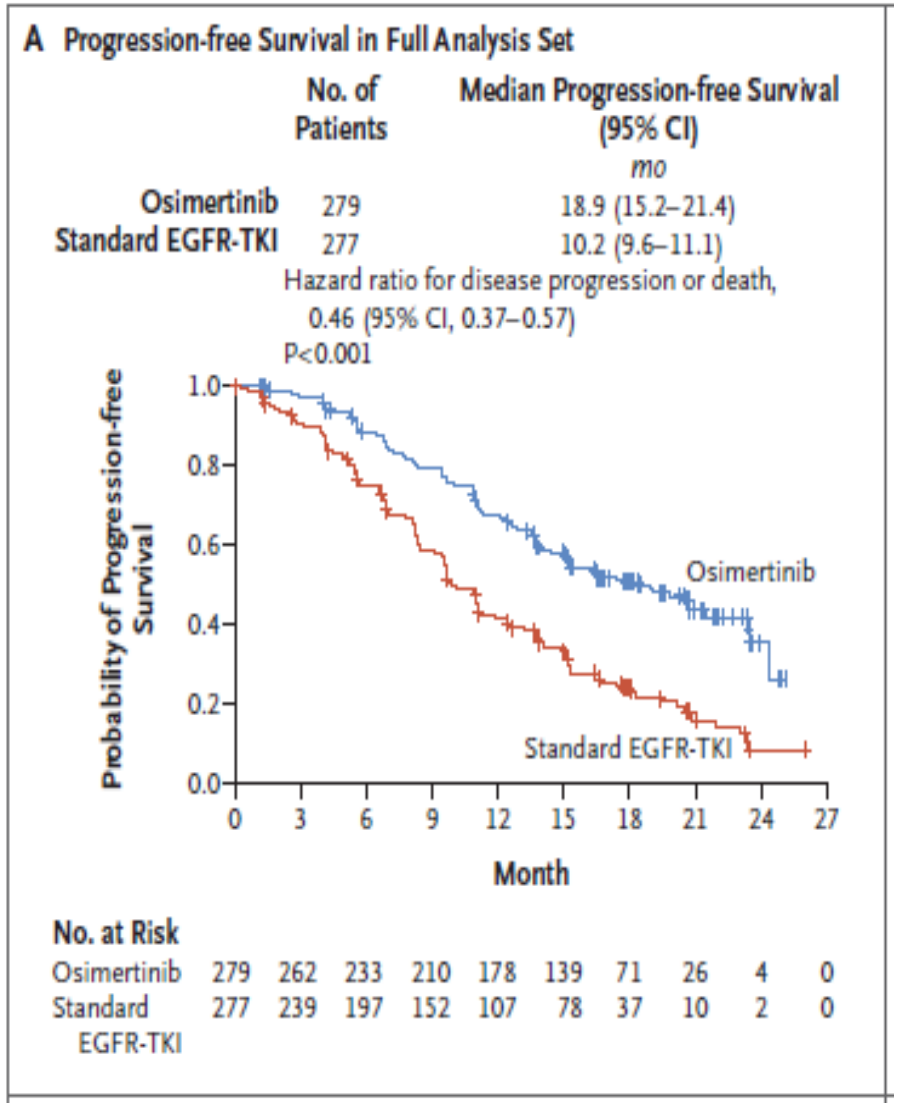
- TKI treatment is superior to platinum doublet in the first line setting
- Efficacy of 1st and 2nd gen TKIs are similar, although PFS with dacomitinib higher
- Using a 2nd gen TKI after a 1st gen TKI is not effective
- 50-60% of patients develop T790M resistance mutation after 1st and 2nd gen TKIs

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

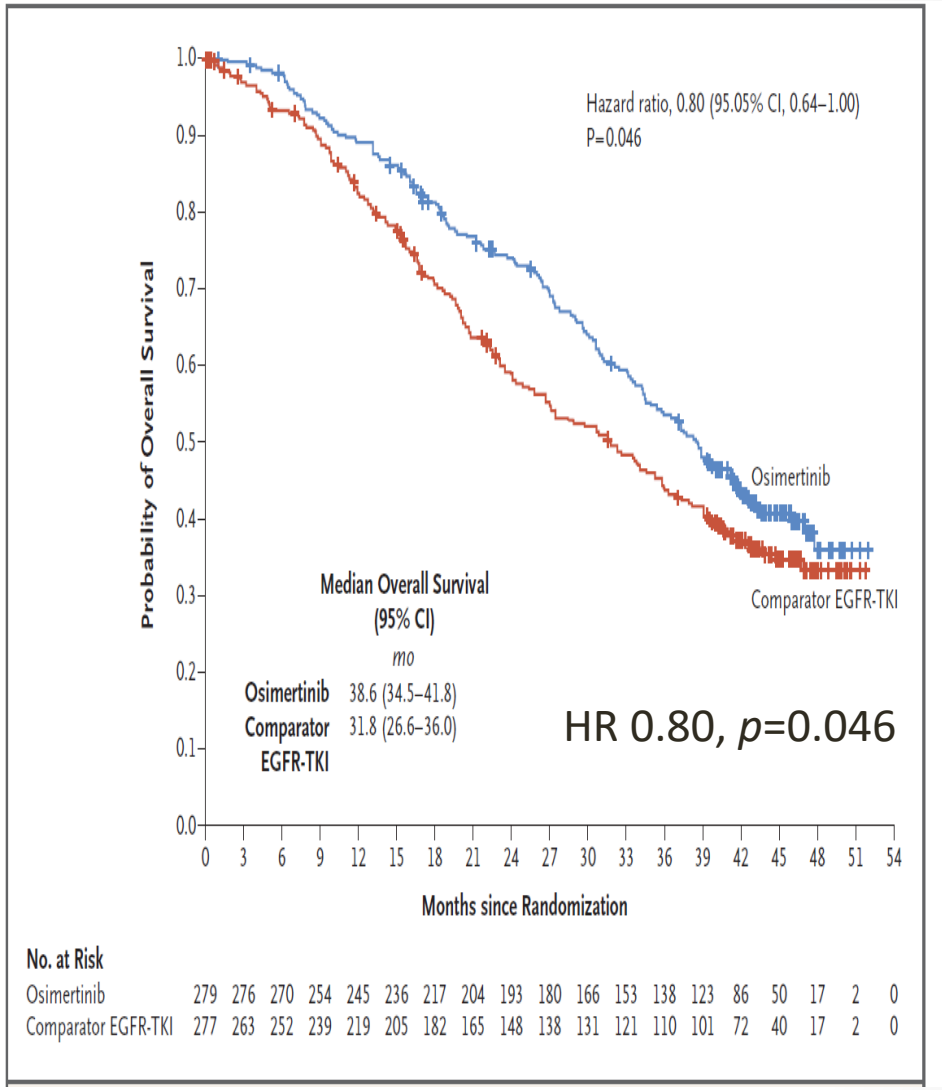
First line osimertinib



Ramalingam ESMO 2017



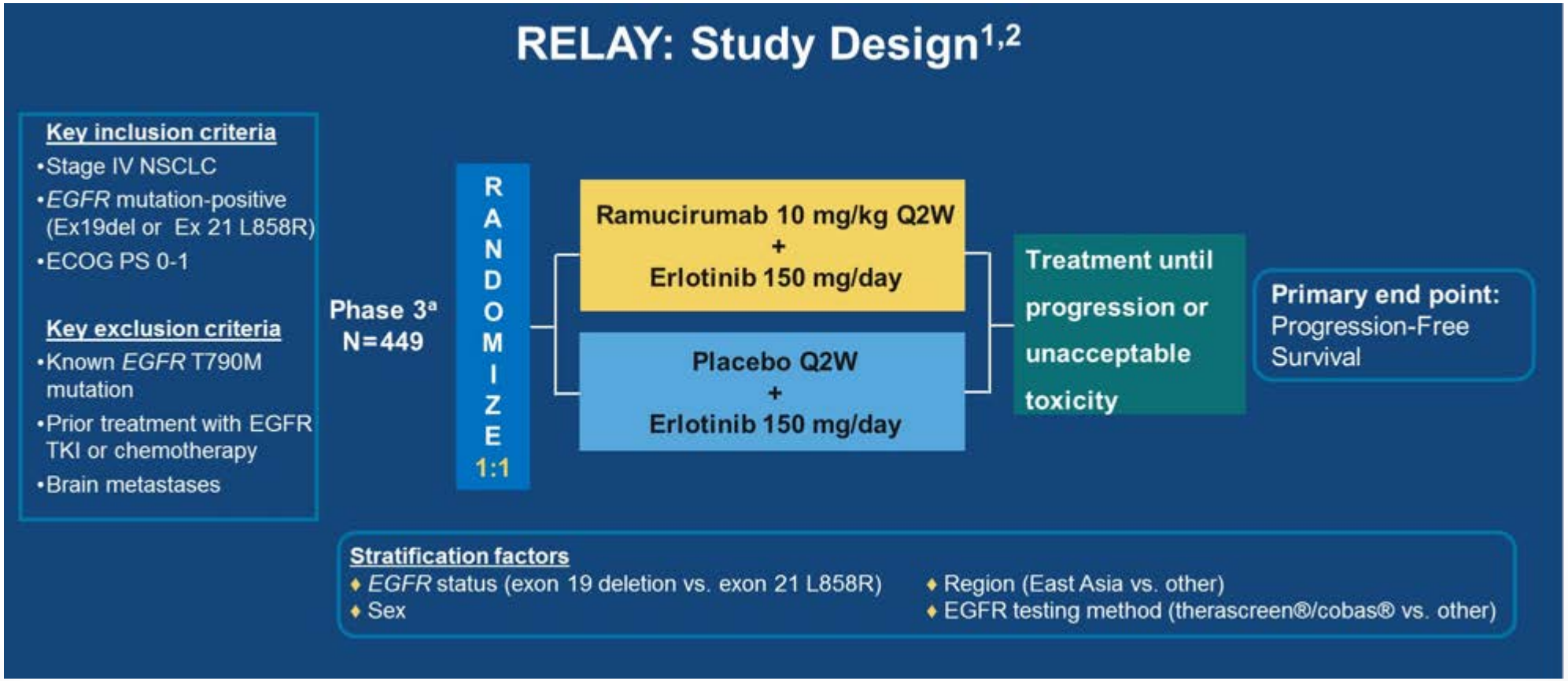
Soria *et al*. NEJM 2018; 378(2): 113-125



