BEST PRACTICES IN ALK+ LUNG CANCER

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Johns Hopkins

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Conquering Thoracic Cancers Worldwide

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Agenda

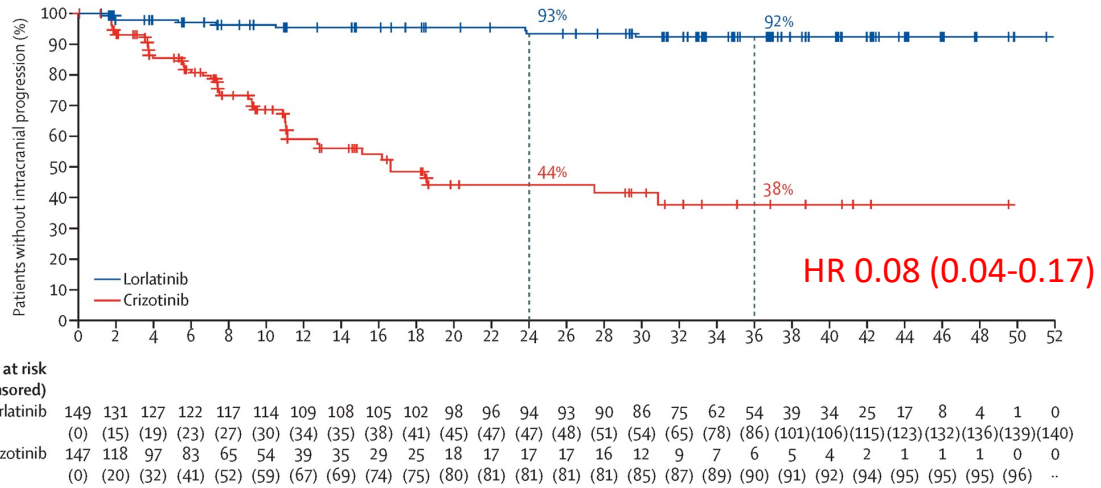
- Should lorlatinib be the **preferred first-line TKI**?
- Opportunities to **consolidate TKI response** and potentially improve survival
- Treatment **options upon TKI progression**

Lorlatinib is the most potent TKI currently FDA-approved

	Crizotinib	Ceritinib	Alectinib	Brigatinib	Ensartinib	Lorlatinib
	1st generation		2nd generation			3rd generation
Trial	PROFILE 1014	ASCEND-4	ALEX	ALTA-1L	eXalt3	CROWN
Comparator	Platinum/pem	Platinum/pem	Crizotinib	Crizotinib	Crizotinib	Crizotinib
ORR	74%	73%	83%	71%	74%	77%
Median PFS	10.9 mo	16.6 mo	25.7 mo *(34.8 updated)*	24.0 mo	25.8 mo	Not reached
PFS HR	0.45	0.55	0.50 *(0.43 updated)*	0.49	0.51	0.27
3-year PFS	-	-	43% (vs 14%)	43% (vs 19%)	-	64% (vs 19%)
Reference	Solomon et al, NEJM 2014	Soria et al, Lancet 2017	Peters et al, NEJM 2017 (Mok et al, Ann Onc 2020)	Camidge et al, NEJM 2018; Camidge et al, JCO 2020	Horn et al, JAMA Onc 2021	Shaw et al, NEJM 2020; Solomon et al, Lancet Resp Med 2023

CNS efficacy is a major differentiator

Intracranial time to progression (IIT)



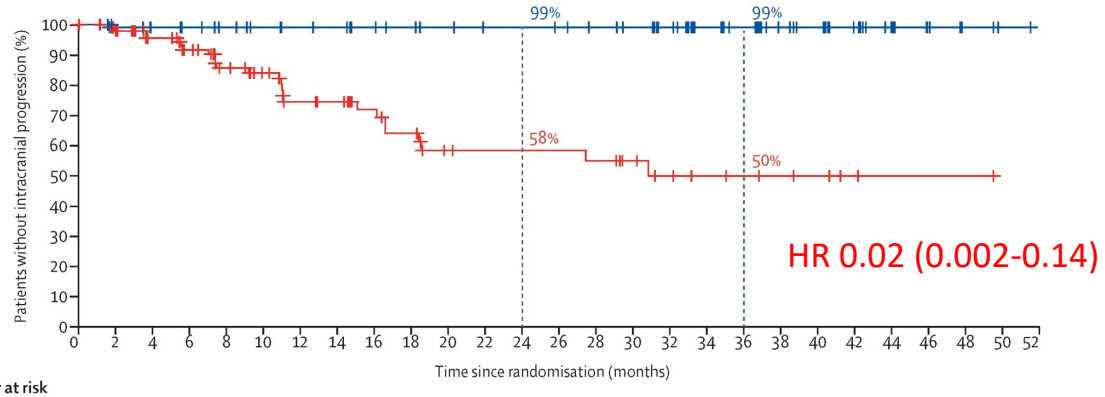
HR 0.08 (0.04-0.17)

Number at risk (number censored)

Lorlatinib	149	131	127	122	117	114	109	108	105	102	98	96	94	93	90	86	75	62	54	39	34	25	17	8	4	1	0
	(0)	(15)	(19)	(23)	(27)	(30)	(34)	(35)	(38)	(41)	(45)	(47)	(47)	(48)	(51)	(54)	(65)	(78)	(86)	(101)	(106)	(115)	(123)	(132)	(136)	(139)	(140)
Crizotinib	147	118	97	83	65	54	39	35	29	25	18	17	17	17	16	12	9	7	6	5	4	2	1	1	1	0	0
	(0)	(20)	(32)	(41)	(52)	(59)	(67)	(69)	(74)	(75)	(80)	(81)	(81)	(81)	(81)	(85)	(87)	(89)	(90)	(91)	(92)	(94)	(95)	(95)	(95)	(96)	..

