Case 4: Stage IV *KRAS*+ NSCLC With Co-Alterations in *KEAP1* or *STK11*

- 72-year-old woman
- Who presents to her GP with a 9 cm lung mass invading the mediastinum and liver metastases on CT
- Biopsy-proven adenocarcinoma (T4N2M1c, stage IV)
- The patient's tumor has a PD-L1 score of <1%
- Her ECOG PS is 1
- Molecular testing results reveal a *KRAS* G12C mutation as well as *KEAP1* and *TP53* alterations

- **What is the most appropriate treatment?**

Patients with *KRAS*-Mutated NSCLC Respond to Frontline IO-Based Therapy

FDA analysis of 1L therapy trial outcomes according to *KRAS* mutation status

	ORR (95% CI)		
	KRASwt N=875	***KRASm*** N=555	***KRAS G12C*** N=157
ICI+Chemo	**51%** (46, 57)	**46%** (39, 53)	**47%** (33, 60)
ICI alone	**33%** (27, 40)	**37%** (29, 46)	**33%** (20, 49)
Chemo alone	**32%** (33, 60)	**33%** (20, 49)	44% (31, 59)

Study Therapy	Median OS, mos (95% CI)		
	KRASwt	***KRASm***	***KRAS G12C***
ICI+chemo	**18.7** (16.0, 25.2) N=313	**22.4** (18.2, NE) N=219	**20.8** (11.3, NE) N=58
	HR 1.12 (95% CI: 0.86, 1.46)		
ICI alone	**16.4** (13.4, 19.7) N=240	**16.2** (11.1, NE) N=135	**11.8** (8.2, NE) N=45
	HR 1.01 (95% CI: 0.76, 1.34)		
Chemo alone	14.9 (12.2, 16.6) N=322	17.1 (12.3, 18.9) N=201	17.5 (10.7, 21.1) N=54
	HR 1.02 (95% CI: 0.81, 1.29)		

CI, confidence interval; FDA, US Food and Drug Administration; HR, hazard ratio; ICI, immune checkpoint inhibitor; IO, immuno-oncology; m, mutation; NE, not evaluated; ORR, objective response rate; OS, overall survival; wt, wild type.

Nakajima EC, et al. ASCO 2022. Abstract 9001.

Survival Benefit With First-Line Nivolumab + Ipilimumab in Advanced NSCLC Regardless of *KRAS*, *STK11*, and *KEAP1* Mutation Status

	***KRAS*-mut**		***KRAS*-WT**		***STK11*-mut**		***STK11*-WT**		***KEAP1*-mut**		***KEAP1*-WT**	
	NIVO+IPI	Chemo	NIVO+IPI	Chemo	NIVO+IPI	Chemo	NIVO+IPI	Chemo	NIVO+IPI	Chemo	NIVO+IPI	Chemo
n	88	75	150	162	39	39	199	198	20	18	218	219
Median OS, mo	17.5	15.7	20.6	17.9	10.8	11.2	21.2	18.5	24.4	8.9	20.1	16.7
95% CI	11.1–28.1	11.9–21.2	16.2–29.4	12.7–21.2	5.8–22.1	7.3–15.0	17.4–29.4	14.5–21.3	5.8–NR	4.8–11.9	16.2–26.2	14.5–19.9
HR	0.79		0.73		0.78		0.75		0.31		0.80	
95% CI	0.55–1.12		0.56–0.95		0.48–1.27		0.59–0.94		0.14–0.70		0.65–1.00	
4-y OS rate, %	27	16	34	22	19	5	34	23	44	0	31	22
95% CI	19–38	10–27	28–43	16–29	10–37	1–21	28–42	18–30	26–73	0–0	25–38	17–28

Chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab.