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

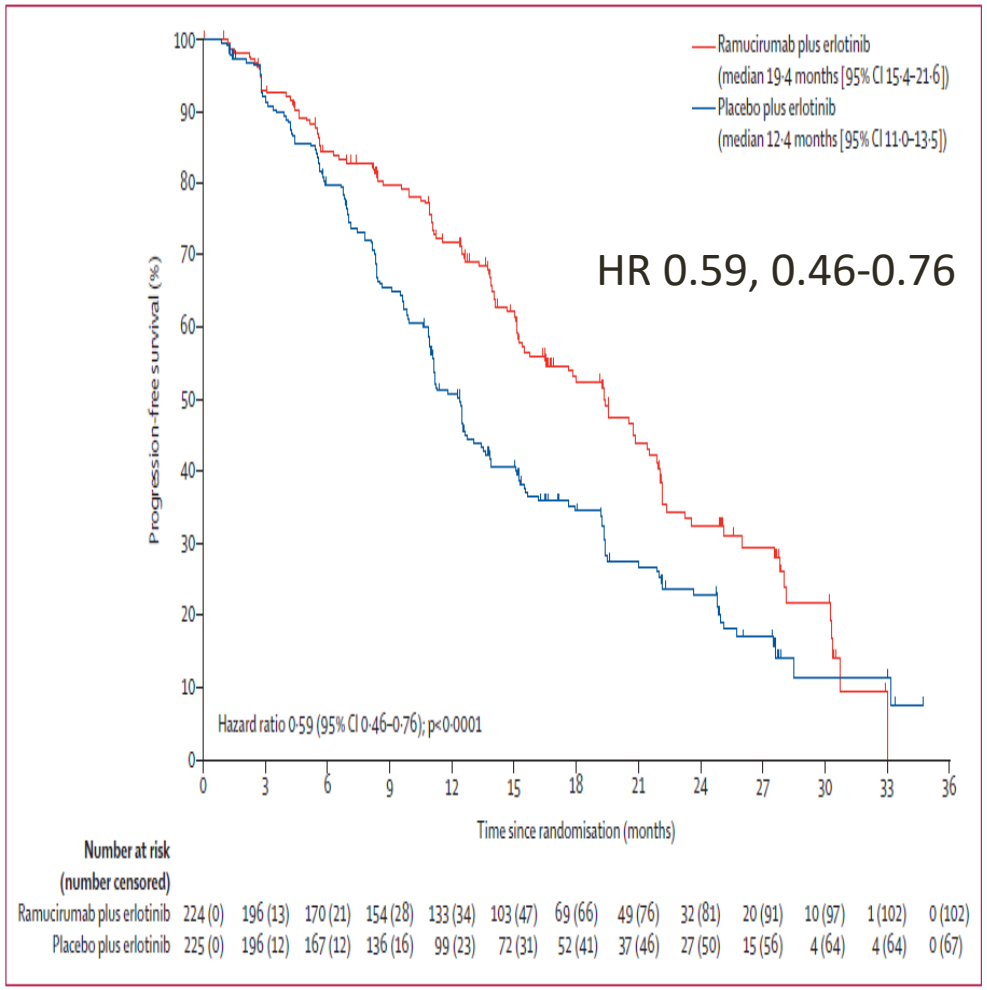
Erlotinib + ramucirumab

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 is 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 rearrangement

- 3-5% NSCLC
- Associated with young age, no smoking
- FDA approved tests:
  - FISH (fluorescence *in situ* hybridization)
  - Immunohistochemistry (D5F3 antibody)

ALK rearranged NSCLC

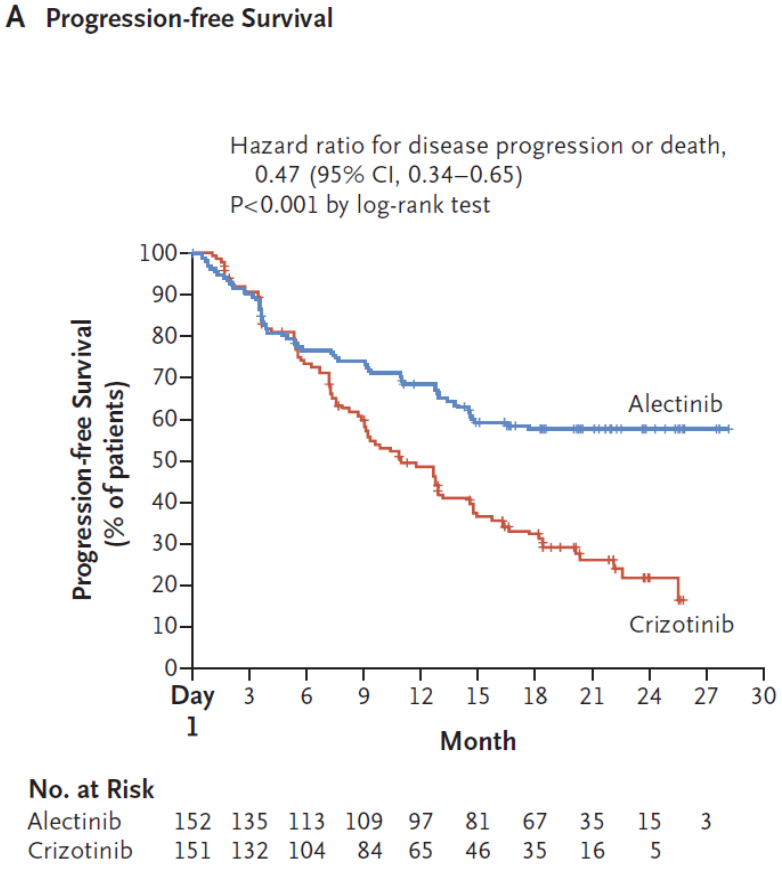
FDA approved ALK inhibitors		
1st generation	2nd generation	3rd generation
Crizotinib	Alectinib	Lorlatinib
	Ceritinib	
	Brigatinib	

General principles

- All of the above TKIs except lorlatinib are approved as first line therapy
- Second generation TKIs have become standard first line therapy, even though crizotinib is an option
- 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

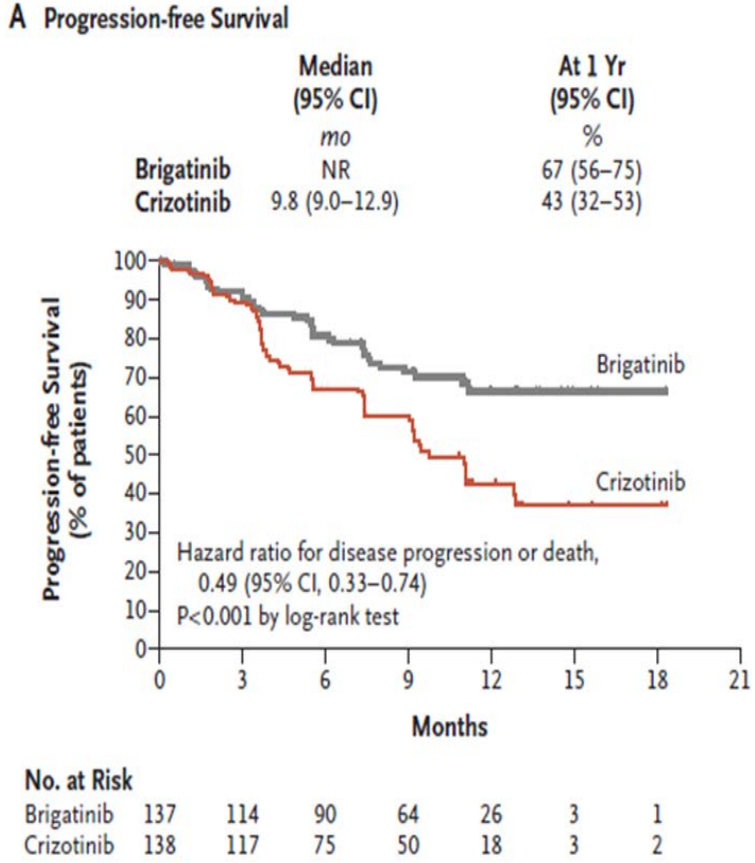
First line therapy:

Alectinib



Peters *et al*. NEJM 2017. DOI: 10.1056/NEJMoa1704795

Brigatinib



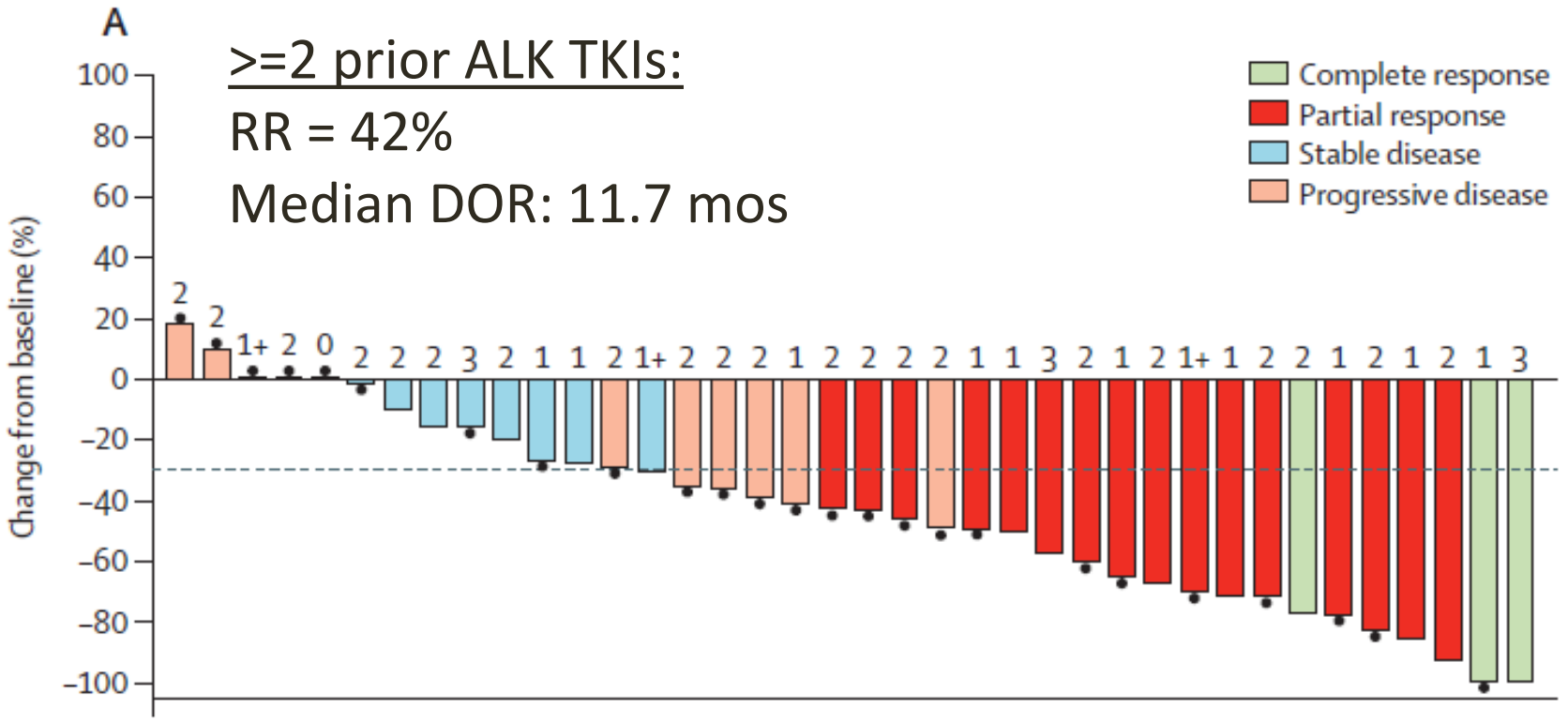
Camidge et al. DOI: 10.1056/NEJMoa191071