	Lorlatinib (n=149)	Crizotinib (n=147)
Events	9	51
Number censored	140	96
Median time to intracranial progression, months (95% CI)	NR (NR–NR)	16·6 (11·1–NR)
HR (95% CI)	0·08 (0·04–0·17)	

Intracranial time to progression (without baseline brain metastasis)



HR 0.02 (0.002-0.14)

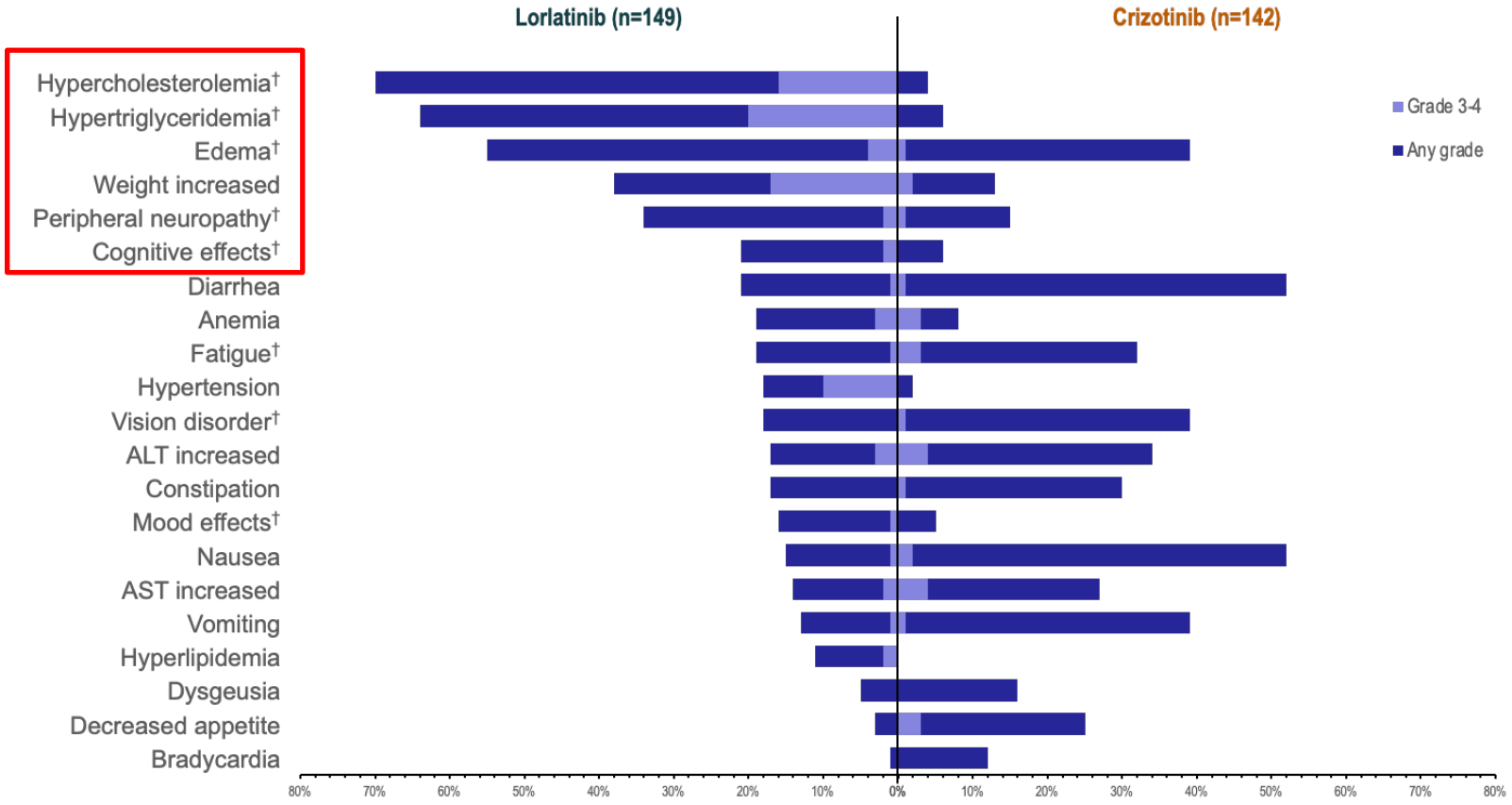
Number at risk (number censored)

Lorlatinib	112	99	96	93	90	87	85	84	81	79	76	74	74	73	71	69	61	49	44	31	27	20	13	7	3	1	0
	(0)	(12)	(15)	(18)	(21)	(24)	(26)	(27)	(30)	(32)	(35)	(37)	(37)	(38)	(40)	(42)	(50)	(62)	(67)	(80)	(84)	(91)	(98)	(104)	(108)	(110)	(111)
Crizotinib	108	89	76	67	54	47	36	34	28	24	18	17	17	17	16	12	9	7	6	5	4	2	1	1	1	0	0
	(0)	(17)	(28)	(34)	(43)	(49)	(55)	(57)	(62)	(63)	(67)	(68)	(68)	(68)	(68)	(72)	(74)	(76)	(77)	(78)	(79)	(81)	(82)	(82)	(82)	(83)	..

	Lorlatinib (n=112)	Crizotinib (n=108)
Events	1	25
Number censored	111	83
Median time to intracranial progression, months (95% CI)	NR (NR–NR)	30·8 (18·4–NR)
HR (95% CI)	0·02 (0·002–0·14)	

