Penn Medicine

EGFR: Common and Uncommon Mutations – What is Next for These Patient Populations?

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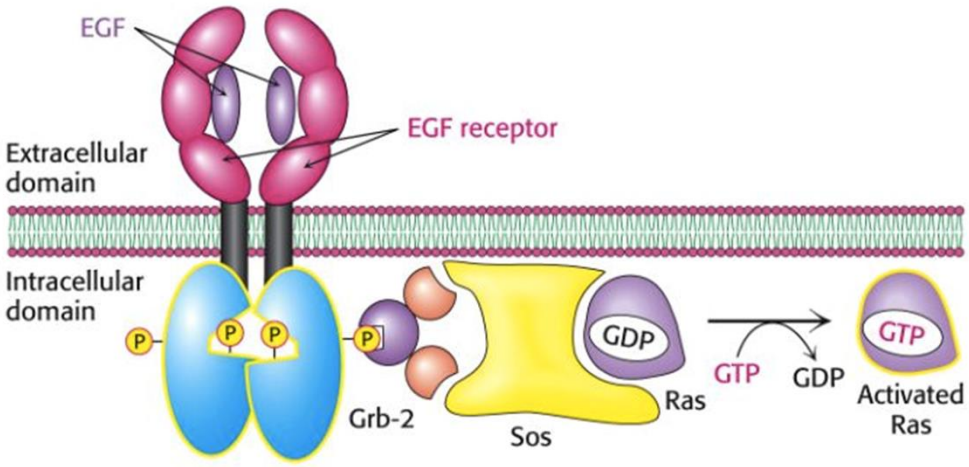
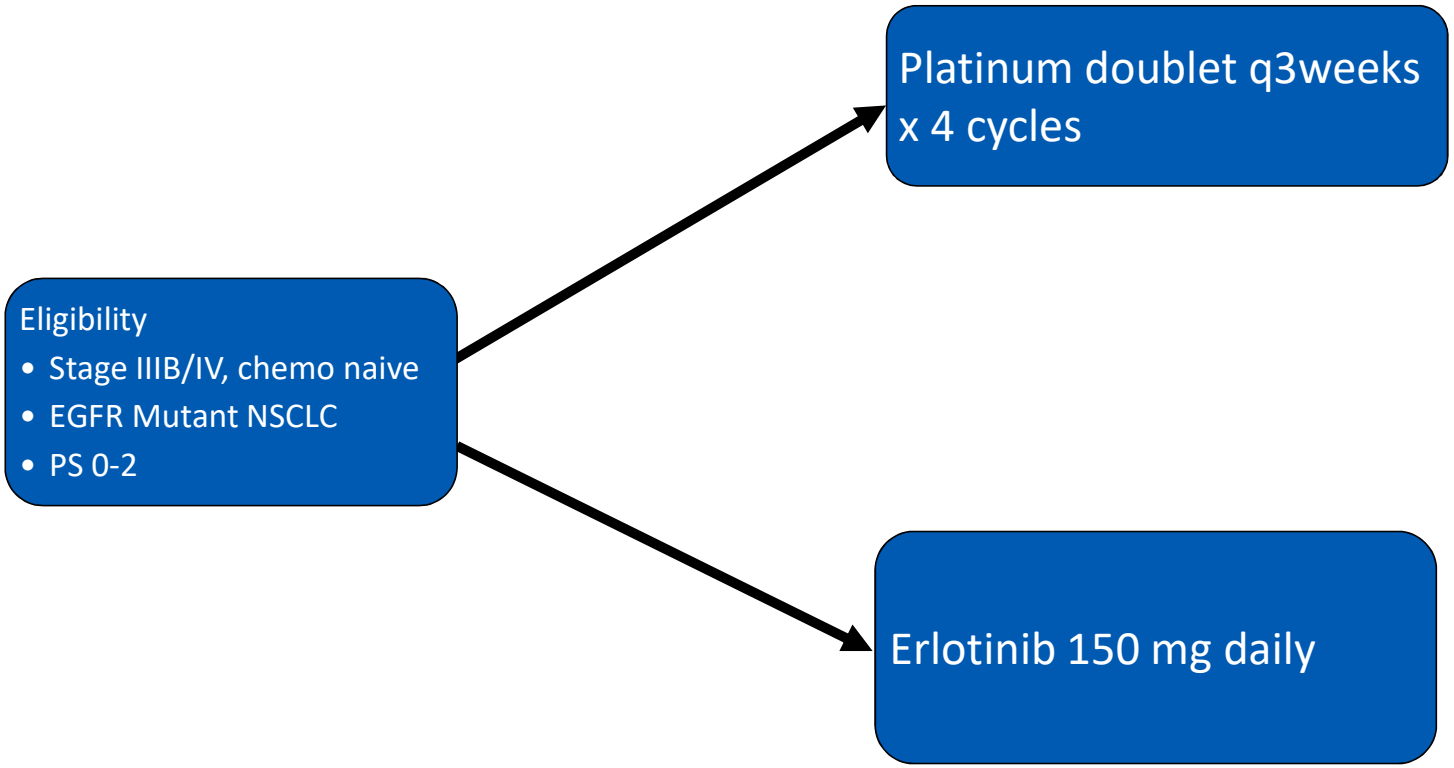
Epidermal Growth Factor Receptor

- Mutations seen 10-15% of Caucasians
  - 30-35% East Asians
- Strongly associated with epidemiology
  - Female
  - Never or light smokers (PY matters!)
- Exon 19 deletion and L8585R