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

(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

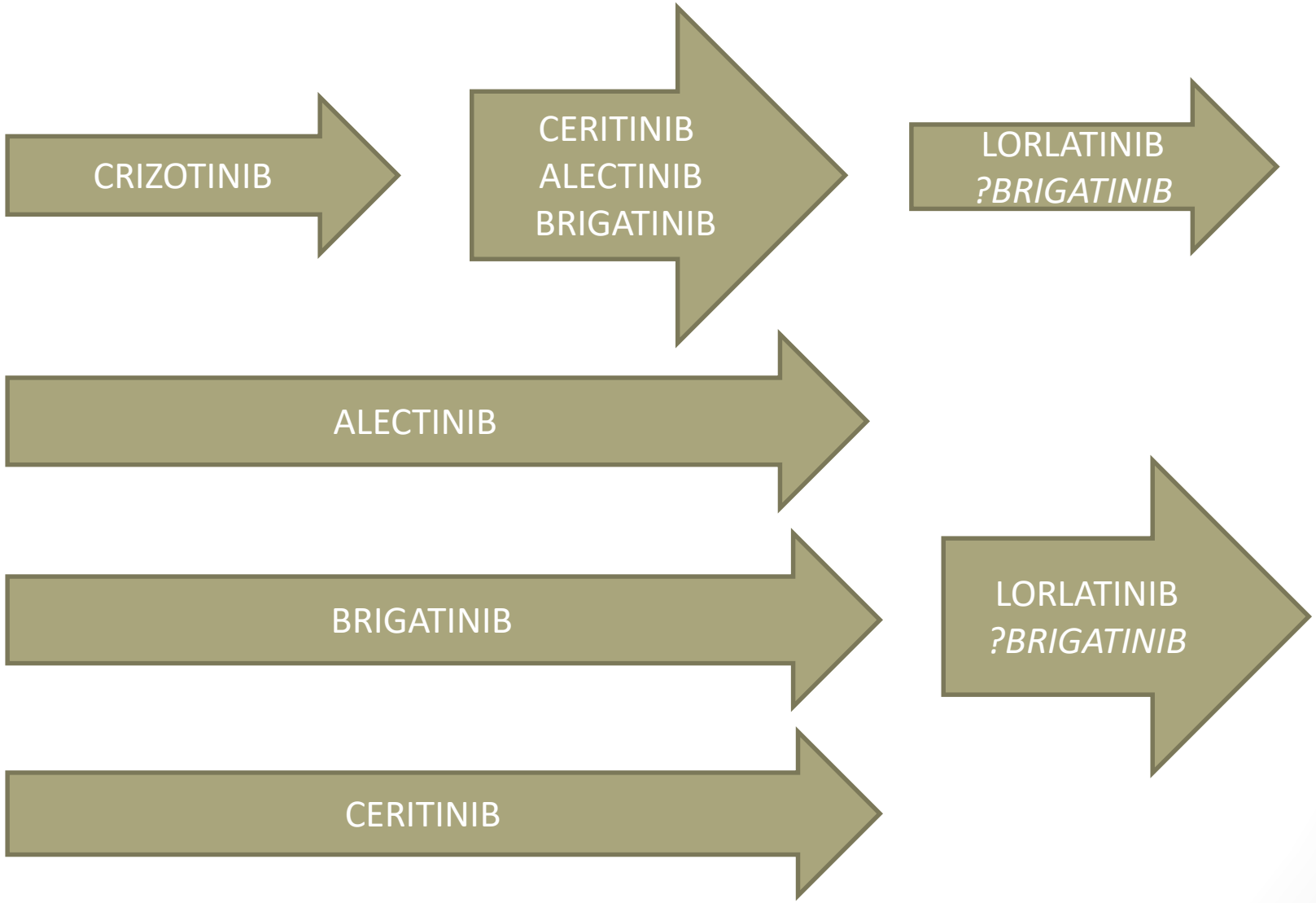
3rd generation ALK inhibitor: Lorlatinib



Shaw *et al*. Lancet Oncol 2017; 18(12): 1590-1599

Currently approved after a second generation TKI

ALK therapy: Optimal sequence?

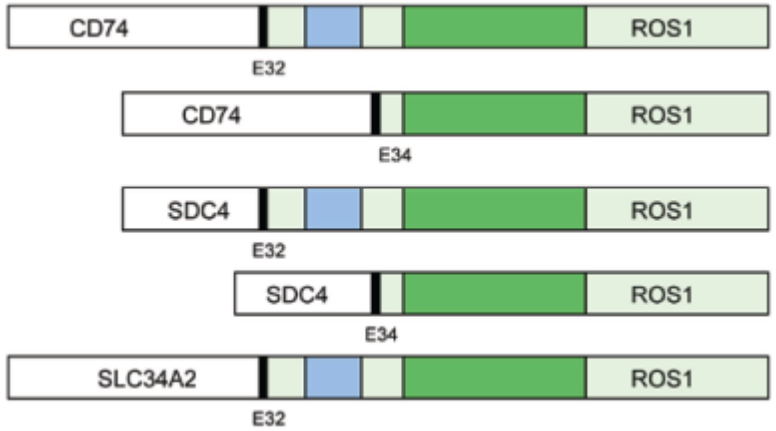


Toxicities

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 (mild)

ROS1 rearranged NSCLC

- Fusion of ROS1 tyrosine kinase domain with 1 of 12 different partner proteins
- Younger patients with no/light smoking history
- Occur in 1-2% of NSCLC



Gainor *et al*. Oncologist 2013;18:865

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 yet FDA approved (ORR 26.5, 12.9-44.4; median PFS 8.5mos)

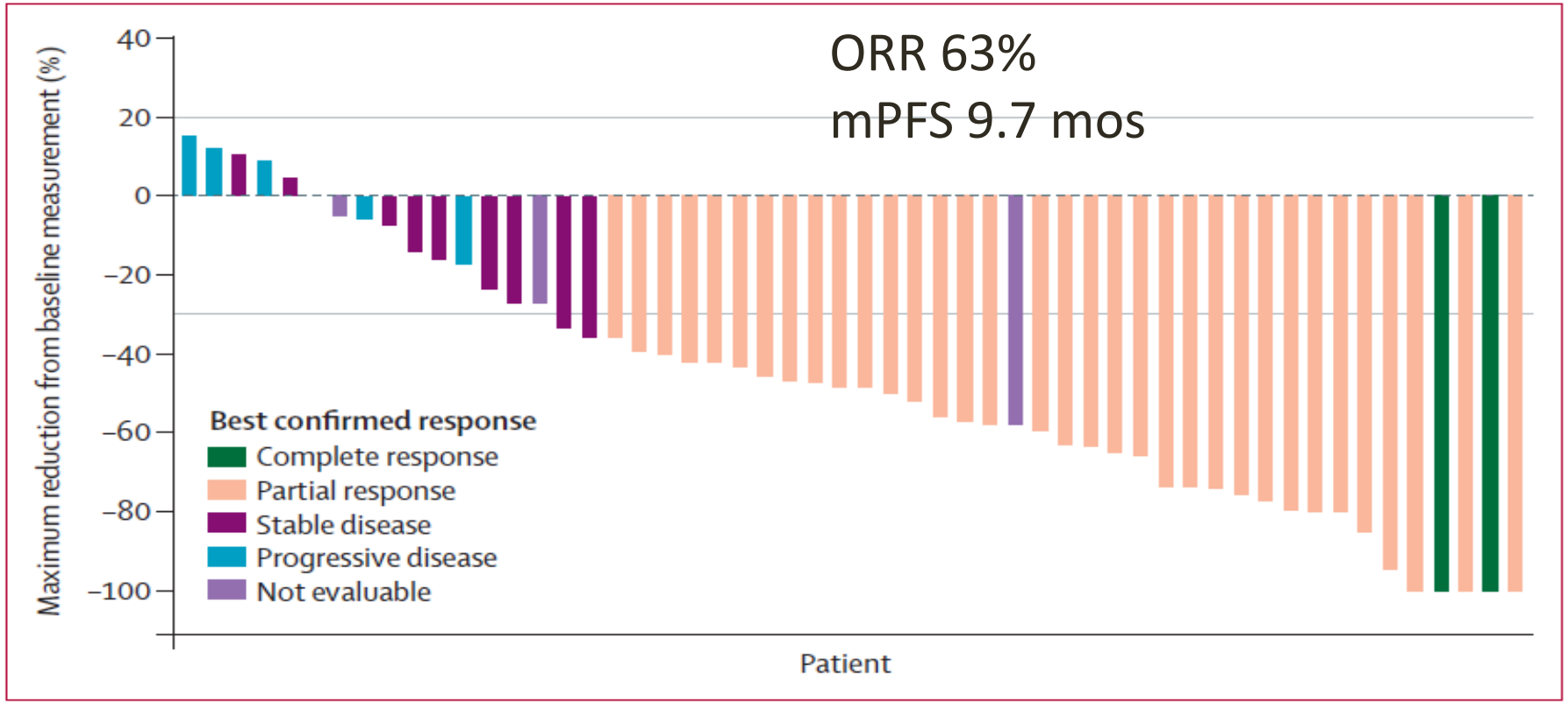
	RR, %	PFS, mos	CNS RR
Crizotinib (n=50)	72 (58-84)	19.2 (14.4-NR)	N/A
Entrectinib (n=53)	77.4 (64-88)	19.0 (12.2-36.6)	55% (n=20)