Solomon et al, Lancet Resp Med 2023

Lorlatinib toxicity is an important consideration



Solomon et al, ESMO 2020

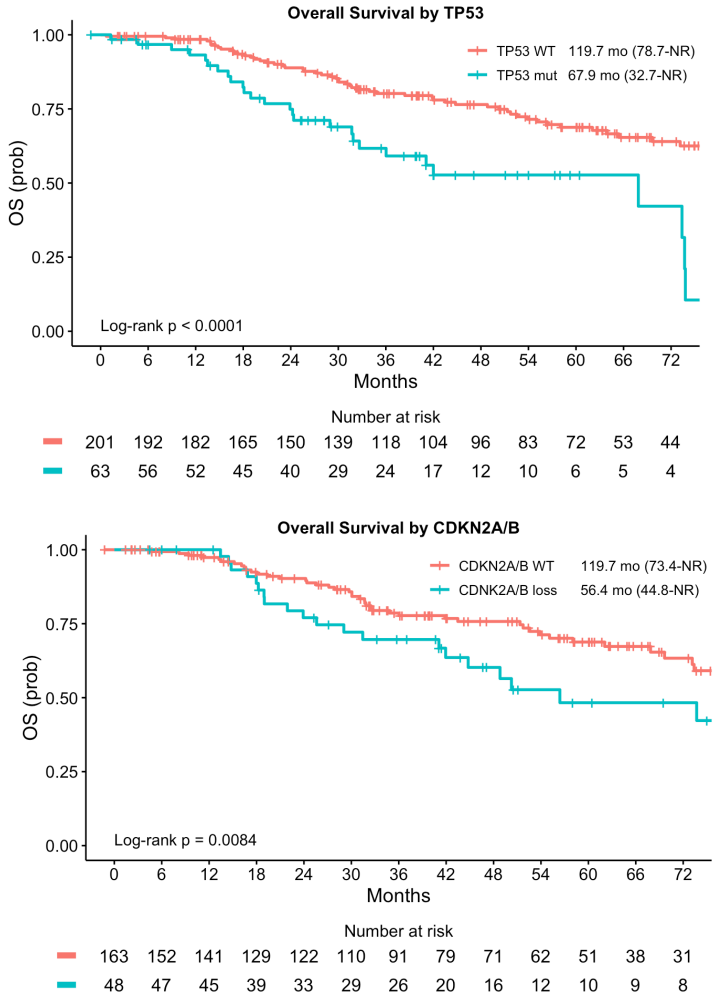
Lorlatinib CNS toxicity

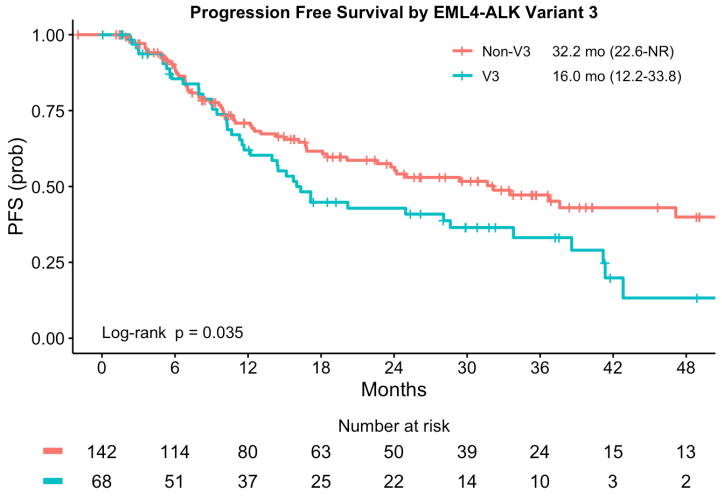
	Grade 1	Grade 2	Grade 3	Total
Any CNS adverse event	32 (21%)	15 (10%)	5 (3%)	52 (35%)
Cognitive effects	20 (13%)	9 (6%)	3 (2%)	32 (21%)
Mood effects	14 (9%)	8 (5%)	2 (1%)	24 (16%)
Speech effects	6 (4%)	0	1 (1%)	7 (5%)
Psychotic effects	4 (3%)	1 (1%)	0	5 (3%)

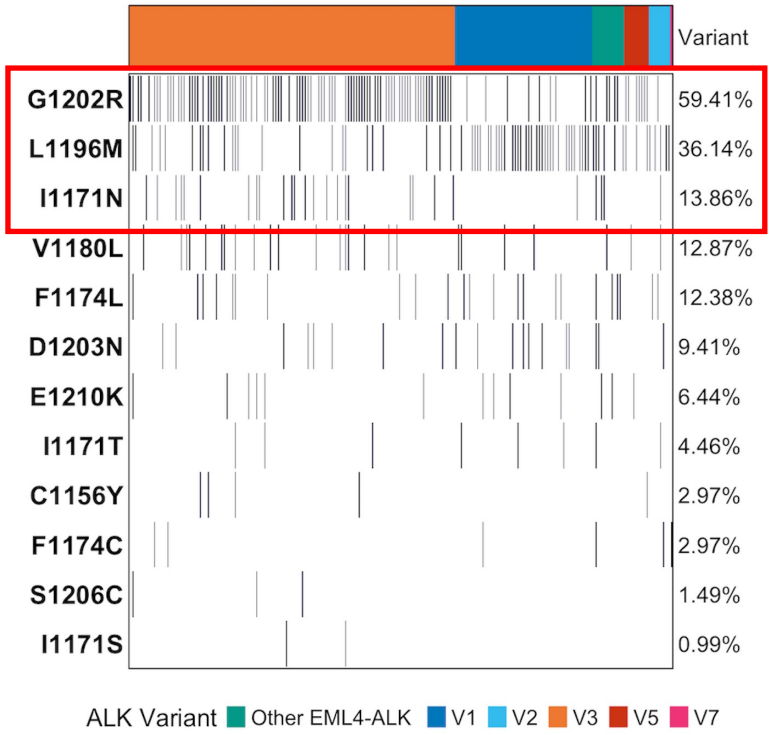
- Large majority of patients do not have CNS adverse events
- 77% of patients with CNS adverse events did not require dose reduction
  - 45% of those CNS adverse events had not resolved
- Potential risk factors for neuro-cognitive adverse events
  - Brain metastasis, prior radiation, psychiatric medications

Solomon et al, JCO 2022
Dagago-Jack et al, JTO 2023

Can we better personalize our first-line ALK TKI approach?