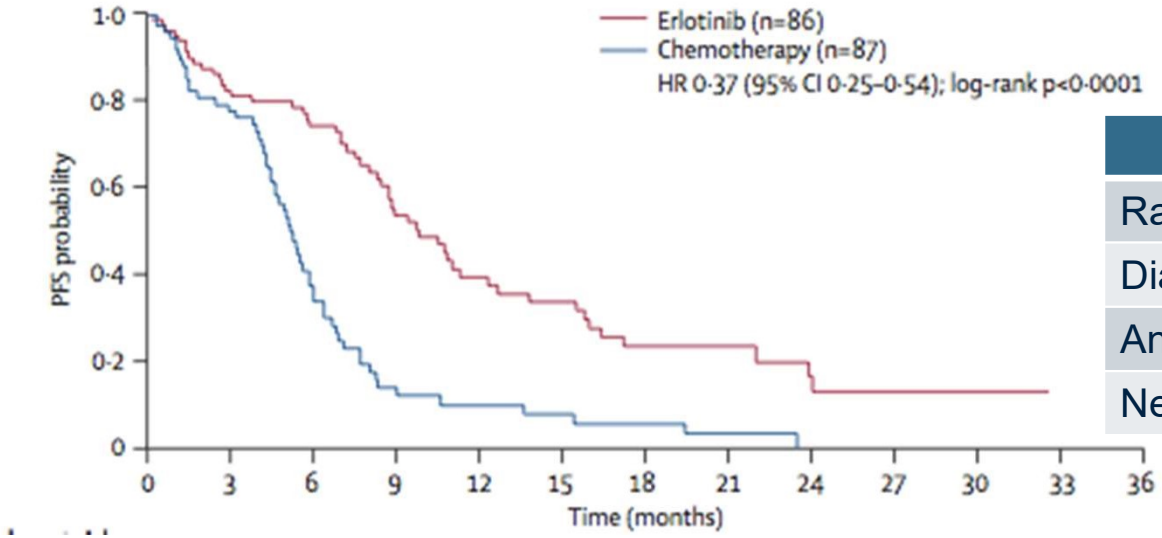


EURTAC: Erlotinib in EGFR Mutant NSCLC



Rosell et al Lancet Oncology 2012

EURTAC Results



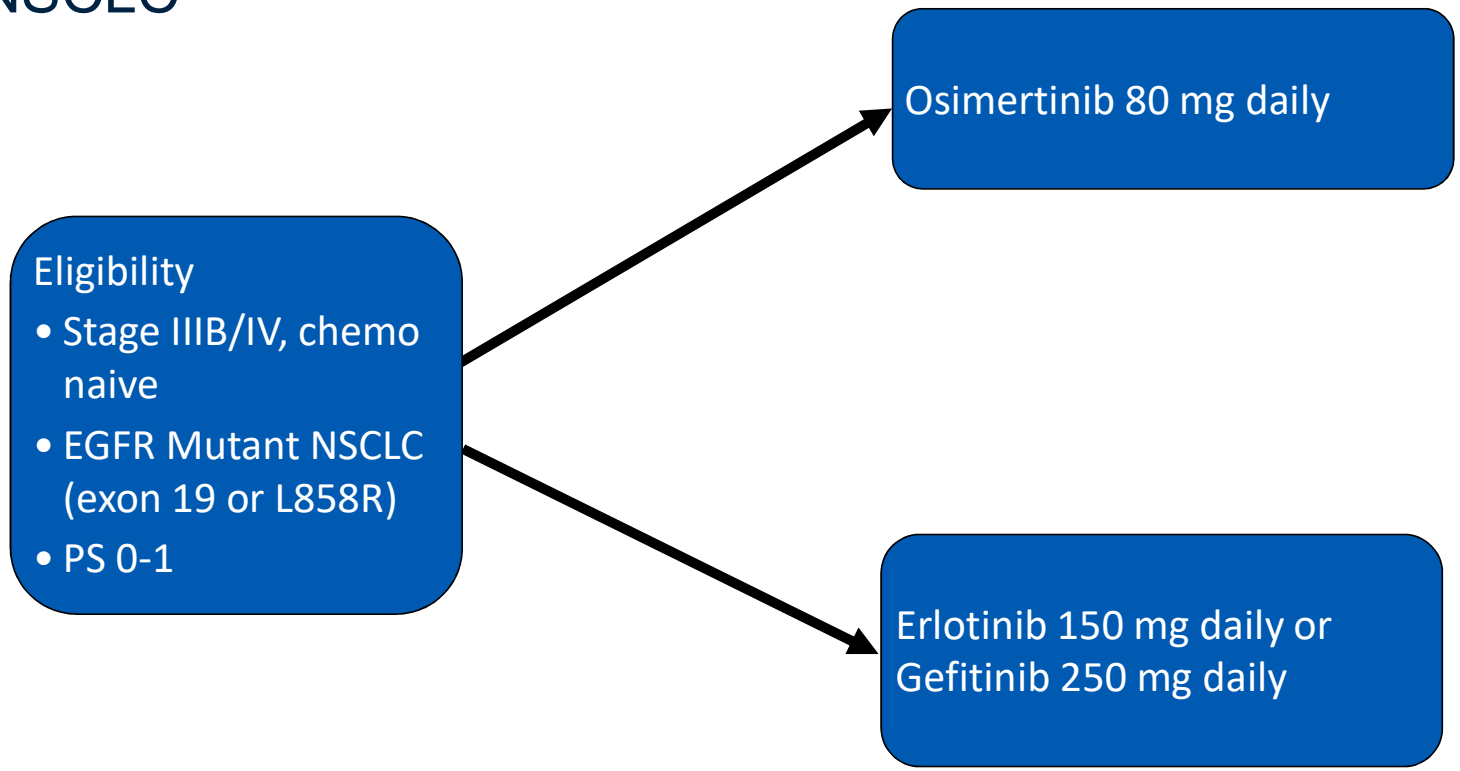
	Erlotinib	Chemotherapy
Rash	80%	5%
Diarrhea	57%	18%
Anemia	12%	49%
Neutropenia	0%	40%

Rosell et al Lancet Oncology 2012

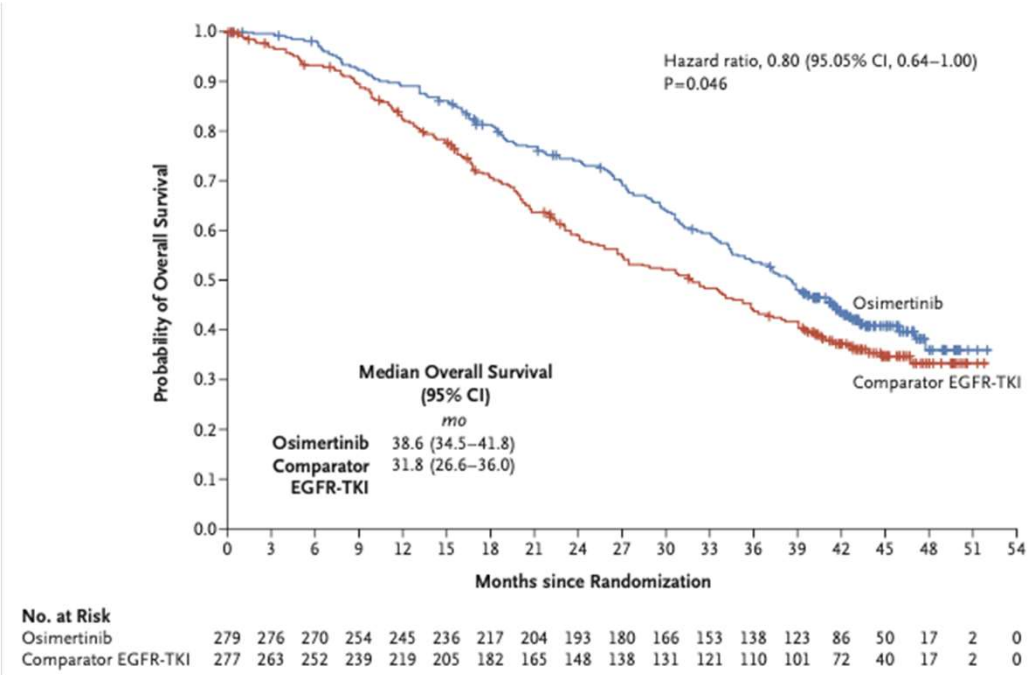
Other RCT's Comparing TKI to Chemo

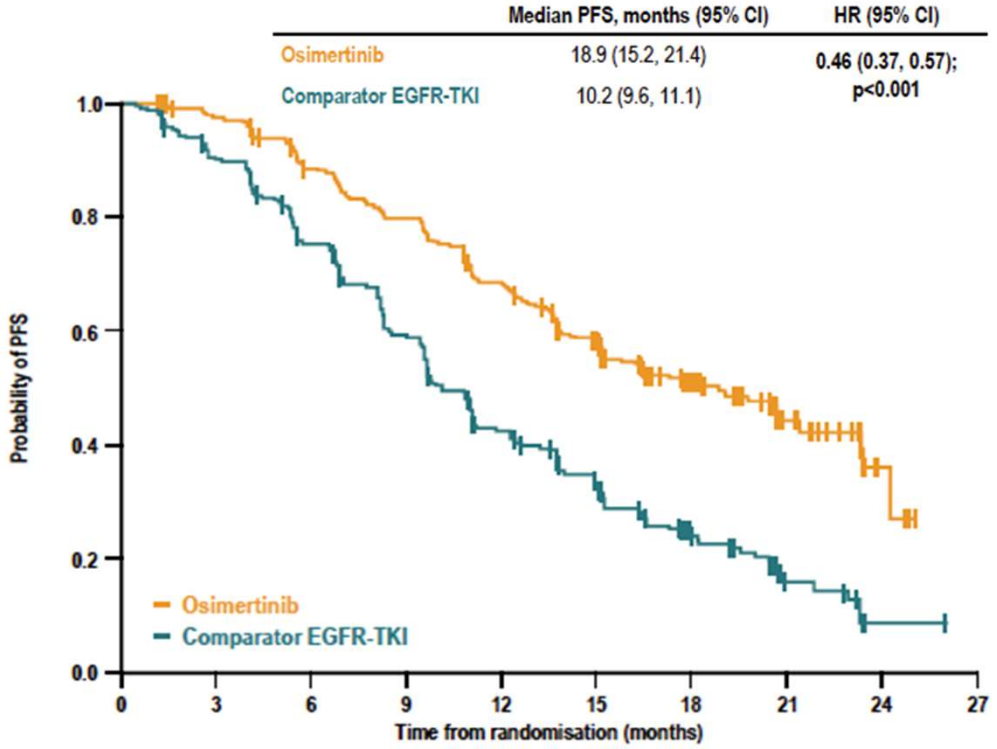
Author	Study	Agent	N (EGFR mut +)	RR	Median PFS (mos)	OS (mos)
Mok et al	IPASS	Gefitinib	261	**71.2% vs 47.3%**	**9.8 vs 6.4**	**21.6 vs 21.9**
Lee et al	First-SIGNAL	Gefitinib	42	**84.6% vs 37.5%**	**8.4 vs 6.7**	**27.2 vs 25.6**
Mitsudomi et al	WJTOG 3405	Gefitinib	177	**62.1% vs 32.2%**	**9.2 vs 6.3**	**35.5 vs 38.8**
Maemondo et al	NEJGSG002	Gefitinib	230	**73.7% vs 30.7%**	**10.8 vs 5.4**	**30.0 vs 23.6**
Zhou et al	OPTIMAL	Erlotinib	154	**83% vs 36%**	**13.1 vs 4.6**	**22.6 vs 28.8**
Rosell et al	EURTAC	Erlotinib	154	**54.5% vs 10.5%**	**9.2 vs 5.4**	**19.3 vs 19.5**
Yang et al	LUX-Lung 3	Afatinib	345	**56% vs 23%**	**13.6 vs 6.9**	**HR 1.12**
Wu et al	LUX-Lung 8	Afatinib	364	**67% vs 23%**	**11.0 vs 5.6**	**HR 0.95**
Mok et al	AURA3	Osimertinib	419	**71% vs 31%**	**10.1 vs 4.4**	**Unk**