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

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)



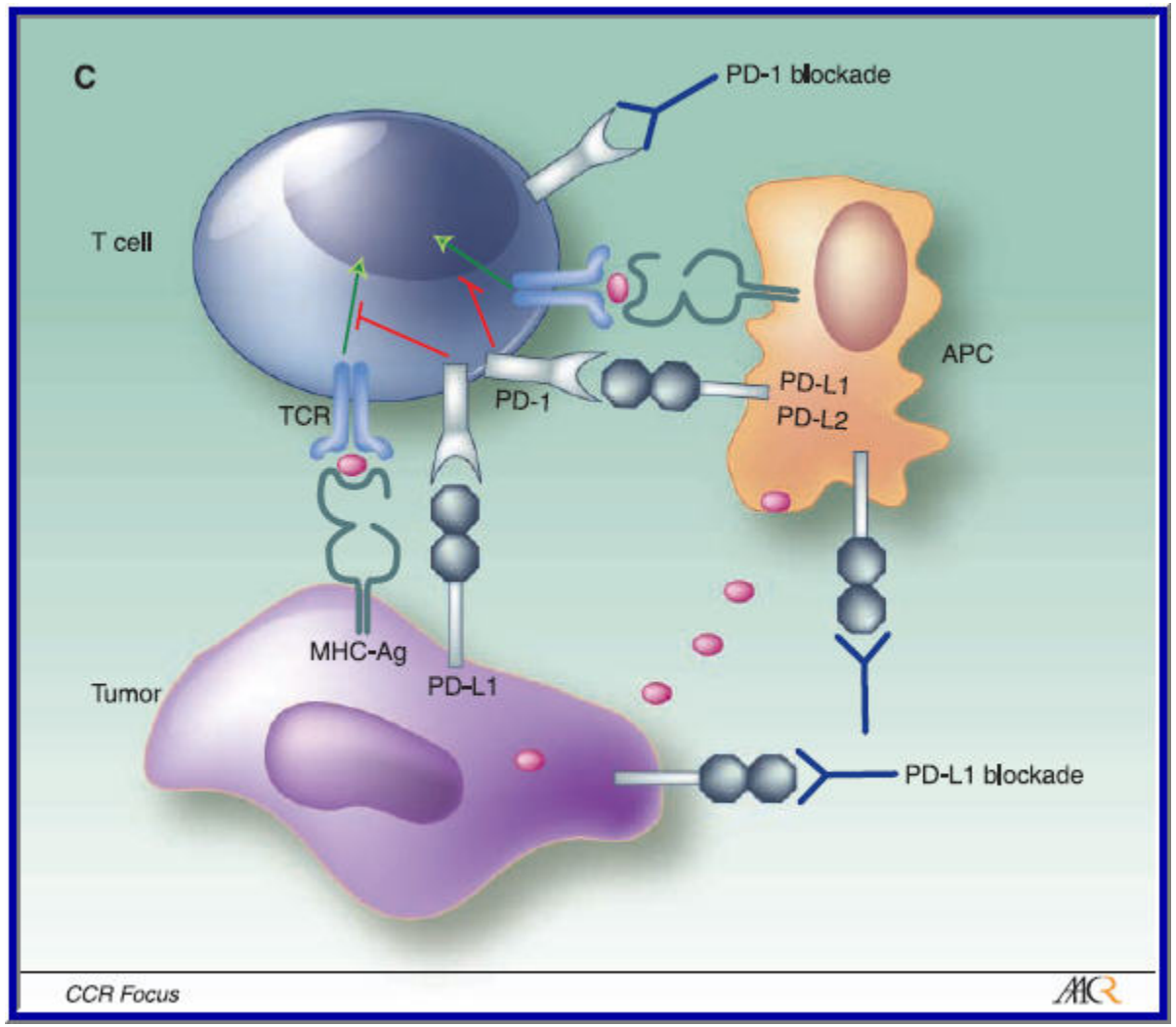
NTRK rearrangement

- 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)

FDA approved (as of July 2020)						
EGFR (non-exon20 ins)	**ALK**	**ROS1**	**BRAF V600E**	**NTRK**	**MET exon14**	**RET**
Erlotinib Gefinitb Afatinib Dacomitinib Osimertinib	Crizotinib Alectinib Ceritinib Brigatinib Lorlatinib	Crizotinib Entrectinib (Lorlatinib)	Dabrafenib + trametinib	Larotrectinib Entrectinib	Capmatinib	Selpercatinib

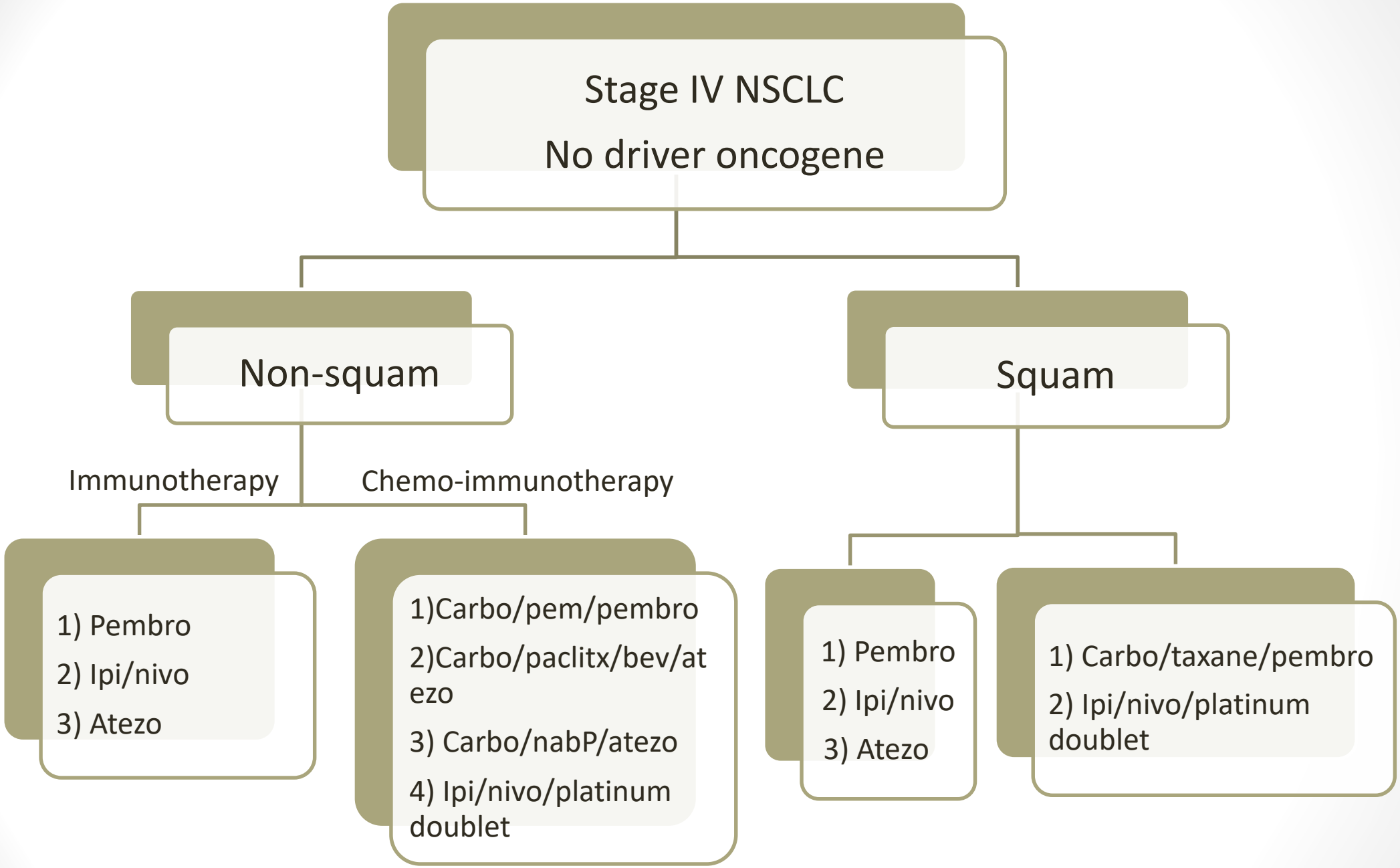
Investigational (active drugs in trials)			
EGFR (exon20 ins)	**HER2**	**KRAS**	**MET amplification**
Poziotinib TAK788 (mobocertinib) Tarloxotinib	Trastuzumab deruxtecan Trastuzumab emtansine Poziotinib TAK788 Tarloxotinib	AMG510 (G12C) MRTX849	Tepotinib Capmatinib Sym015 Savolitinib

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


Stage IV NSCLC
No driver oncogene
Non-squam
Squam
Immunotherapy
Chemo-immunotherapy
1) Pembro
2) Ipi/nivo
3) Atezo
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
1) Carbo/taxane/pembro
2) Ipi/nivo/platinum doublet