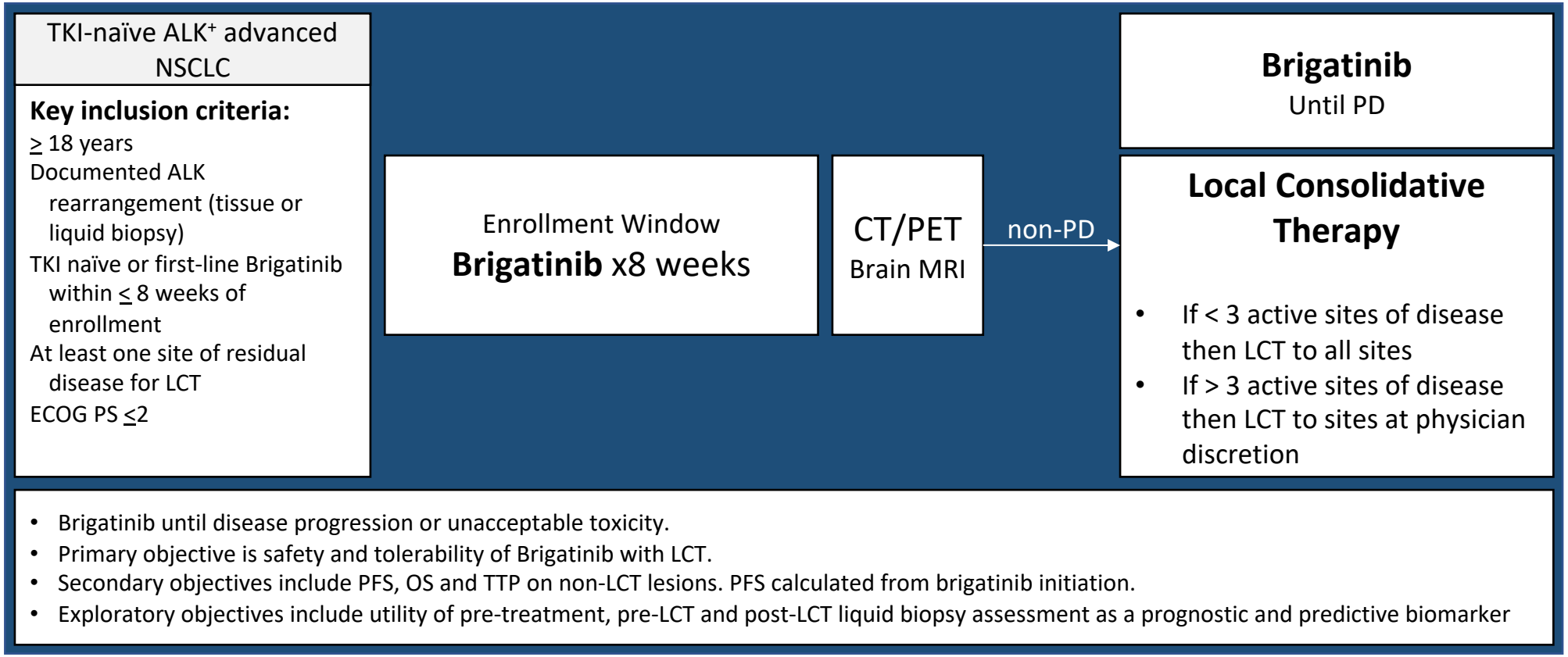




- Lorlatinib strongly preferred for *EML4-ALK* v3?
- Prioritize *TP53*-mut or *CDKN2A/B* loss for treatment intensification trials?

Nakazawa et al, Cancer Res Comm 2024

Local consolidative therapy – BRIGHTSTAR

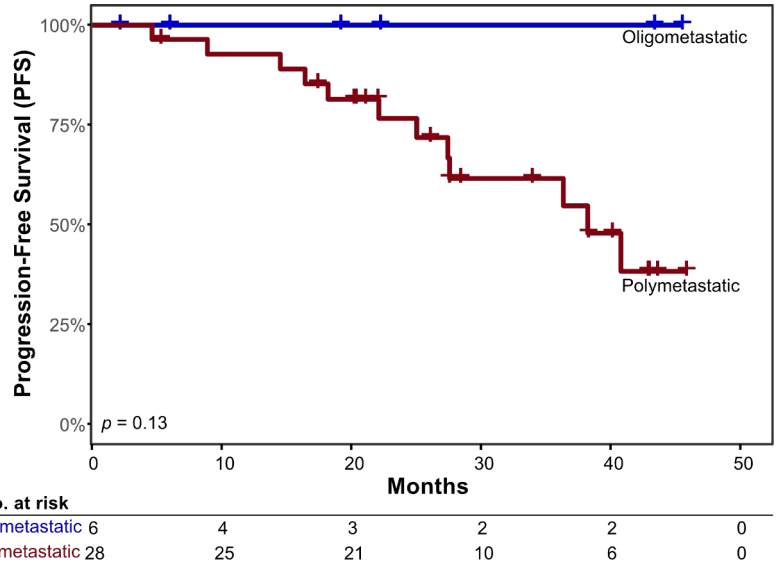


Elamin Y et al, WCLC 2023

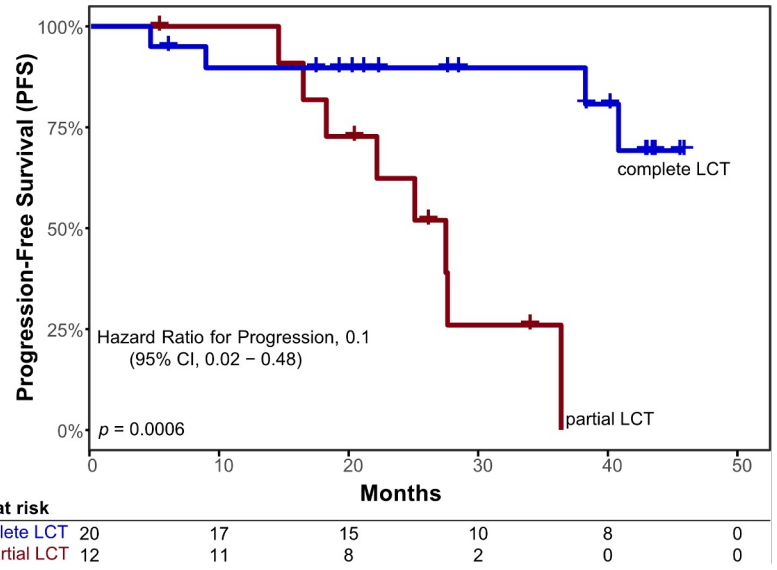
Encouraging PFS with local consolidative approach

PFS Rate	BrightStar	ALTA 1L (pts without PD at week 12)
1-yr	94%	80%
2-yr	80%	56%
3-yr	66%	47%