FLAURA: Osimertinib vs SOC in 1st Line EGFR Mutant NSCLC



FLAURA Results



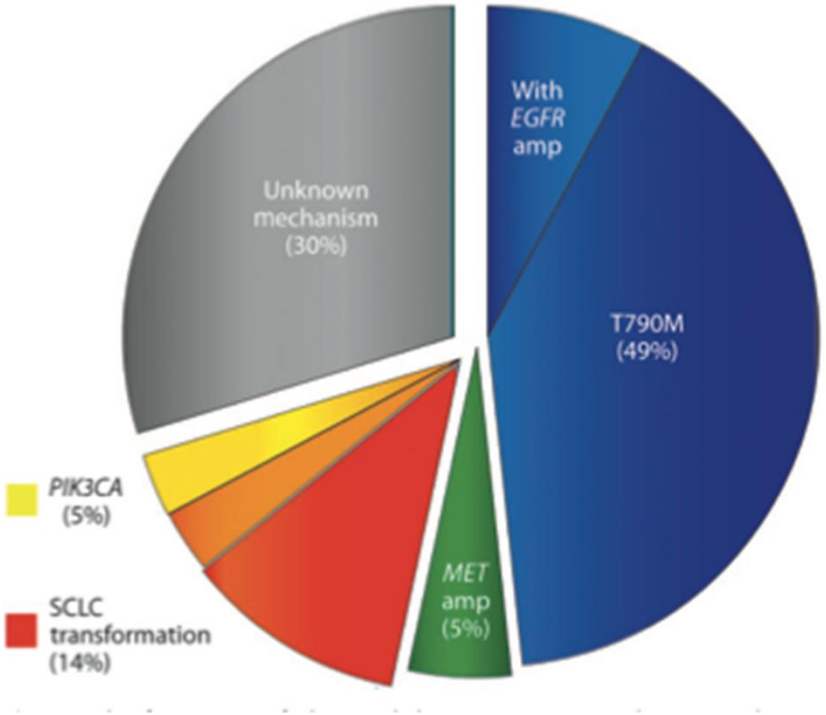


	Osimertinib	SOC
Rash	25%	48%
Diarrhea	58%	57%
Stomatitis	29%	20%

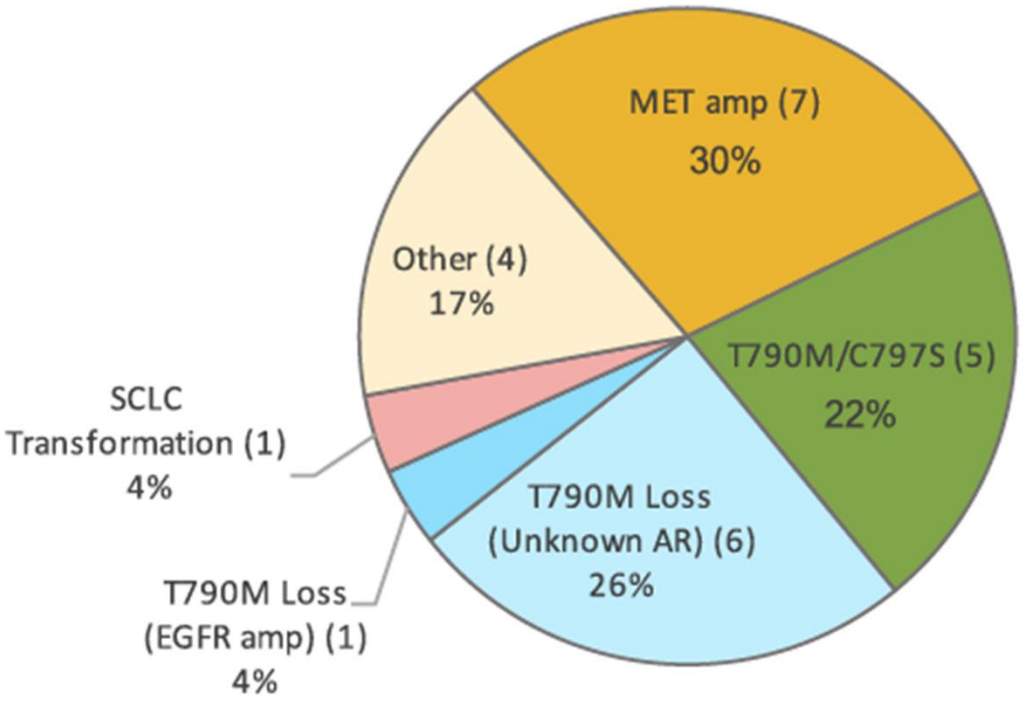
Ramalingam et al NEJM 2019
Ramalingam et al ESMO 2019

What happens after osimertinib?