First-line: Pembrolizumab

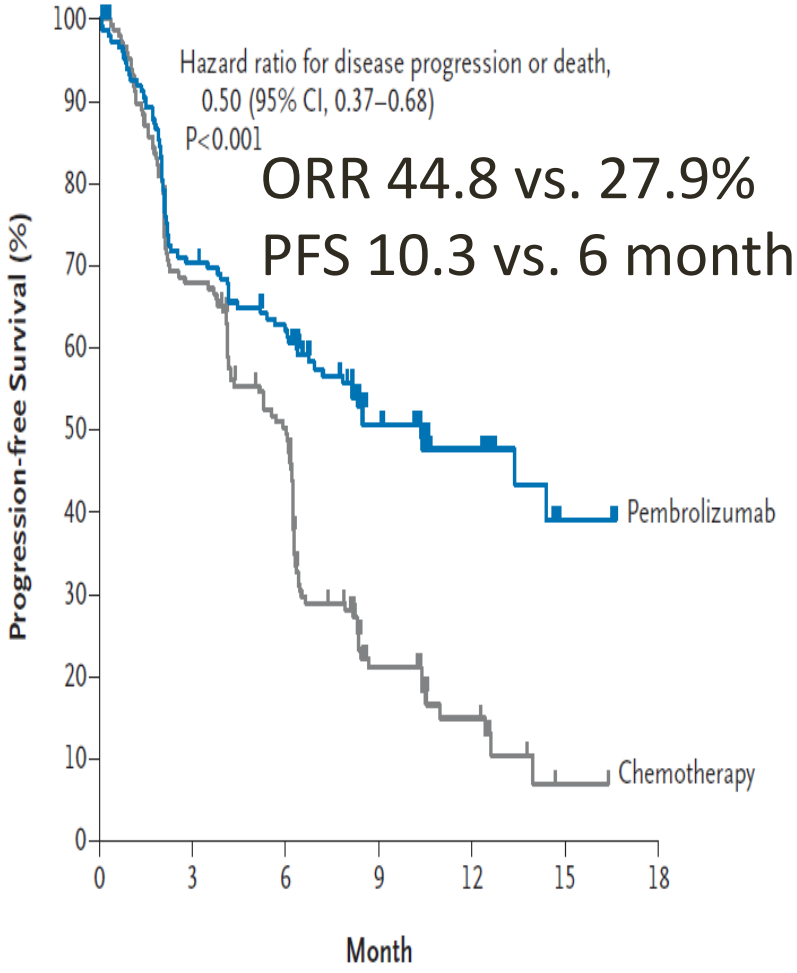
- Metastatic NSCLC
- No EGFR / ALK
- ECOG 0-1
- No untreated CNS met
- No history of pneumonitis
- PDL1 >=50% (KN-24)
- PDL1 >=1% (KN-42)

→ Pembrolizumab 200mg q3wk x 2 years

→ Platinum doublet chemo

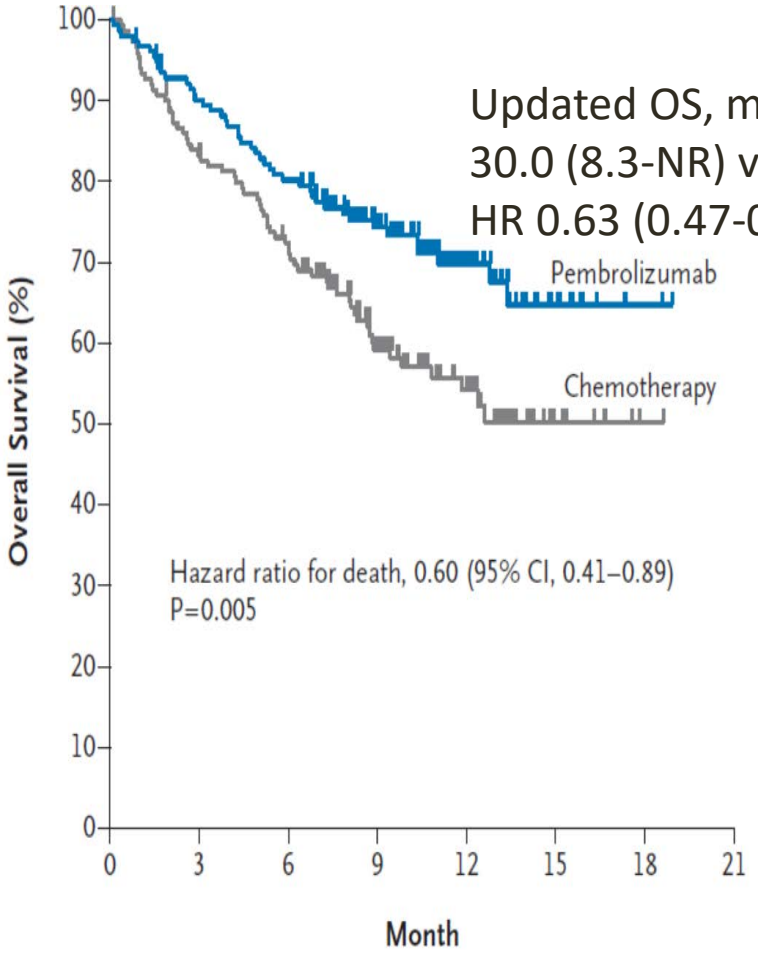
Brahmer *et al*. ASCO 2017 abs #9000
Lopes et al. ASCO 2018 abs LBA4

Pembrolizumab: ≥ 50% PD-L1



ORR 44.8 vs. 27.9%

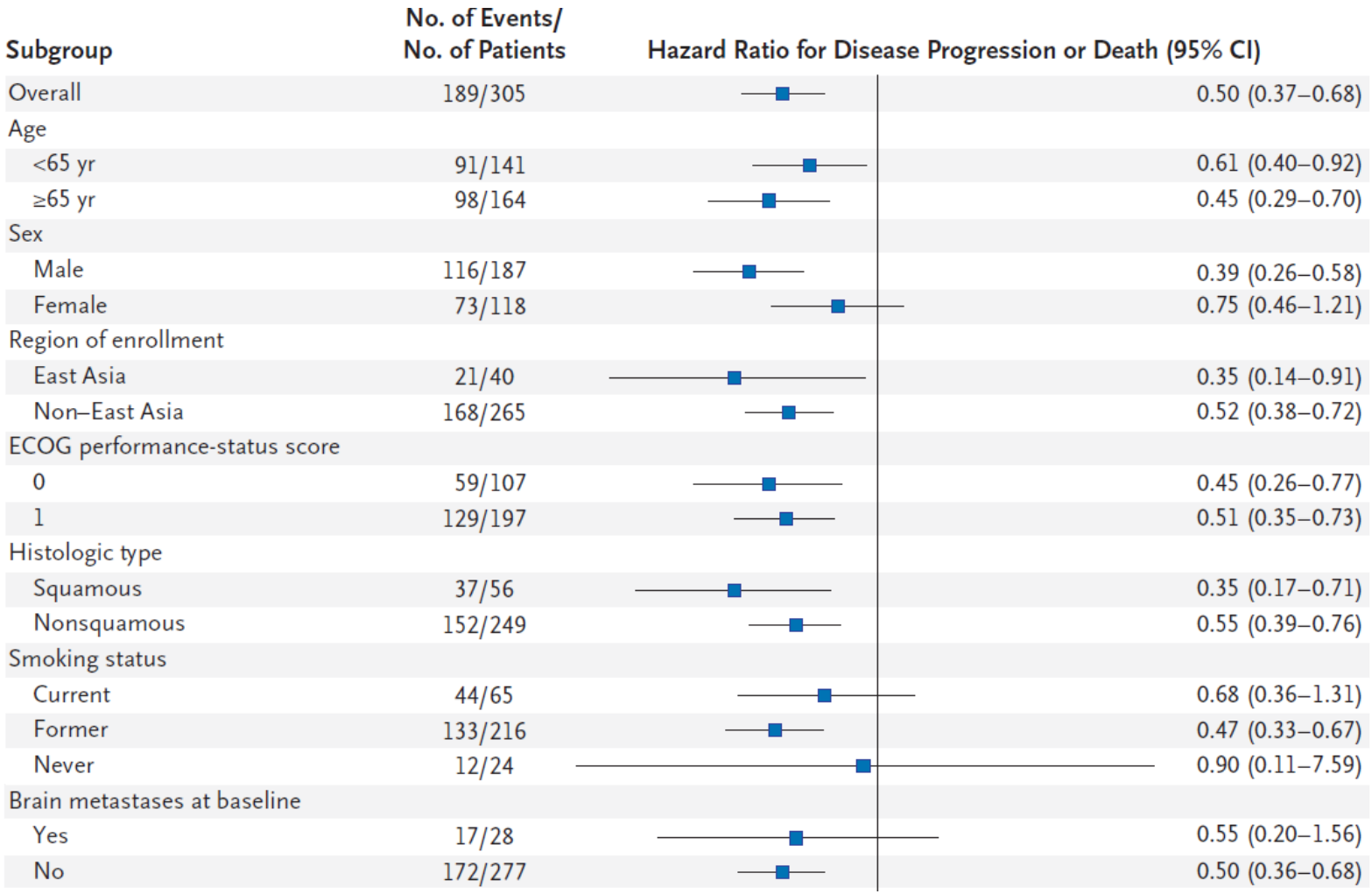
PFS 10.3 vs. 6 months



Updated OS, mos:
30.0 (8.3-NR) vs 14.2 (9.8-19)
HR 0.63 (0.47-0.86)

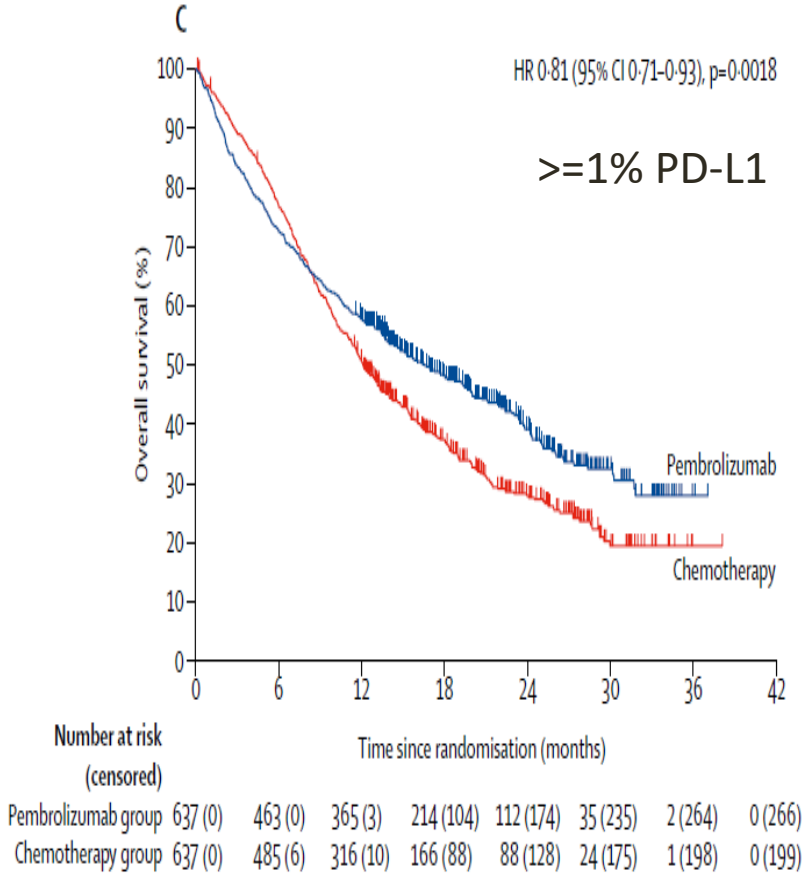
Reck *et al*. NEJM 2016; 375 (19):1923-1833
Reck et al. JCO 2019; 37:537-546