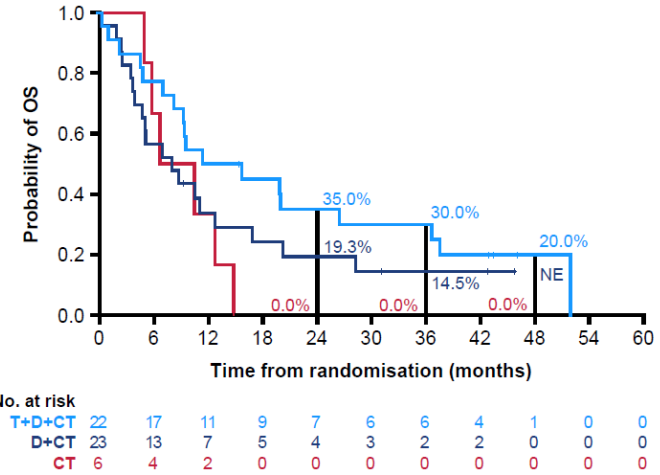
Ramalingam SS, et al. *Ann Oncol*. 2021;32(suppl 7):S1375-S1376.

Do Additional Mutations Impact IO Efficacy in Driver Mutation-Negative NSCLC – *KEAP1*

POSEIDON[1]

KEAP1-mut

	T+D+CT	D+CT	CT
Events/patients, n/N	18/22	19/23	6/6
mOS, months (95% CI)	**13.7** (7.2–26.5)	**8.1** (4.0–12.9)	**8.7** (5.1–NE)
HR* (95% CI)	**0.43** (0.16–1.25)	**0.77** (0.31–2.15)	–

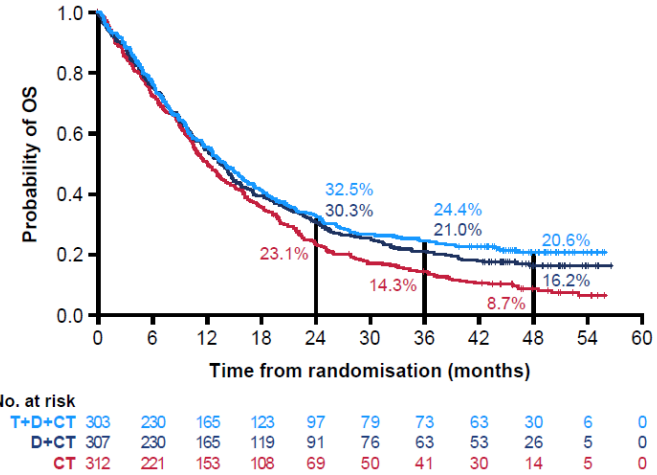


No. at risk

T+D+CT	22	17	11	9	7	6	6	4	1	0	0
D+CT	23	13	7	5	4	3	2	2	0	0	0
CT	6	4	2	0	0	0	0	0	0	0	0

KEAP1-wt

	T+D+CT	D+CT	CT
Events/patients, n/N	236/303	253/307	278/312
mOS, months (95% CI)	**14.0** (11.8–16.1)	**13.5** (11.7–14.9)	**12.2** (10.6–13.9)
HR* (95% CI)	**0.75** (0.63–0.89)	**0.81** (0.69–0.97)	–



No. at risk

T+D+CT	303	230	165	123	97	79	73	63	30	6	0
D+CT	307	230	165	119	91	76	63	53	26	5	0
CT	312	221	153	108	69	50	41	30	14	5	0

CheckMate 9LA[2]

	KEAP1-mut		*KEAP1-wt*	
Outcomes	**Nivo/Ipi + CT (2-cycles) (n=16)**	**Chemotherapy (CT) (n=16)**	**Nivo/Ipi + CT (2-cycles) (n=150)**	**Chemotherapy (CT) (n=131)**
Median OS, months (95% CI)	13.2 (6.6-22.7)	5.0 (2.8-9.8)	16.8 (13.2-20.5)	14.1 (11.4-17.4)
HR (95% CI)	0.51 (0.24-1.08)		0.94 (0.71-1.23)	