First Generation Resistance

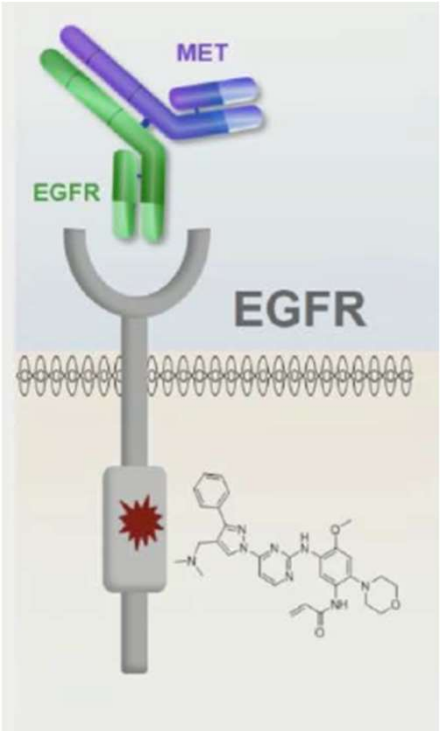


Osimertinib Resistance

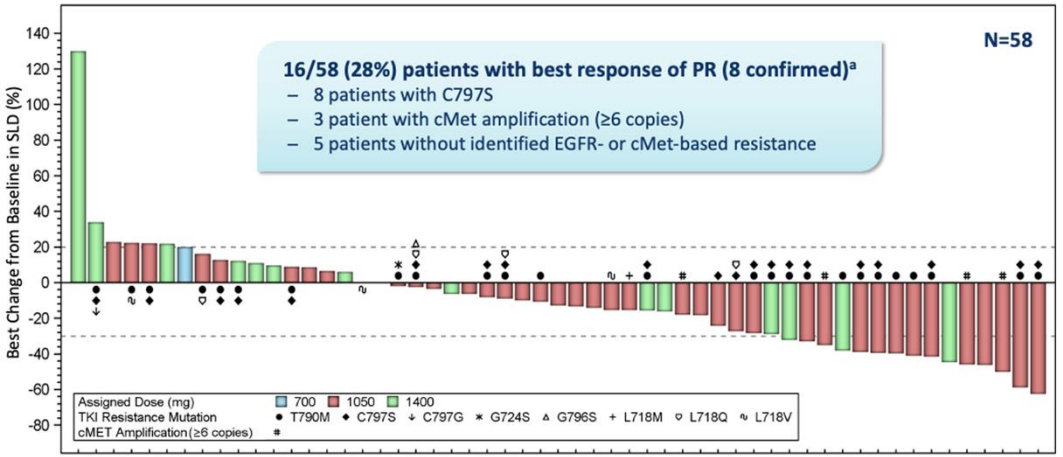


Sequist et al Sci Transl Med 2011
Piotrowska et al ASCO 2017

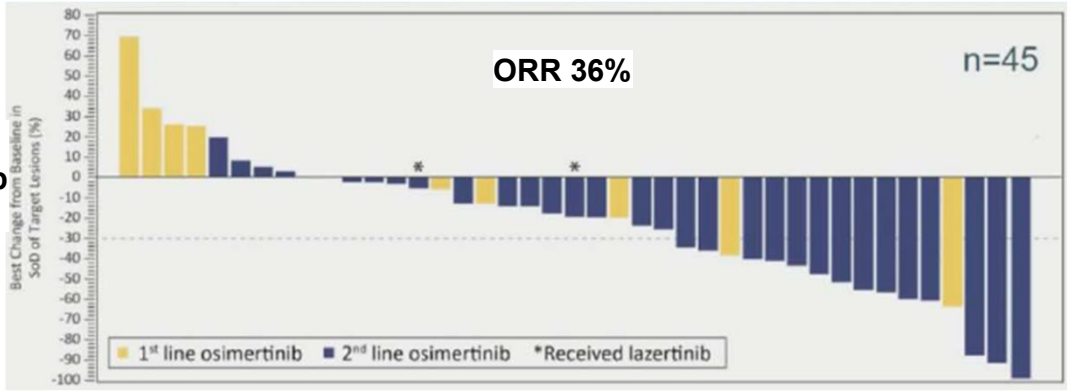
Amivantamab +/- Lazertinib efficacy



Amivantamab After 3G TKI

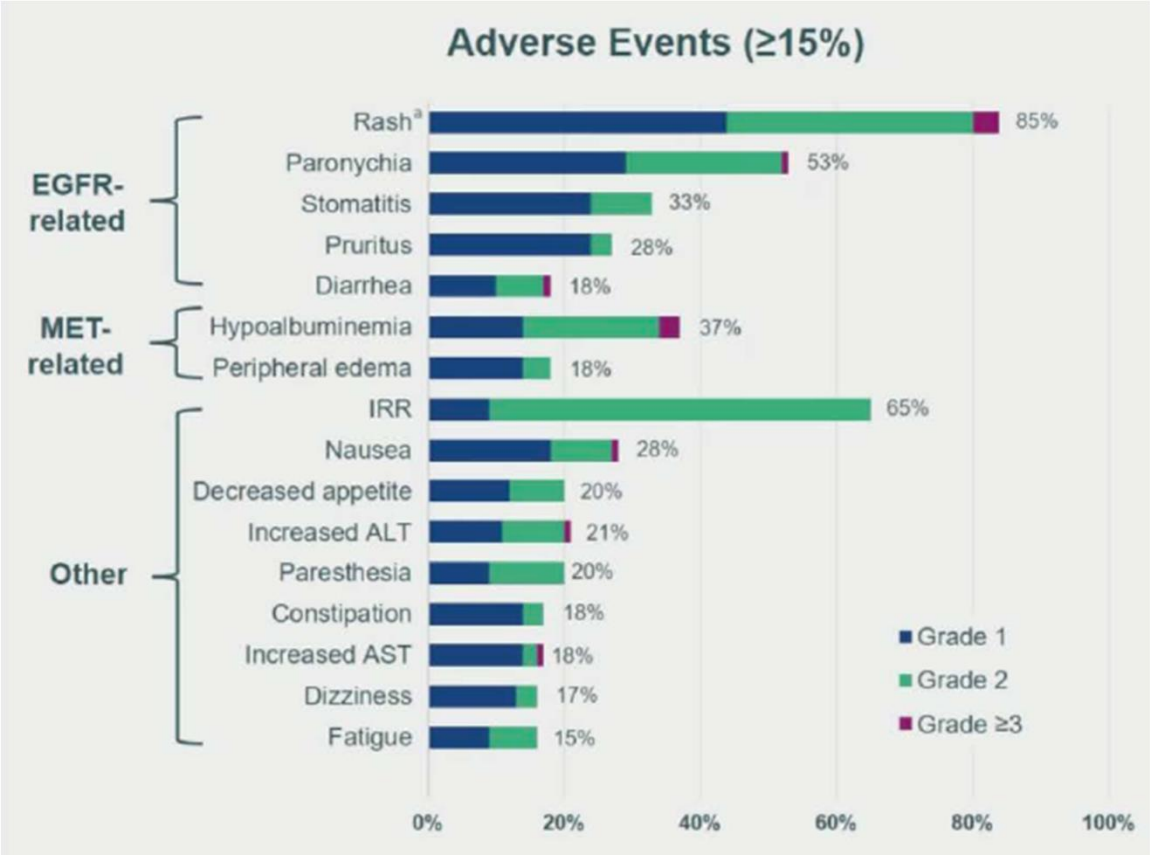


Amivantamab and Lazertinib After 3G TKI



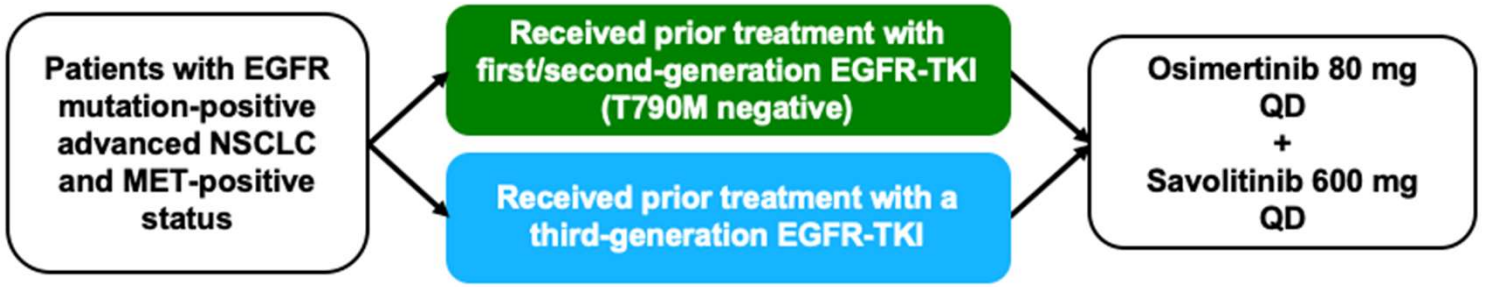
Haura et al ASCO 2019
Cho et al ESMO 2020

Amivantamab/Lazertinib Toxicity



Cho et al ESMO 2020

Osimertinib/savolitinib



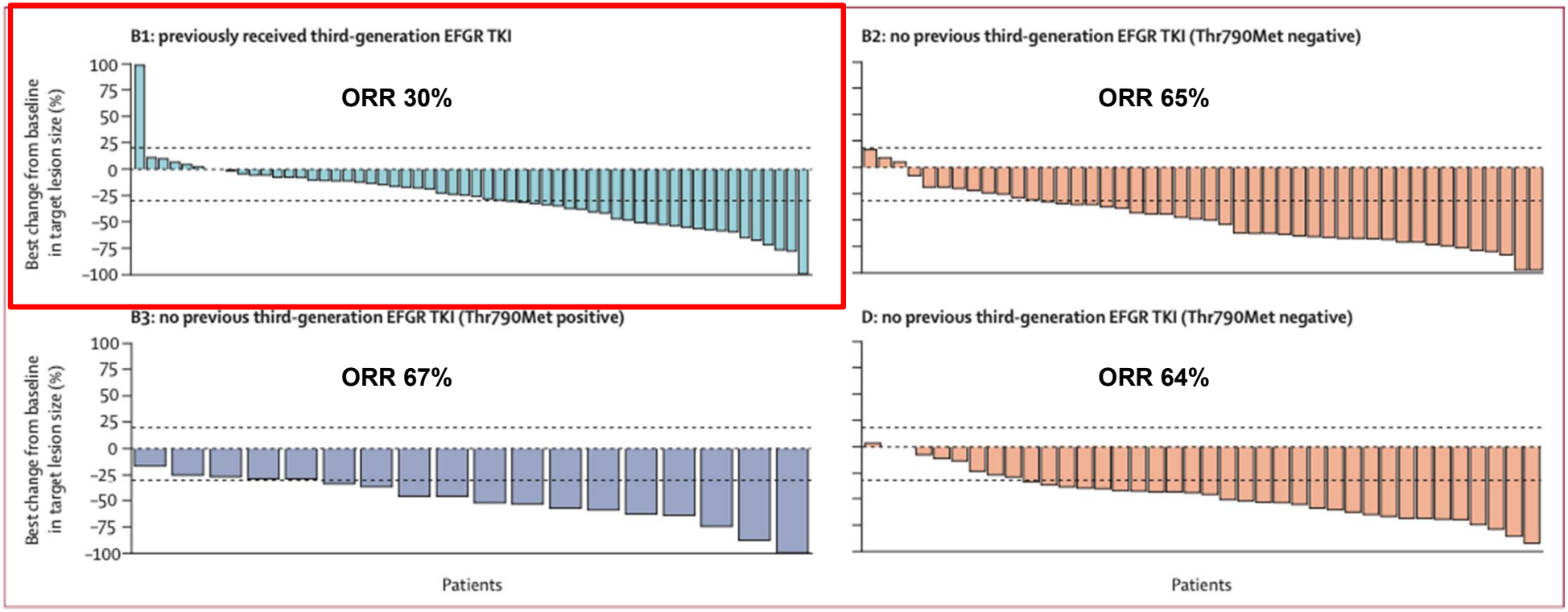
Primary endpoint:
- Safety and tolerability