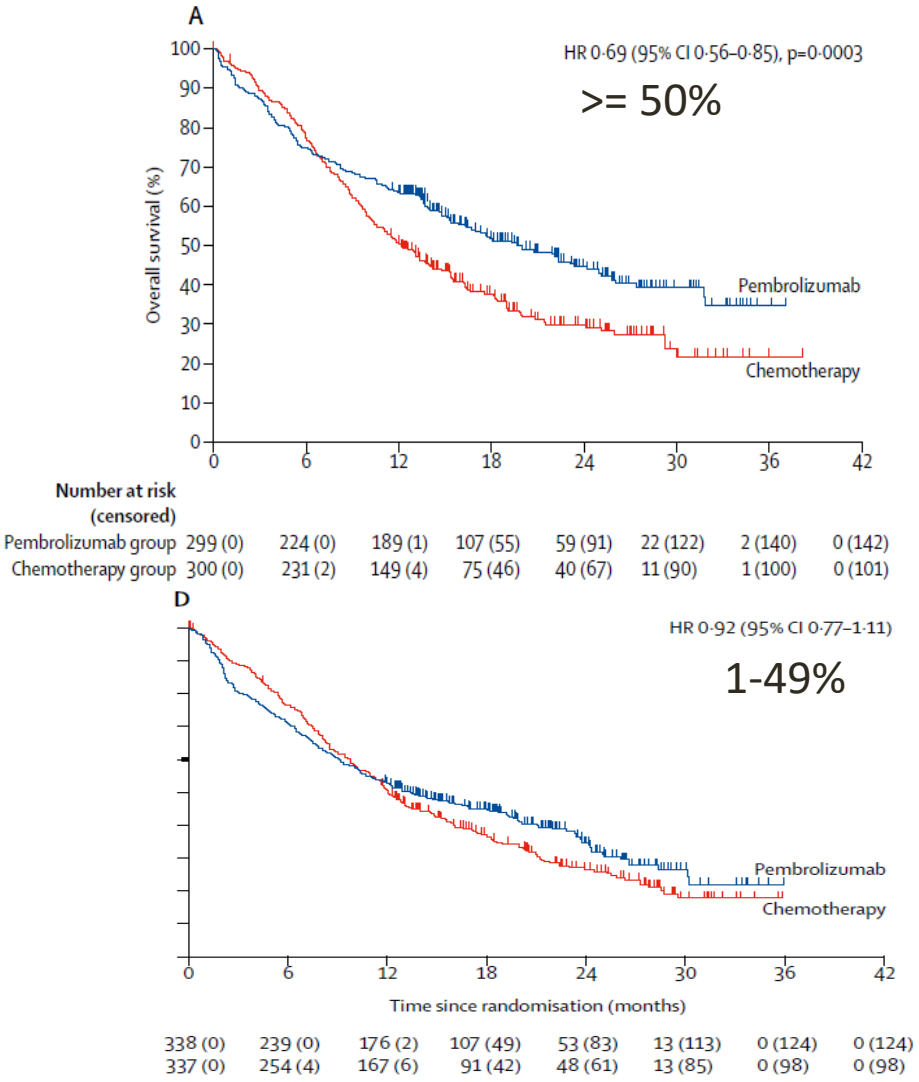
First-line pembrolizumab



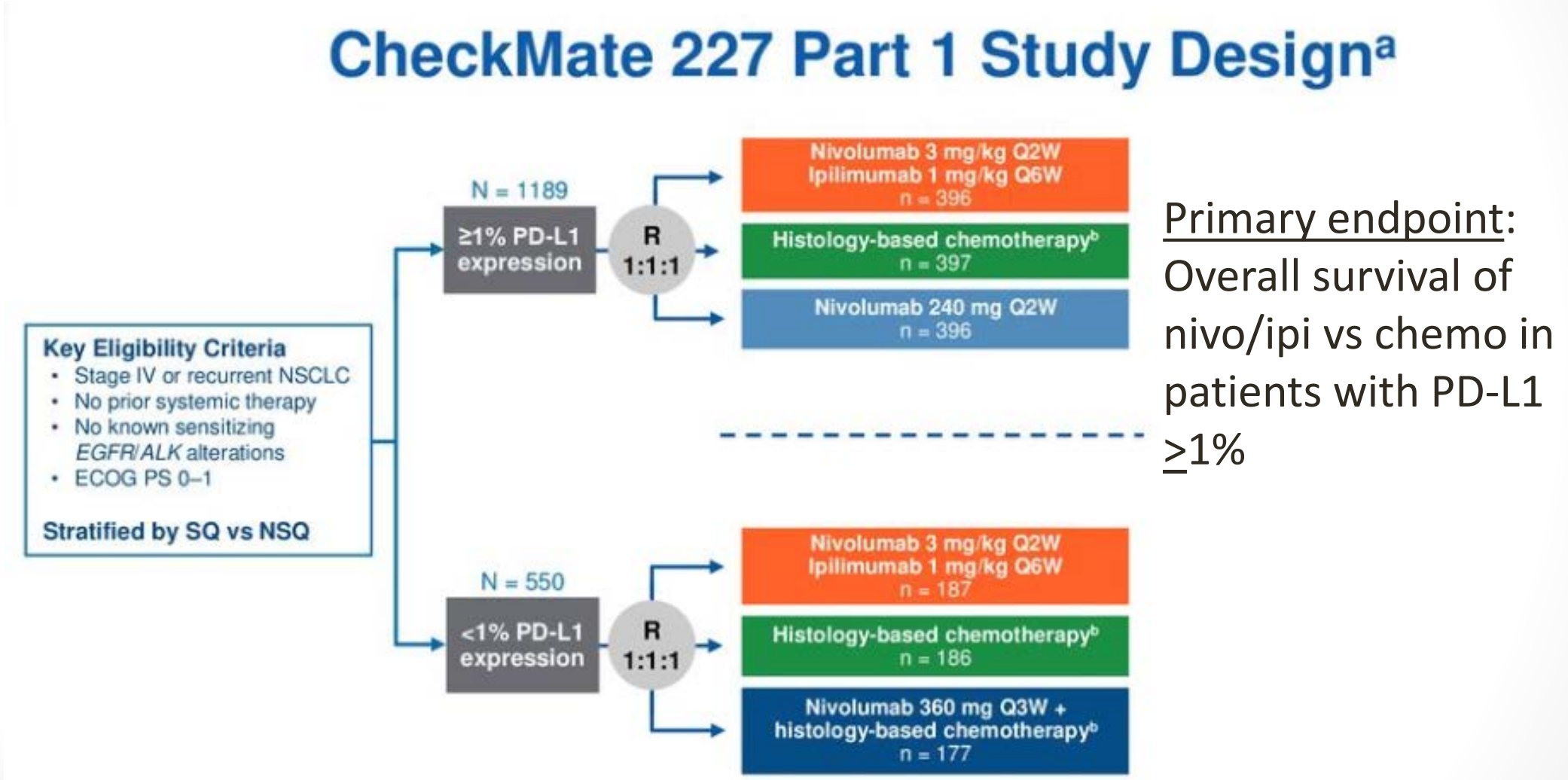
Reck *et al*. NEJM 2016; 375 (19):1923-1833