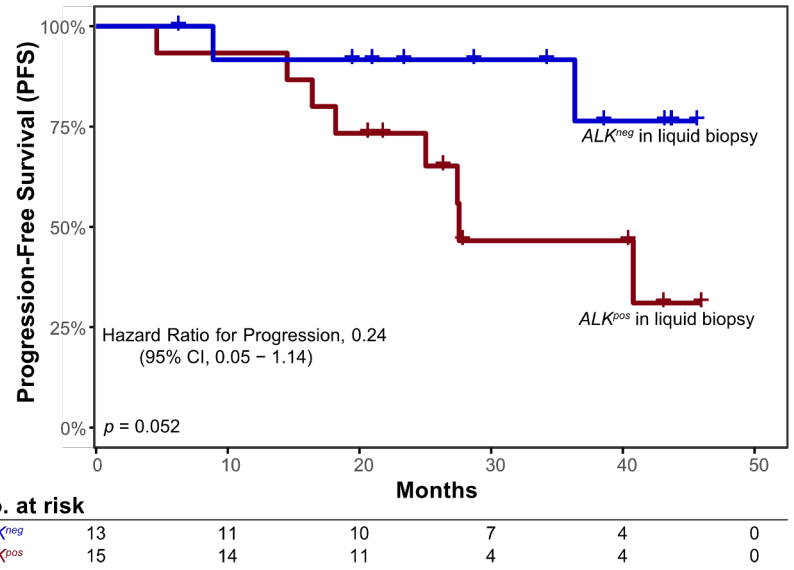
No of mets at baseline



Extent of LCT



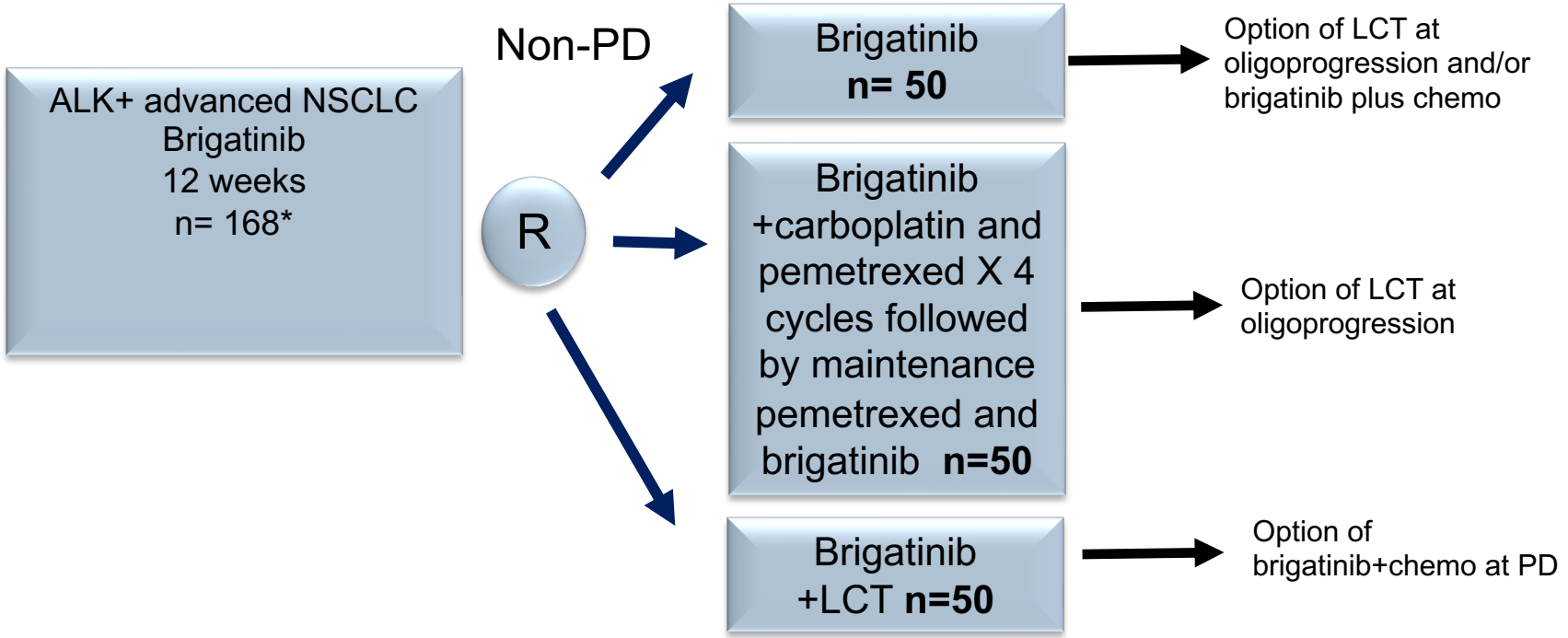
ALK status in plasma at baseline



LCT to all sites of residual disease and negative ALK status in plasma at baseline were associated with better outcomes

Elamin Y et al, WCLC 2023

Local vs chemotherapy consolidation – BRIGHTSTAR 2

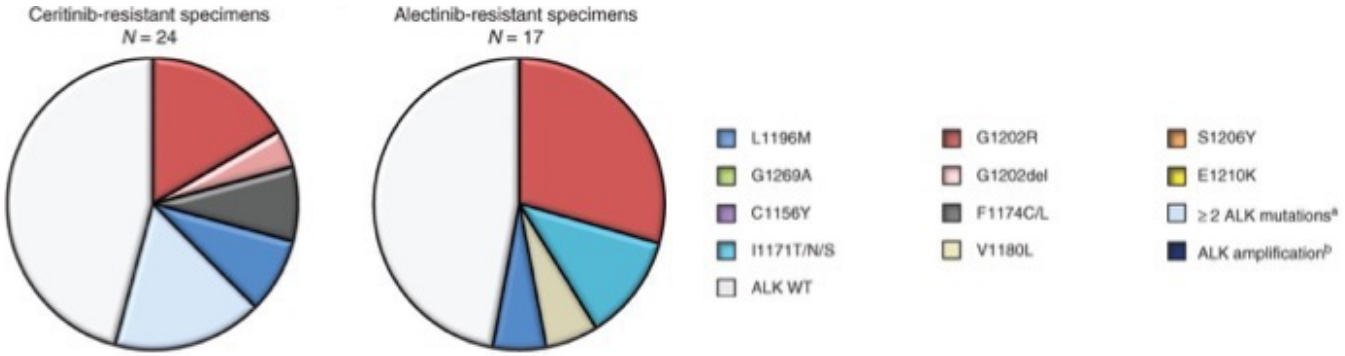


Stratification: PR vs non-PR, presence of CNS metastases, >3 metastases vs ≤ 3 metastases