Secondary endpoint:
- Preliminary assessment of anti-tumor activity (RECIST v1.1): ORR, DoR, time to response

MET Amplification could be defined by
FISH: GCN≥5 or MET:CEP7 ≥2
IHC: MET 3+ in ≥50% tumor
NGS: ≥5 copies of MET
Dose changed to 300 mg daily for expansion

Sequist et al AACR 2019
Sequist et al Lancet 2020

Osimertinib/savolitinib efficacy



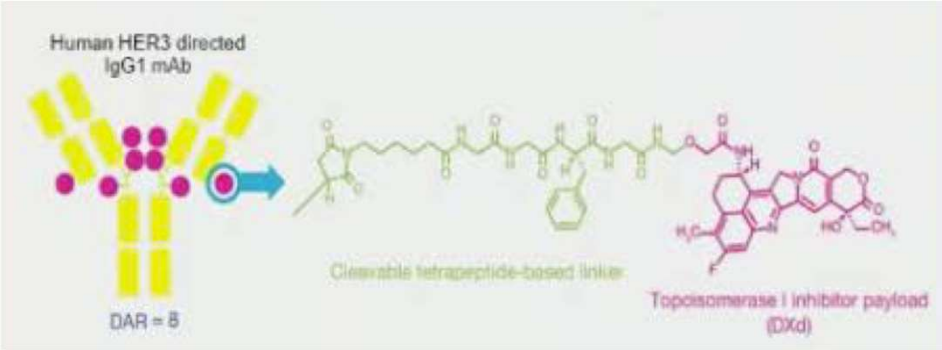
Sequist et al Lancet 2020

Osimertinib/savolitinib toxicity

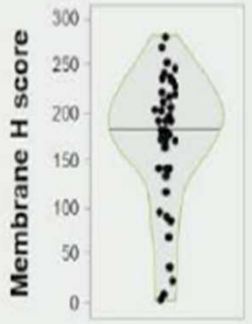
	Part B: osimertinib 80 mg plus savolitinib 600 mg or 300 mg (n=138)*					Part D: osimertinib 80 mg plus savolitinib 300 mg (n=42)				
	All part B patients†	Grade 1–2	Grade 3	Grade 4	Grade 5	All part D patients	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	67 (49%)	63 (46%)	4 (3%)	0	0	13 (31%)	13 (31%)	0	0	0
Decreased appetite	47 (34%)	39 (28%)	5 (4%)	0	0	6 (14%)	5 (12%)	1 (2%)	0	0
Fatigue	48 (35%)	40 (29%)	6 (4%)	0	0	4 (10%)	4 (10%)	0	0	0
Peripheral oedema	44 (32%)	40 (29%)	3 (2%)	0	0	8 (19%)	8 (19%)	0	0	0
Vomiting	46 (33%)	40 (29%)	6 (4%)	0	0	5 (12%)	5 (12%)	0	0	0
Diarrhoea	39 (28%)	35 (25%)	4 (3%)	0	0	8 (19%)	6 (14%)	2 (5%)	0	0
Paronychia	30 (22%)	27 (20%)	3 (2%)	0	0	7 (17%)	7 (17%)	0	0	0
Pyrexia	29 (21%)	28 (20%)	1 (1%)	0	0	6 (14%)	6 (14%)	0	0	0
Rash	26 (19%)	23 (17%)	3 (2%)	0	0	8 (19%)	8 (19%)	0	0	0
Stomatitis	26 (19%)	26 (19%)	0	0	0	4 (10%)	4 (10%)	0	0	0
Constipation	26 (19%)	24 (17%)	0	0	0	3 (7%)	3 (7%)	0	0	0
Pruritus	24 (17%)	23 (17%)	1 (1%)	0	0	5 (12%)	5 (12%)	0	0	0
Myalgia	22 (16%)	17 (12%)	3 (2%)	0	0	6 (14%)	5 (12%)	1 (2%)	0	0
Cough	22 (16%)	21 (15%)	0	0	0	4 (10%)	3 (7%)	1 (2%)	0	0
Headache	23 (17%)	23 (17%)	0	0	0	3 (7%)	3 (7%)	0	0	0
Dizziness	20 (14%)	20 (14%)	0	0	0	5 (12%)	5 (12%)	0	0	0
White blood cell count decreased	20 (14%)	16 (12%)	4 (3%)	0	0	4 (10%)	4 (10%)	0	0	0
Alanine aminotransferase increased	20 (14%)	13 (9%)	7 (5%)	0	0	3 (7%)	3 (7%)	0	0	0
Aspartate aminotransferase increased	21 (15%)	12 (9%)	8 (6%)	1 (1%)	0	2 (5%)	2 (5%)	0	0	0

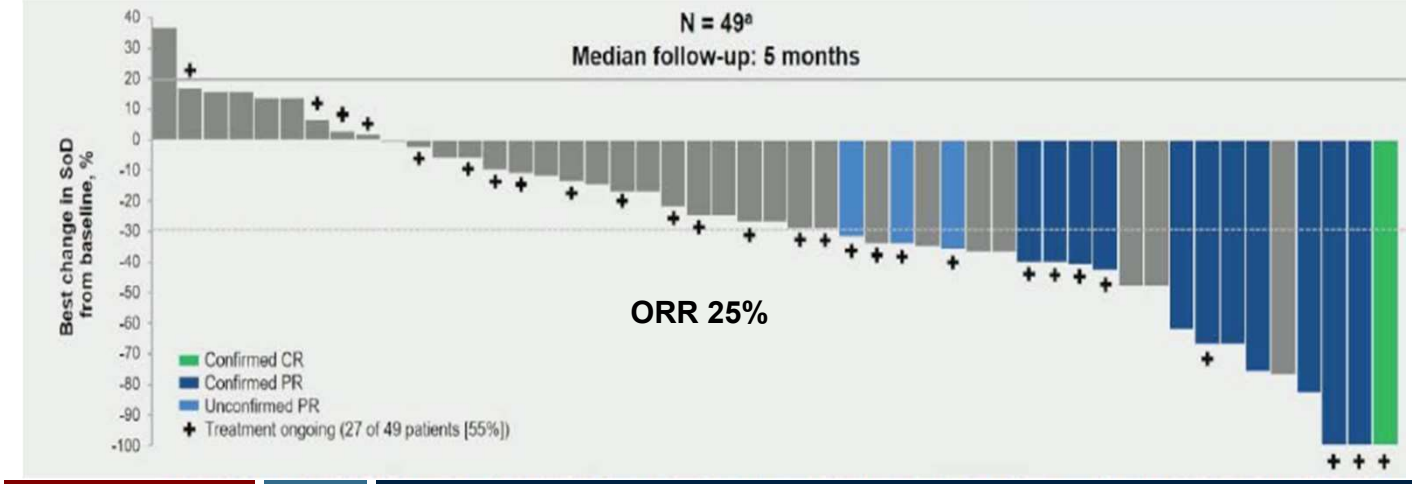
Sequist et al Lancet 2020

Patritumab Deruxtecan



HER3 expression	
Evaluable patients, n	43
Median membrane H score (range)	180 (2-280)