Pembrolizumab: ≥1%



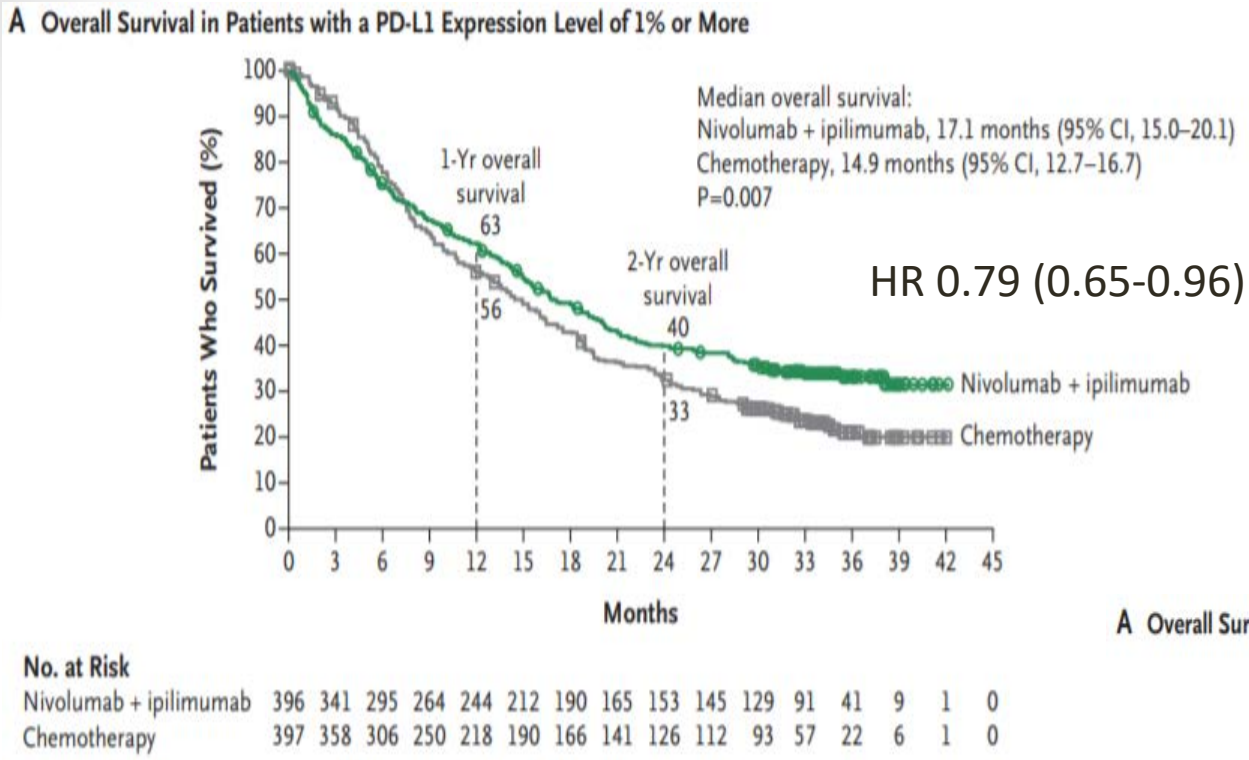


First line ipilimumab and nivolumab



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

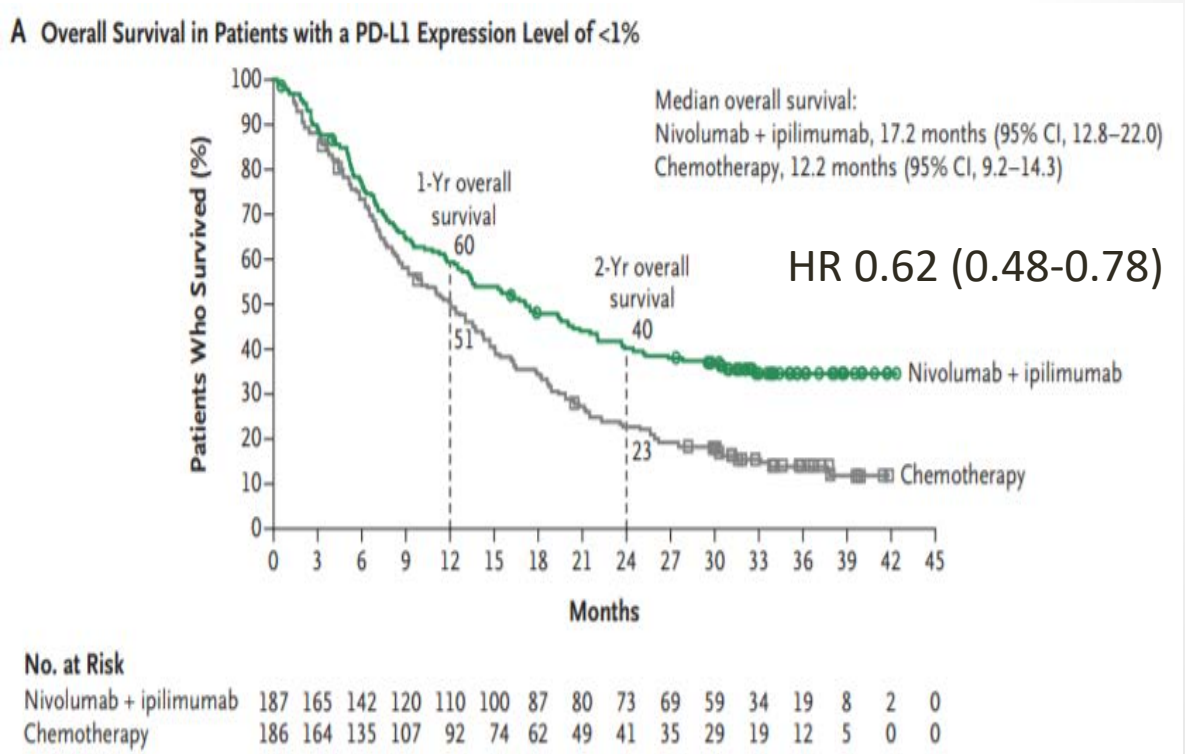
Hellmann et al. NEJM 2019; 381:21



HR 0.79 (0.65-0.96)

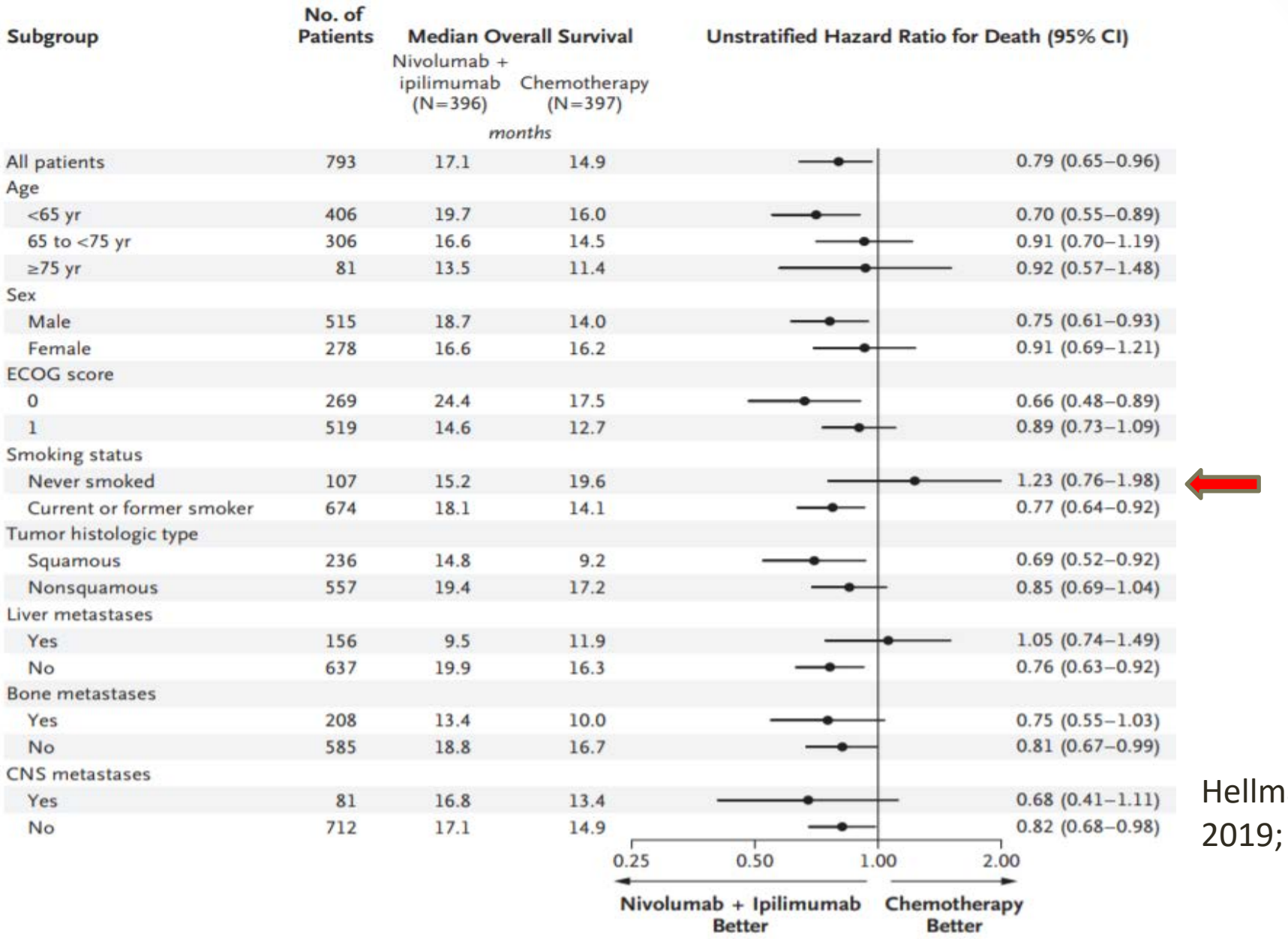
PD-L1 negative

PD-L1 positive



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

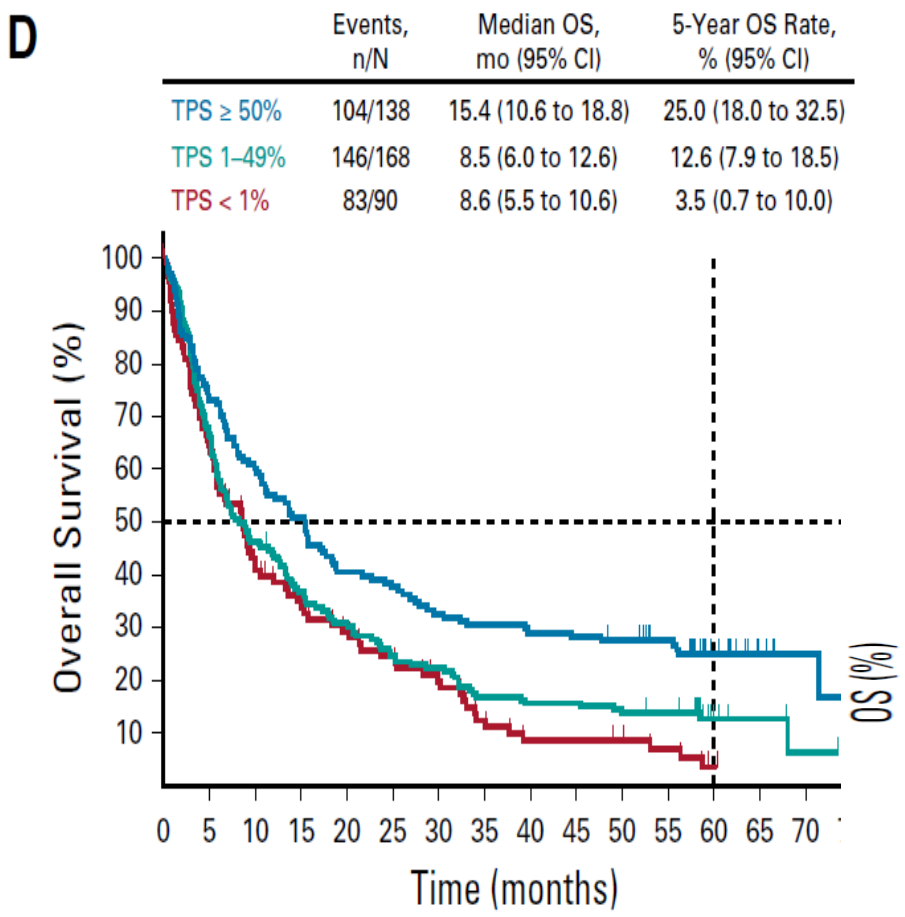
Second line ICI therapy (compared to docetaxel)