Primary Endpoint PFS rate at 2 years
Arms 2 and 3 compared independently to arm 1

Elamin Y, MD Anderson

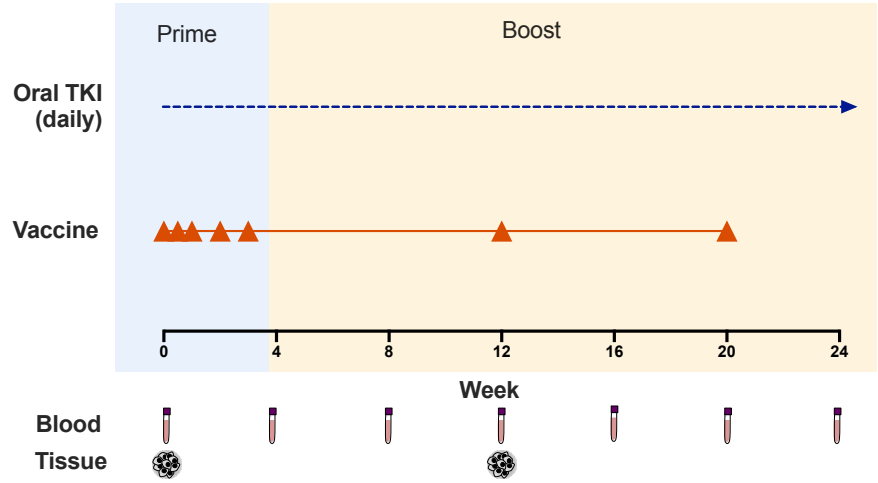
ALK-specific vaccine as systemic consolidation



50-60% of acquired resistance to 2nd generation ALK TKI arises from ALK kinase domain mutations

- ALK is an ideal vaccine target
- Acquired resistance mutations can be immunogenic
- Vaccines work best in non-progressive disease

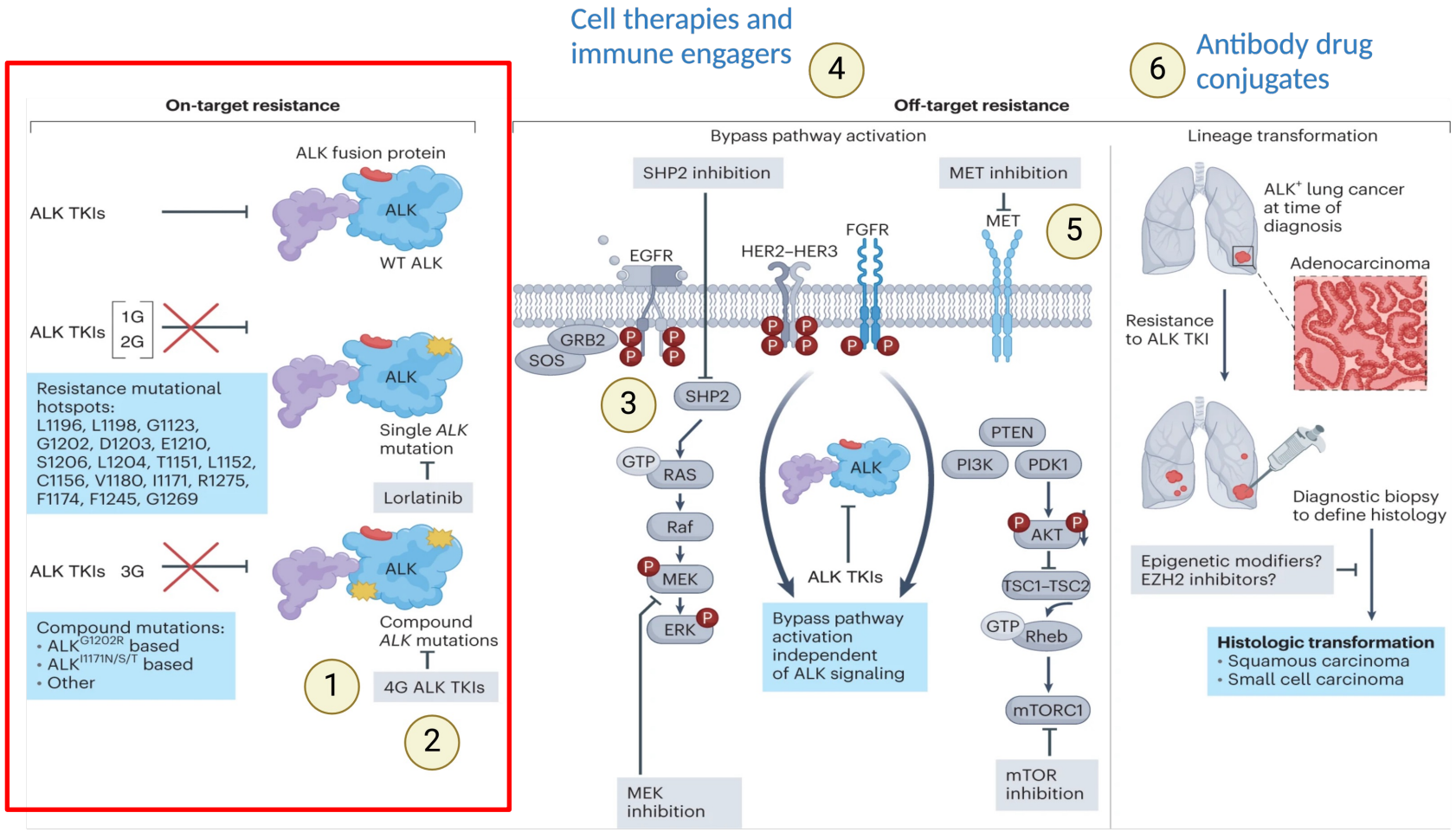
Can prophylactically targeting expected acquired resistance mutations in forestall TKI resistance in patients with stable disease?