Yu et al ESMO 2020

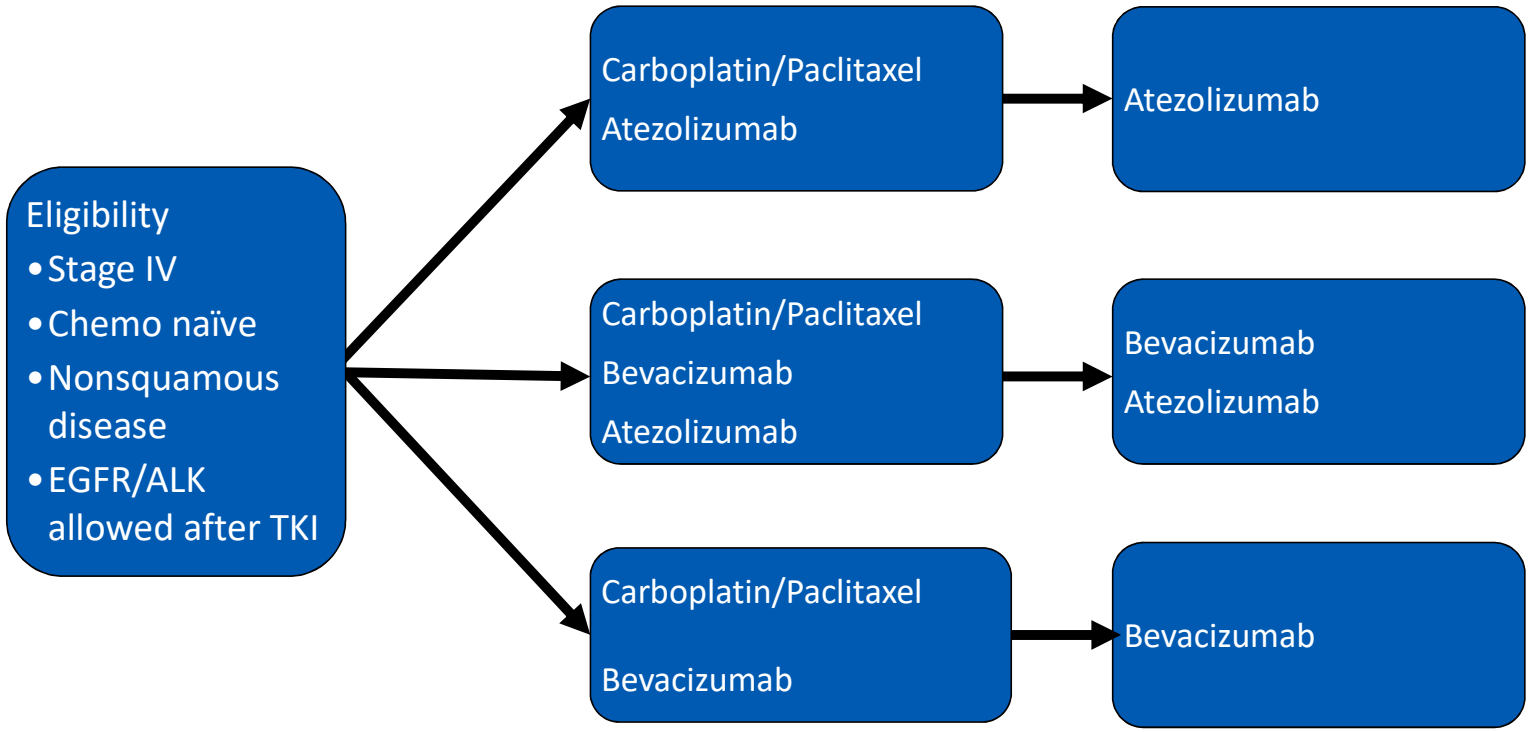
Patritumab deruxtecan Toxicity

TEAEs (regardless of causality), n (%)	N = 57
TEAEs	57 (100)
Grade ≥3	38 (67)
Associated with discontinuation	5 (9)
Associated with dose reduction	10 (18)
Associated with dose interruption	17 (30)
Associated with death	3 (5)
Treatment-emergent SAEs	21 (37)
Grade ≥3	18 (32)
Treatment related	11 (19)

TEAEs in ≥20% of patients, n (%)	N = 57	
	All grades	Grade ≥3
Fatigue	33 (58)	5 (9)
Nausea	31 (54)	2 (4)
Thrombocytopenia[a]	30 (53)	16 (28)
Decreased appetite	20 (35)	1 (2)
Neutropenia[b]	19 (33)	11 (19)
Vomiting	17 (30)	1 (2)
Alopecia	17 (30)	NA
Anemia[c]	15 (26)	5 (9)
Constipation	14 (25)	0