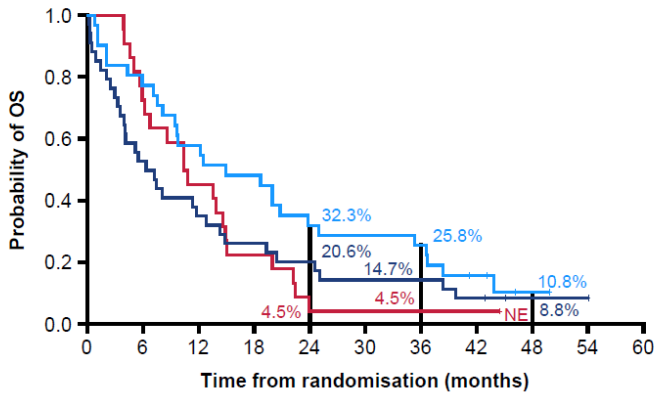
1. Johnson ML, et al. ESMO 2022. Abstract LBA59. 2. Paz-Ares LG, et al. *J Thorac Oncol.* 2023;18:204-222.

Do Additional Mutations Impact IO Efficacy in Driver Mutation-Negative NSCLC – *STK11*

POSEIDON[1]

STK11-mut

	T+D+CT	D+CT	CT
Events/patients, n/N	27/31	31/34	21/22
mOS, months (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.62** (0.34–1.12)	**1.06** (0.61–1.89)	–

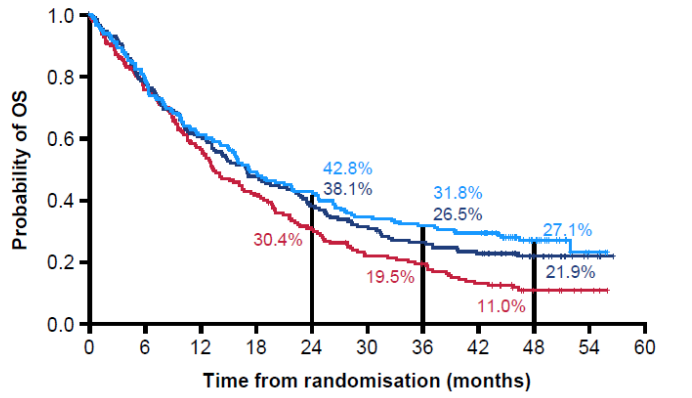


No. at risk

T+D+CT	31	24	18	15	10	9	8	4	1	0	0
D+CT	34	18	12	9	7	5	5	3	1	0	0
CT	22	16	10	5	1	1	1	1	0	0	0

STK11-wt

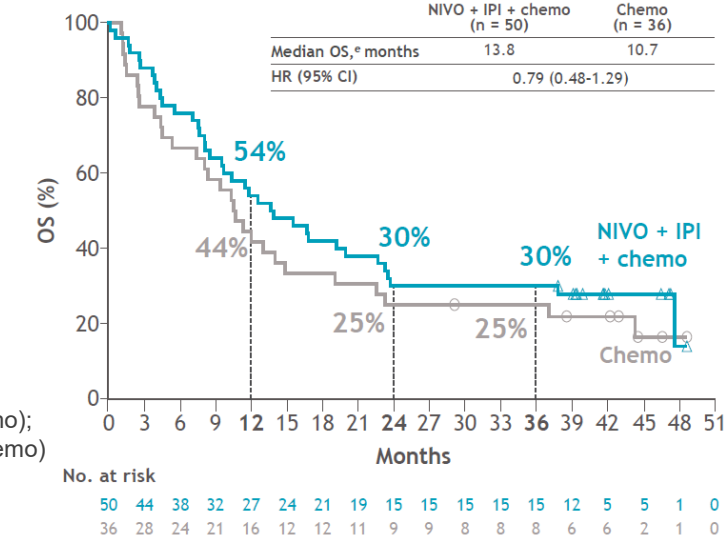
	T+D+CT	D+CT	CT
Events/patients, n/N	127/177	129/169	151/179
mOS, months (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.70** (0.55–0.89)	**0.77** (0.61–0.98)	–