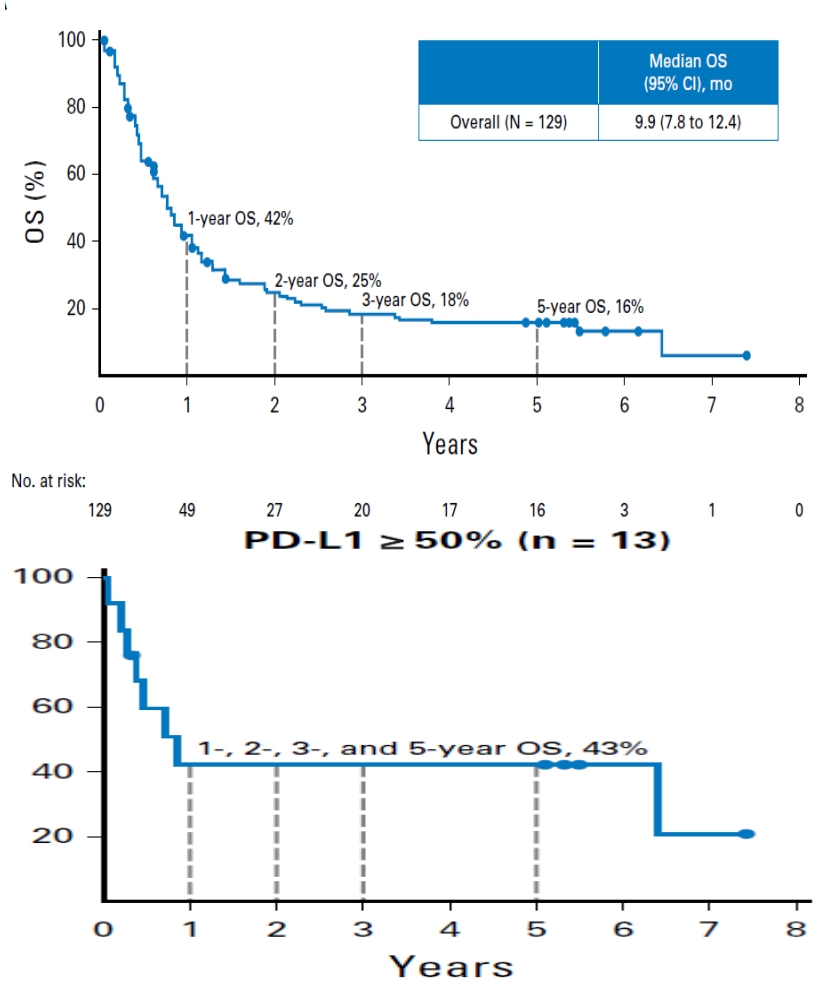
Drug	PD-L1 IHC	ORR (%)	PFS (mos)	OS (mos)
Nivolumab* (1)	Not required	19 vs 12	2.3 vs 4.2	12 vs 9.4
Pembrolizumab**(2)	>=1% (22C3)	18 vs 9	3.9 vs 4.0	10.4 vs 8.5
Atezolizumab (3)	Not required	14 vs 13	2.8 vs 4.0	13.8 vs 9.6

(1) Borghaei *et al*. CheckMate-057. NEJM 2015; 373 (17): 1627-39
(2) Herbst *et al*. KEYNOTE-010. Lancet 2016; 387: 1540-50
(3) Rittmeyer *et al*. OAK. Lancet 2017; 389: 255-265

* Non-squamous histology
**2mg/kg

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

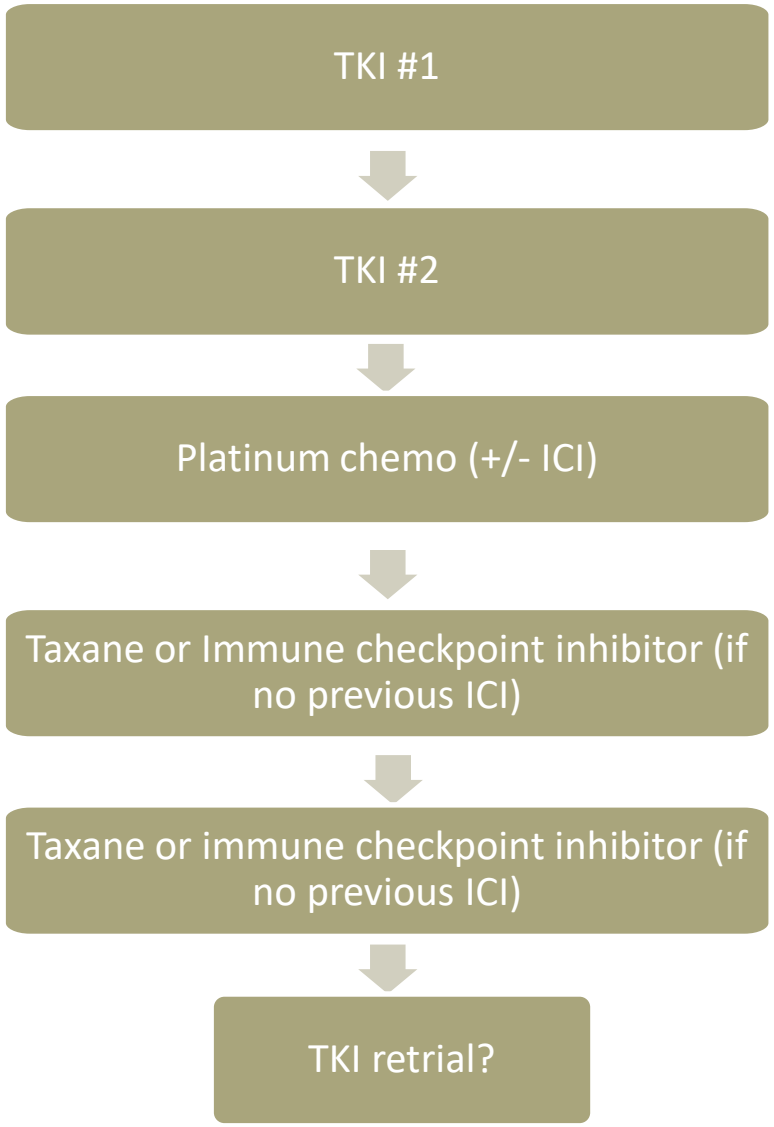
Summary - Immune checkpoint inhibitor

- Pembrolizumab or atezolizumab monotherapy is a reasonable option for PD-L1 high tumors (e.g. >50% using 22C3 IHC) 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)
- 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 (fatal hemoptysis)
  - Ramucirumab with docetaxel can be used in select patients
- 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)

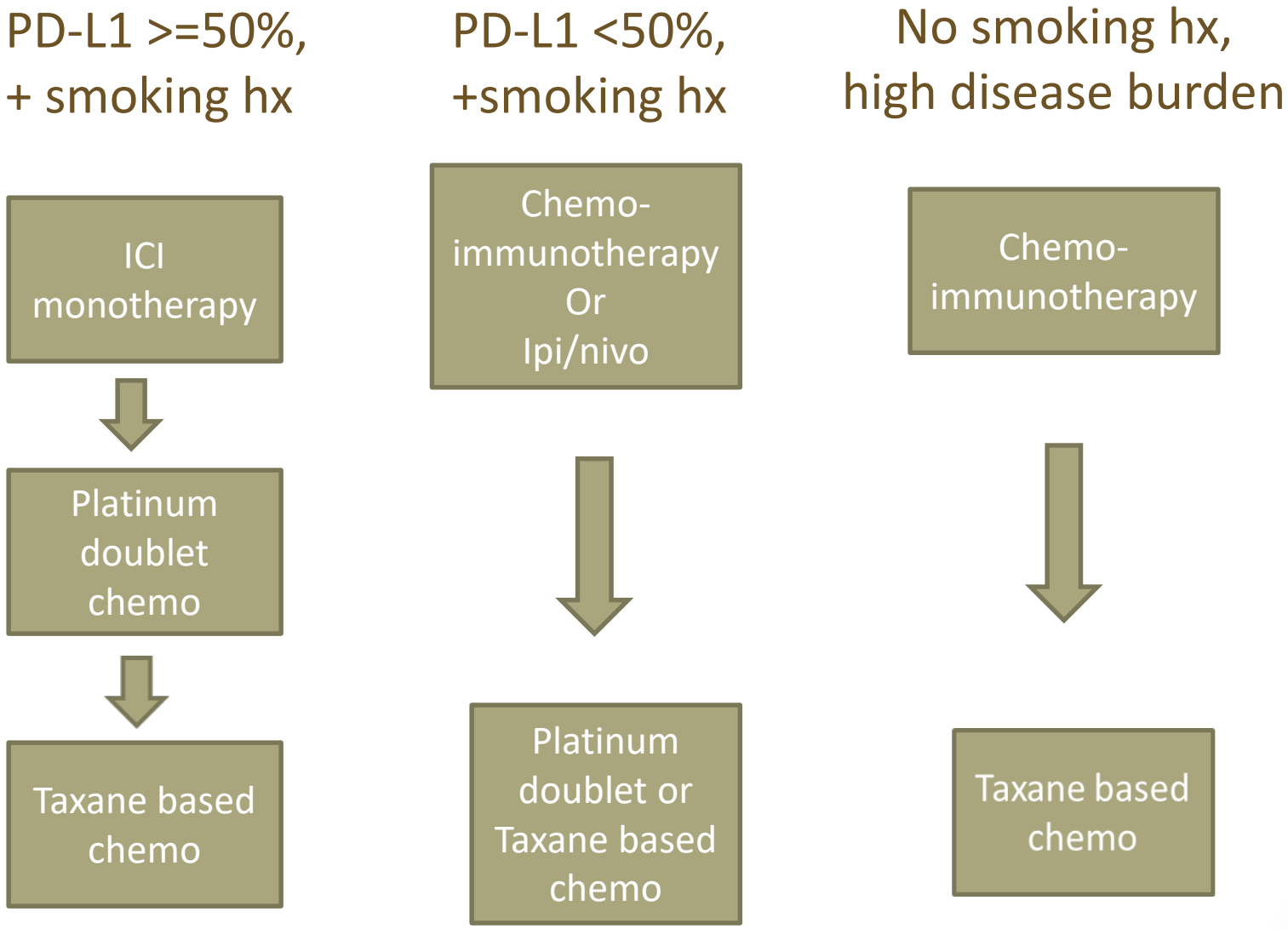
+ Molecular target



Data for frontline TKI:

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

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

- 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