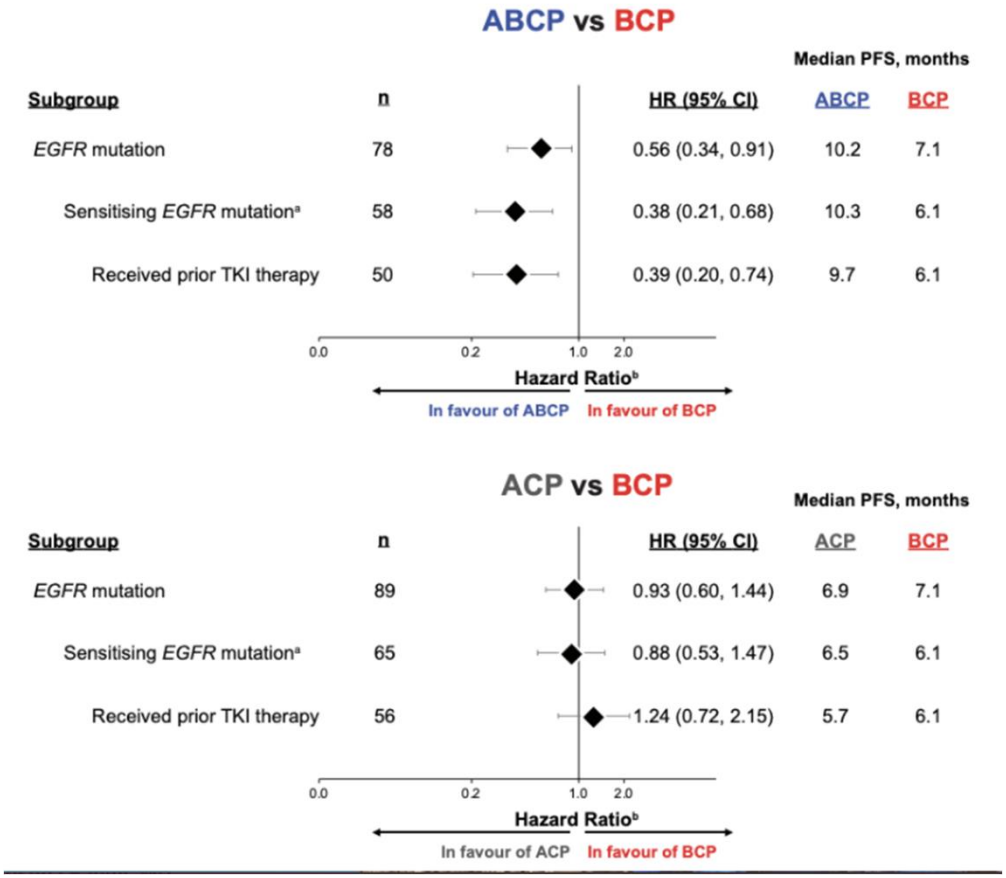
Yu et al ESMO 2020

What about IMPOWER 150



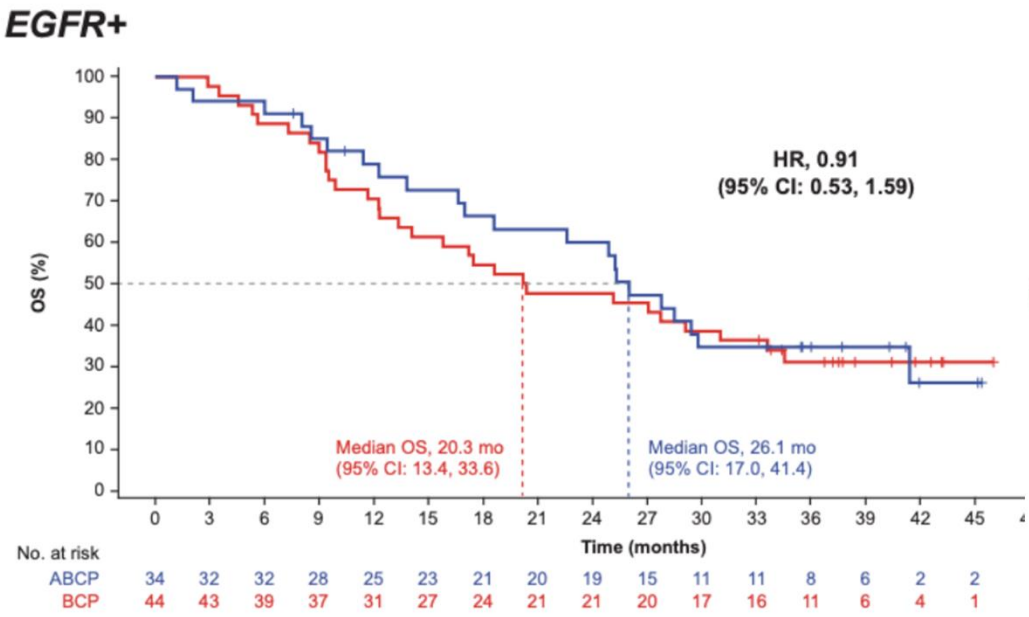
Socinski et al NEJM 2018

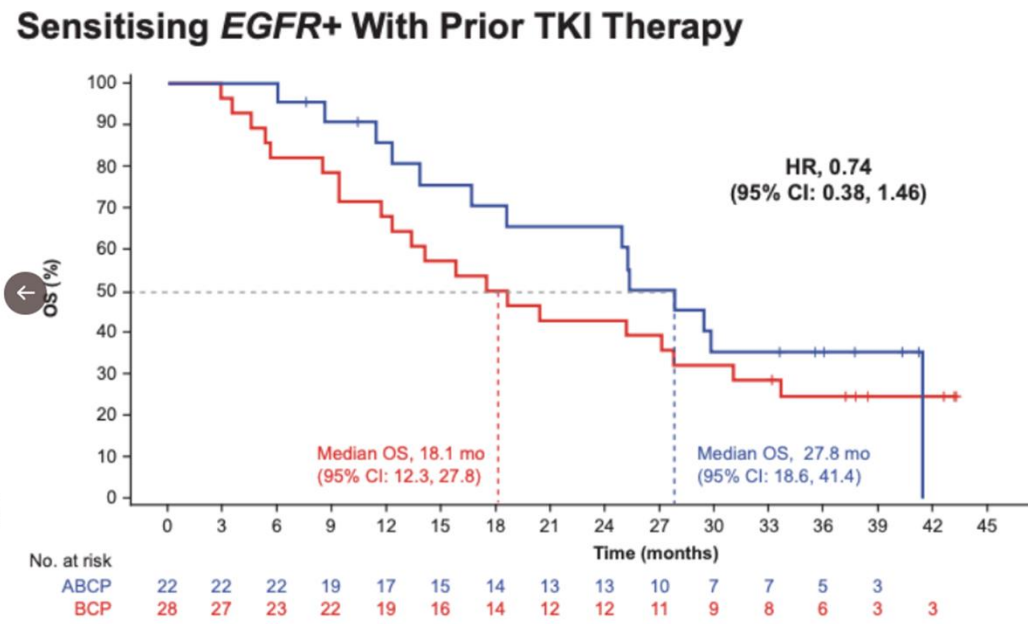
IMPOWER 150 Updated EGFR Results



Reck et al ESMO 2020

IMPOWER 150 Updated EGFR Results





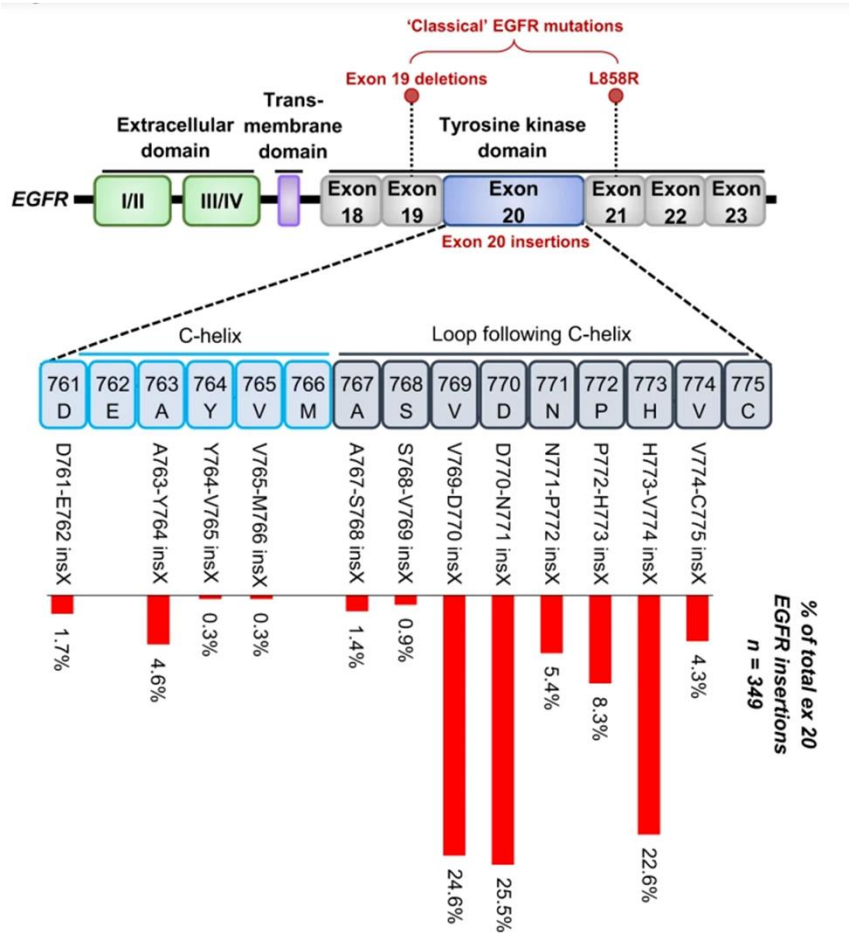
Reck et al ESMO 2020

What do I do now?

- Repeat molecular interrogation
  - Including MET FISH!
- If MET+ trial or adding on MET inhibitor
- If MET- and no trial, I generally do osi+chemo

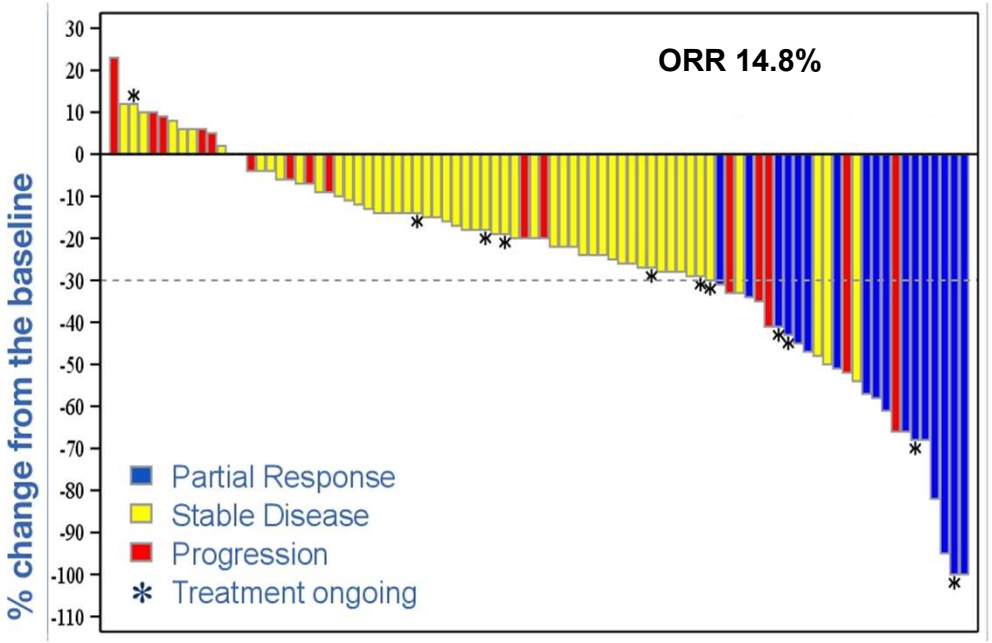
EGFR Exon 20 Insertions

- 4-10% of all EGFR mutant NSCLC
  - This could be limited by testing type
- Traditional TKI's have limited activity
- Worse prognosis than other EGFR+ NSCLC



Vyse et al Signal Transduction and Targeted Therapy 2019

Poziotinib

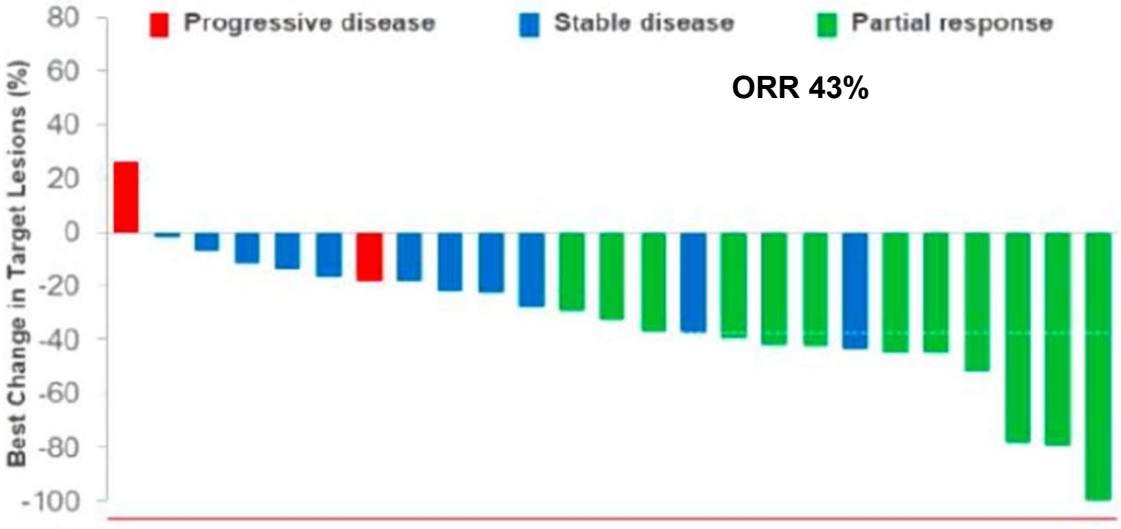


	N=90, n (%)
Treatment-related AE	88 (98)
Treatment-related Serious AE	13 (14)
Dose interruptions	78 (87)
Dose reductions	70 (78)
AE related permanent discontinuation	11 (12)