No. at risk

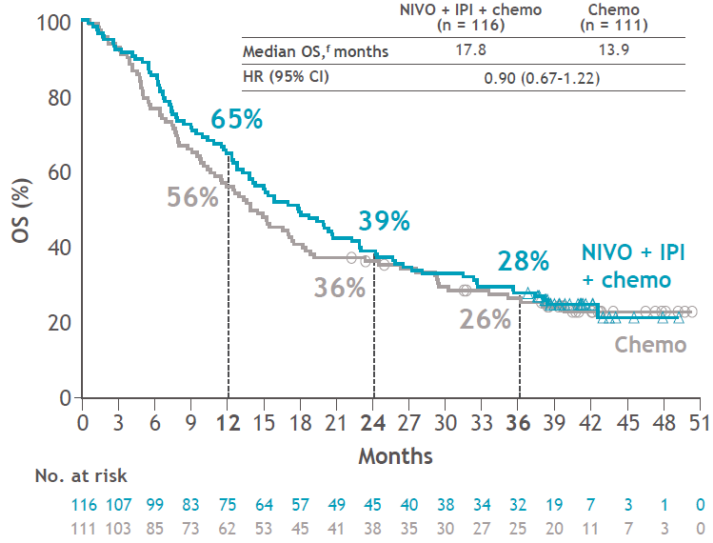
T+D+CT	177	140	107	85	74	60	55	51	23	3	0
D+CT	169	130	100	79	63	52	43	37	19	4	0
CT	179	131	97	71	51	36	31	21	9	4	0

CheckMate 9LA[2]



No. at risk

	50	44	38	32	27	24	21	19	15	15	15	15	15	12	5	5	1	0
	36	28	24	21	16	12	12	11	9	9	8	8	8	6	6	2	1	0



No. at risk

	116	107	99	83	75	64	57	49	45	40	38	34	32	19	7	3	1	0
	111	103	85	73	62	53	45	41	38	35	30	27	25	20	11	7	3	0

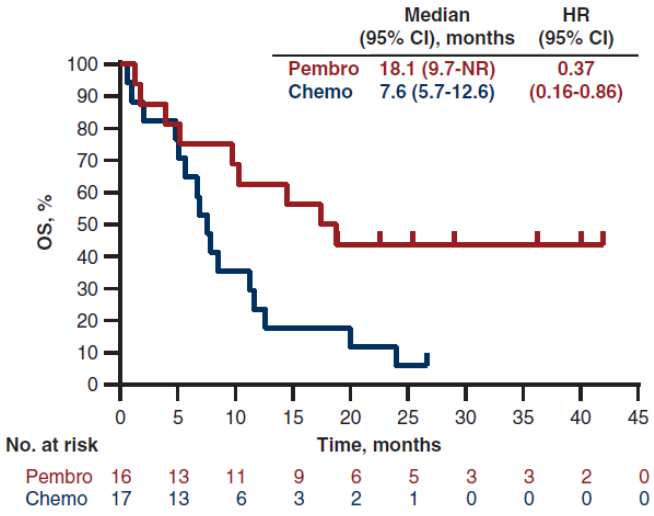
e 95% CI, 8.6-22.7 (N+I + chemo) and 5.4-14.9 (chemo);
f 95% CI, 13.2-22.8 (N+I + chemo) and 10.6-17.4 (chemo)
CT, chemotherapy; D, durvalumab; Mut, mutation;
T, tremelimumab.