Pilot clinical trial of an ALK neopeptide vaccine (NCT05950139)

Adapted from Gainor et al, Cancer Discov 2016
Mota et al, Nat Cancer 2023

Tissue profiling to help inform options upon progression



Select clinical trials

1. **NVL-655 (ALKOVE-1)**
   NCT05384626
2. **Gilteritinib**
   NCT06225427
3. **Lorlatinib + MET/MEK/SHP2**
   NCT04292119
4. **CD40L-Augmented TILs**
   NCT05681780
5. **Amivantamab + TKI**
   NCT05845671
6. **TROP2 Dxd (TROPION-PanTumor01)**
   NCT03401385

Adapted from Schneider et al, Nat Cancer 2023

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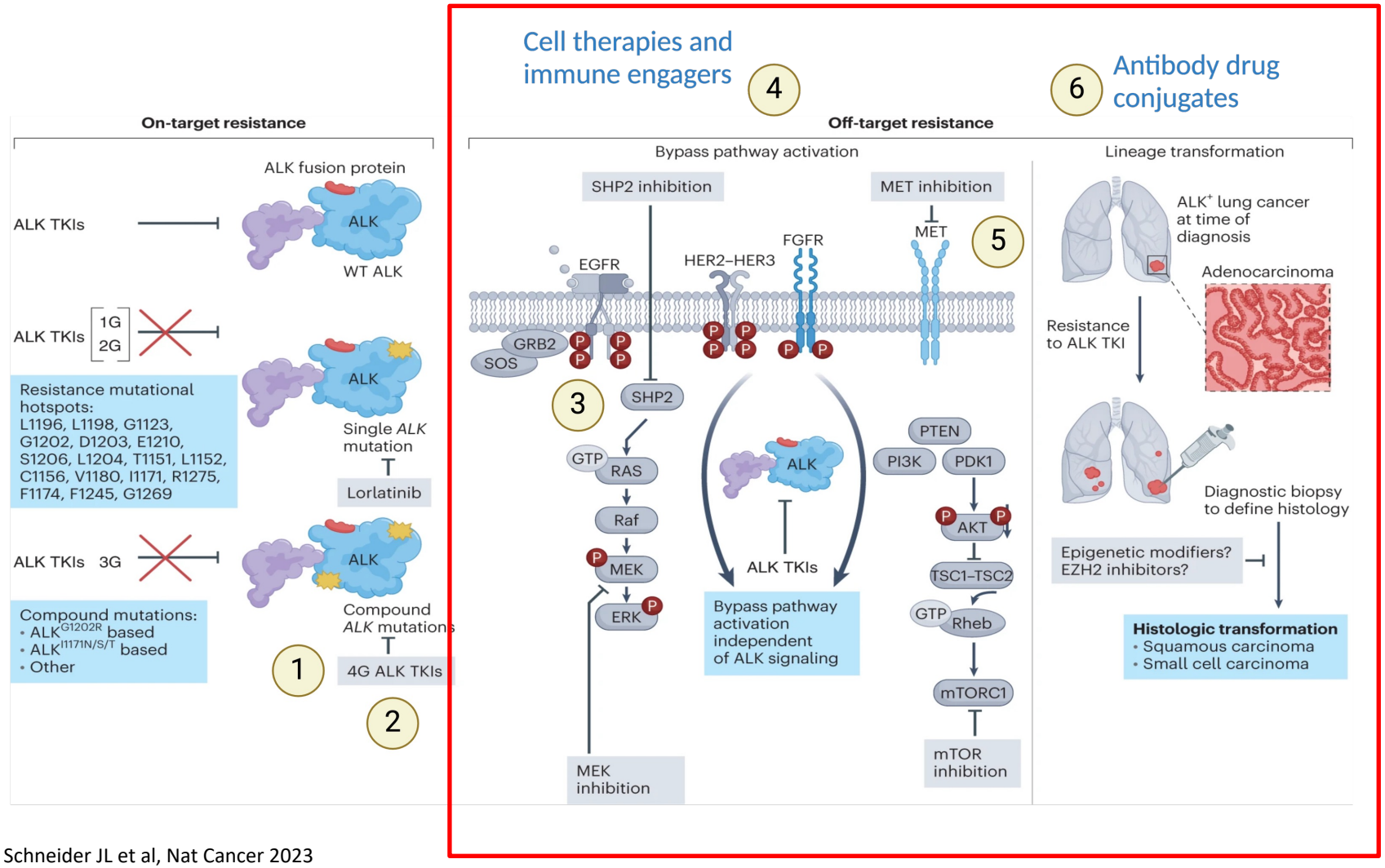