Preferred Term (PT)	N=90, n (%)		
	Any Grade	Grade 3	Grade 4
Diarrhea	74 (82)	23 (26)	0
Rash	61 (68)	27 (30)	0
Stomatitis / Mucosal Inflammation	59 (66)	20 (22)	1 (1)
Paronychia	34 (38)	1 (1)	0
Pneumonitis	1 (1)	0	0

Le et al ASCO 2020
Socinski et al ESMO 2020

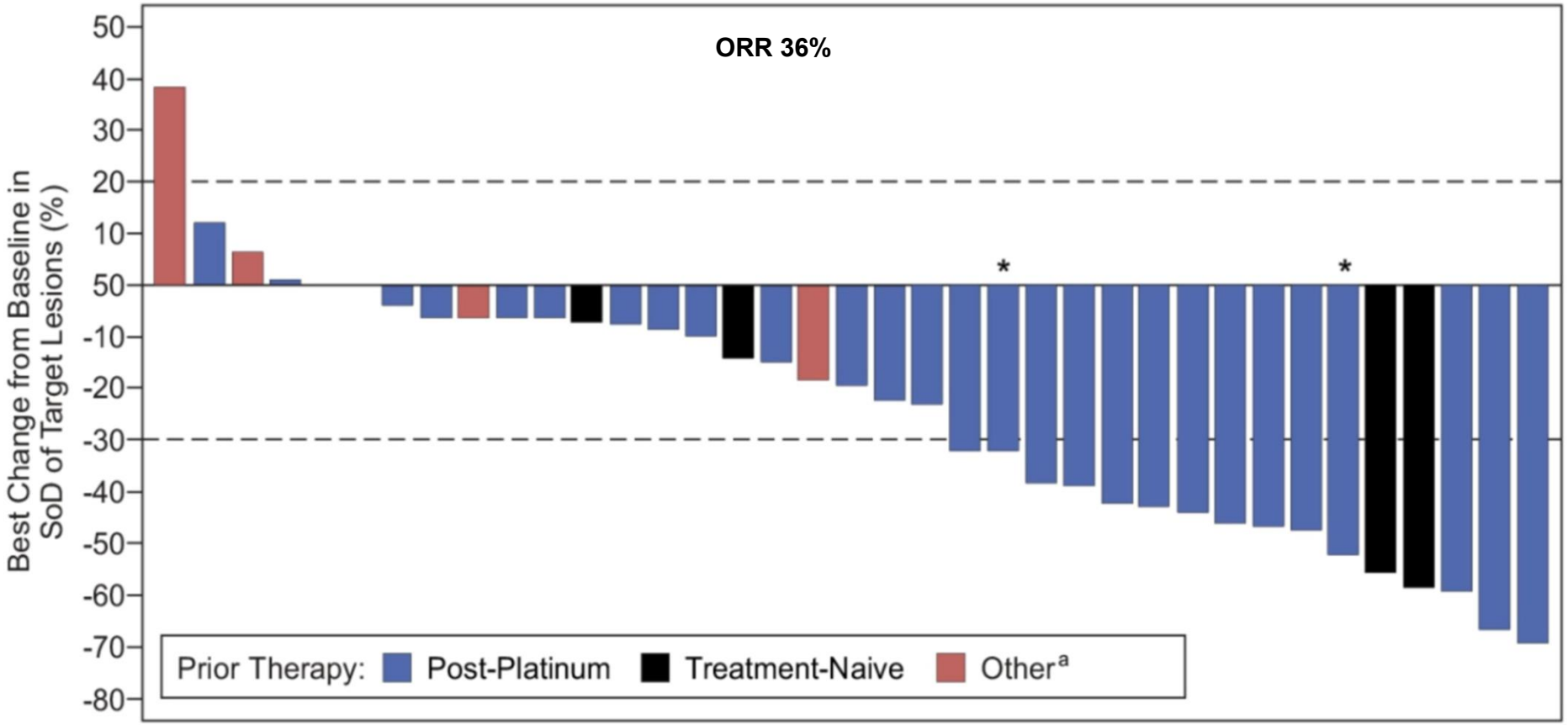
Mobocertinib



Any grade: ≥20% of all patients Grade ≥3: ≥5% of all patients	Patients With *EGFR* Exon 20 Insertions Treated at 160 mg qd (n=28)		All Patients Treated at 160 mg qd[a] (n=136)	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Diarrhea	82	32	83	21
Nausea	39	11	43	4
Rash	46	0	33	1
Vomiting	36	7	26	4
Decreased appetite	39	0	26	1
Dry skin	18	0	21	0
Fatigue	14	4	22	1

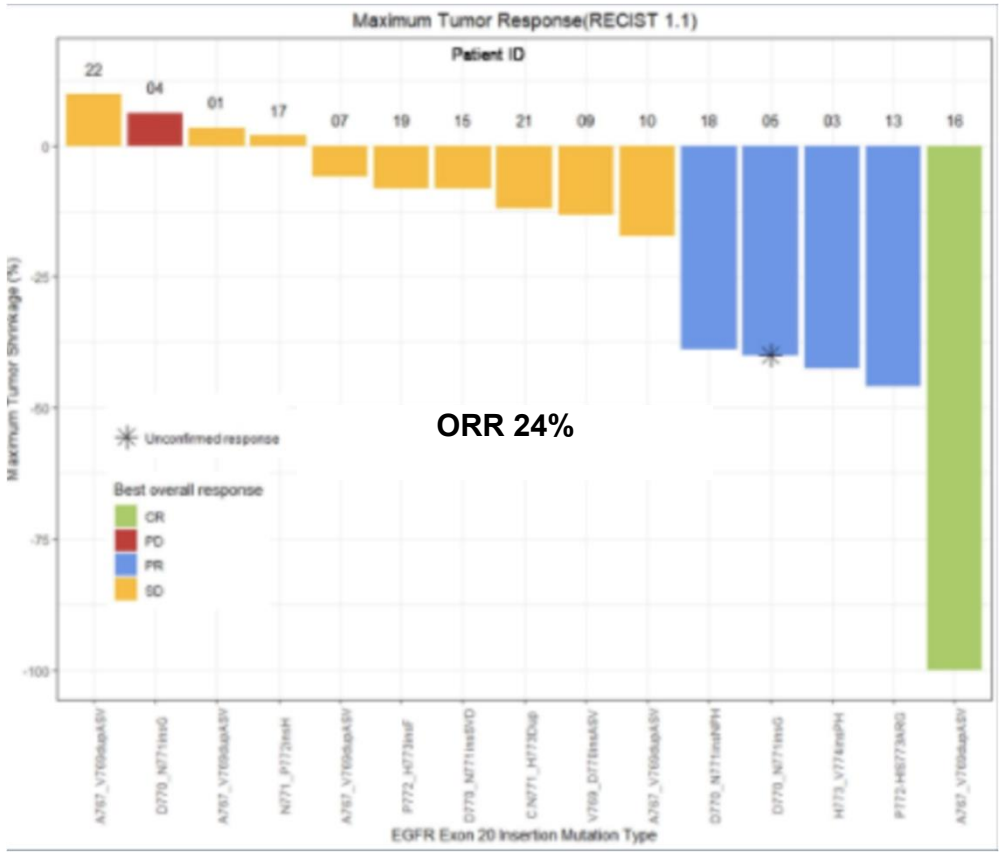
Riely et al ESMO 2020

Amivantamab



Park et al ASCO 2020

High dose osimertinib



Piotrowska et al ASCO 2020

What do I do now?

- Trials are critical!
- Osimertinib is accessible off label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