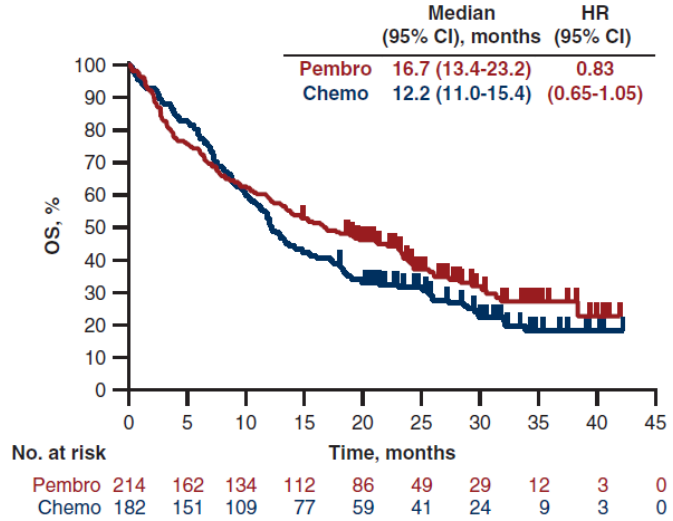
1. Johnson ML, et al. ESMO 2022. Abstract LBA59.
2. Paz-Ares LG, et al. ASCO 2022. Abstract LBA9026.

Do Additional Mutations Impact IO Efficacy in Driver Mutation-Negative NSCLC – Data Are Mixed?