Adapted from Schneider JL et al, Nat Cancer 2023

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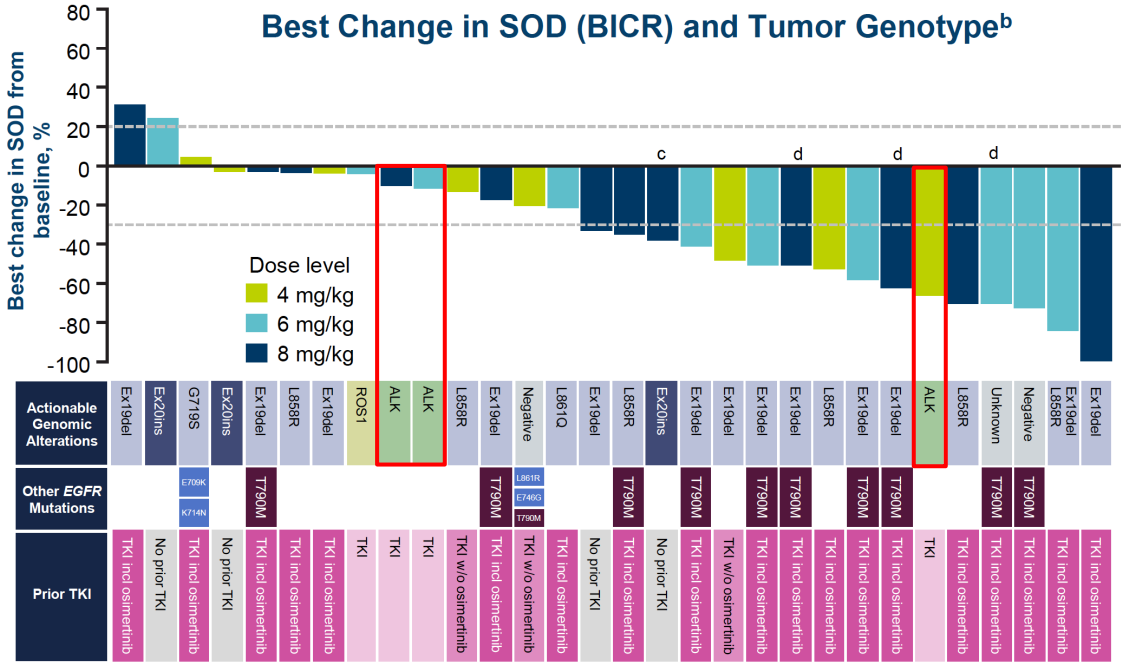
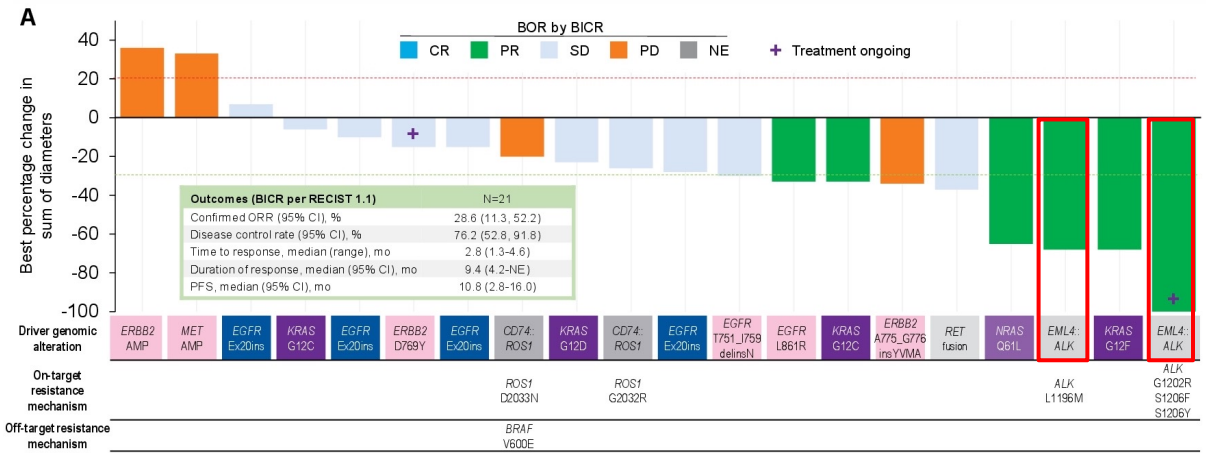
Activity of TROP2 and HER3 ADC in ALK+ lung cancer

TROP2 Dxd (TROPION-PanTumor01)



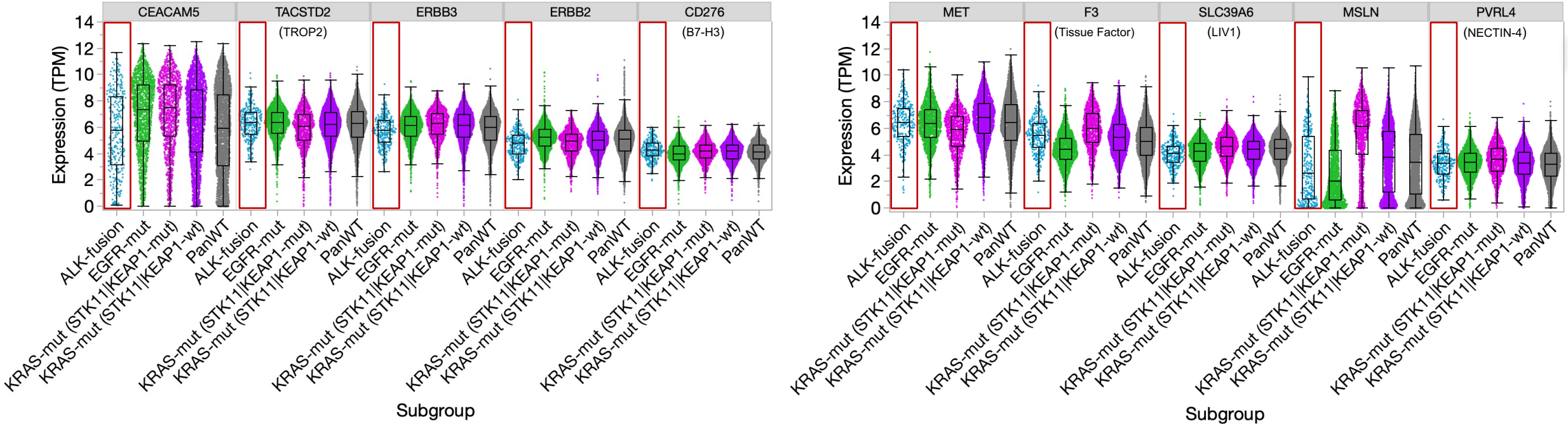
Garon et al, ESMO 2022

HER3 DXd (Patritumab Phase 1)



Steuer et al, ASCO 2022

ALK gene expression for emerging ADC targets



- Potentially lower Mesothelin expression
- Otherwise, expression appears similar to other major lung adenocarcinoma subtypes

Swartz et al, AACR 2023

Summary

- There are multiple highly effective TKIs for advanced ALK+ lung cancer
- Lorlatinib has compelling PFS and intracranial activity, though toxicity remains a significant consideration
- Patient factors and emerging biomarkers (e.g. variant 3, co-mutations, ctDNA dynamics) have potential to inform optimal first-line approach
- Consider consolidation trials – understanding and targeting residual disease state may be critical for cure
- Molecular and histologic profiling should be obtained (if feasible) to inform treatment options upon TKI progression