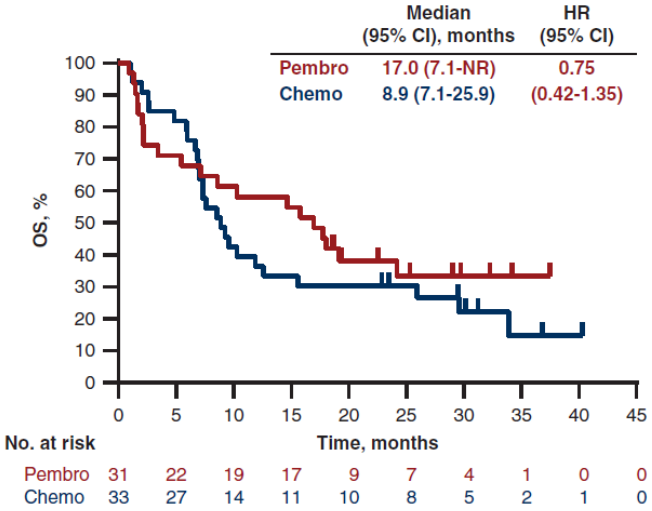
Mutated | ***Wild-Type***

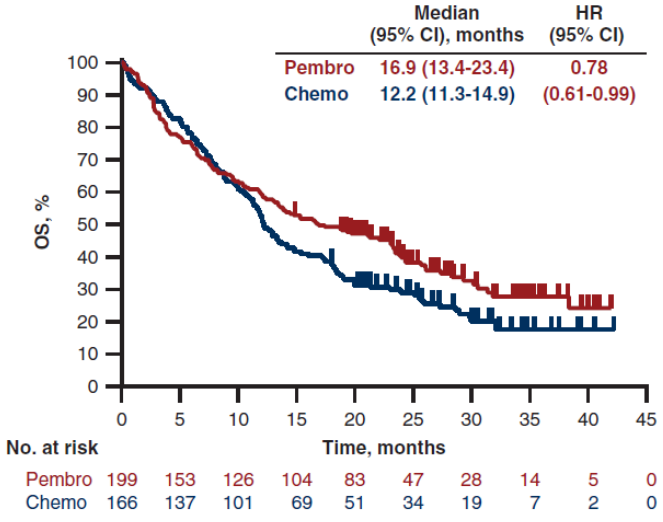
STK11





KEAP1

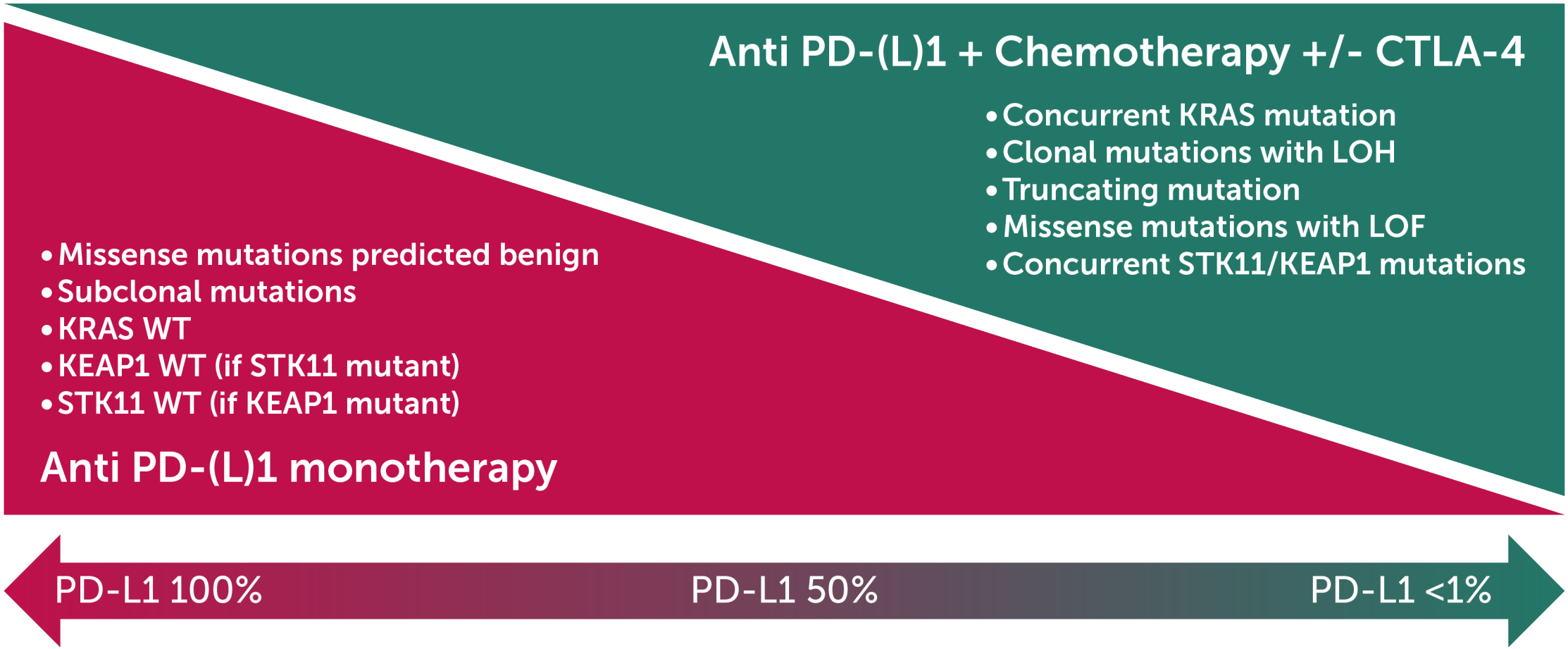




Pembro, pembrolizumab.

Mok TSK, et al. *Ann Oncol.* 2023;34:377-88.

Potential First-Line Options for NSCLC With *STK11* or *KEAP1* Mutations



Ricciuti B and Garassino MC. *J Thorac Oncol.* 2024;19(6):877-882.

Summary

- Patients with NSCLC who have a mutation in *KRAS* and no other known driver alterations should be treated with a frontline therapy strategy that incorporates immunotherapy +/- chemotherapy
- Emerging evidence suggests certain molecular alterations, such as *STK11* and *KEAP1,* may impact the efficacy of anti-PD(L)1-based treatments in advanced NSCLC
- Prospective randomized data are needed to determine the best treatment strategy for patients who harbor a mutation in *STK11* or *KEAP1*

We should try to give our best treatment upfront. We never quite know if we're going to get to second line.

Jarushka Naidoo, MRCPI