FIRST LINE THERAPY FOR ADVANCED NSCLC WITHOUT DRIVER MUTATIONS

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JOHNS HOPKINS
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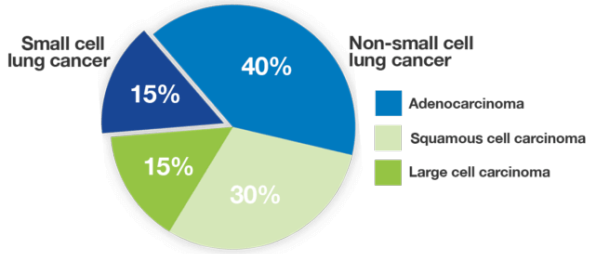
COMPREHENSIVE CANCER CENTER

Disclosures

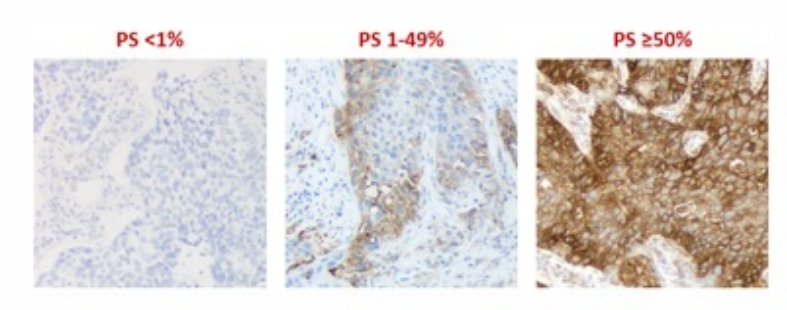
- Advisory Board
  - GlaxoSmithKline
  - AstraZeneca
  - Johnson & Johnson
  - Mestag
  - Amgen
  - Summit Therapeutics
  - Genmab
- Research Funding
  - AstraZeneca
  - Bristol Myers Squibb

How Are Therapy Decisions Made for Patients With Advanced NSCLC?

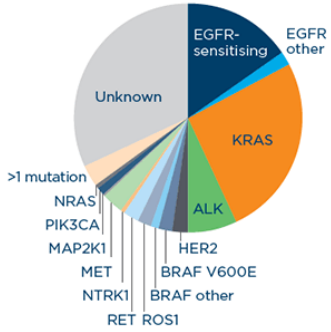
Histology



PD-L1 Expression Level



Presence of a Targetable Mutation



Patient-Related Factors

- Preference/goals of tx
- Overall health (PS)
- History of autoimmune disease or transplant

Treatment Options for Advanced NSCLC

- For patients with PD-L1 High (≥ 50%) single agent IO is approved for use.
- Chemo-IO is approved for use regardless of PD-L1 status.
- IO-IO +/- chemo is also approved for use, but when do we use it?

IO-IO combinations

- Avoid chemotherapy? CM227
- Decrease the amount of chemotherapy? CM 9LA
- Decrease the amount of CTLA4 but continue chemotherapy? Poseidon

What about PD-L1 High Disease?

Single Agent PD-1 Pathway Blockade in PD-L1 "High" NSCLC Across Histologies

	Pembro KN 024	Atezo IMpower 110	Cemiplimab EMpower
OS median (mo)	26.3 (HR-0.62)	20.2 (HR-0.59)	22.1 (HR-0.68) or NR (HR-0.57)
PFS median (mo)	7.7 (HR-0.5)	8.1 (HR-0.63)	6.2 or 8.2 in confirmed PD-L1 (HR-0.54)
ORR	46%	38.3%	36.5% or 39.2%
Median DOR (mo)	29.1		21

Reck M et al JCO 2021, Herbst R et al NEJM 2020, Sezer A Ann Oncol 2020 LBA52, Paz-Ares L et al ASCO 2021 #9016,

Chemo IO Combination Trials PD-L1 High Subgroup

Outcome	KEYNOTE-189: Pembrolizumab + Platinum CT (n = 132)[1]	IMpower150: Atezolizumab + Bevacizumab, Carboplatin/nab-Paclitaxel (n = 71)[2,3]	IMpower130 Atezolizumab + Platinum CT (n = 88)[4]
Median OS, mo	29.6	30.0	17.3
OS HR (95% CI)	0.68 (0.49-0.96)	0.70 (0.46-1.08)	0.84 (0.51-1.39)
ORR, %	62.1	69	NR

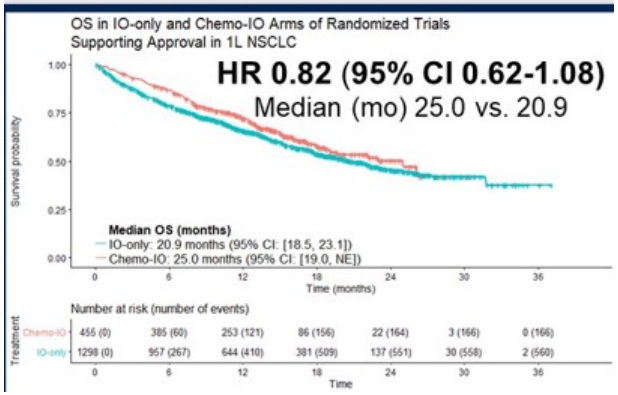
KEYNOTE-407 5-Yr Outcomes: PD-L1 ≥50%	Pembro + CT (n = 73)	HR (95% CI)
ORR, %	64.4	
5- Yr PFS, %	15.0	0.48 (0.33-0.69)
5- Yr OS, %	23.3	0.68 (0.47-0.97)

1. Garassino. ESMO 2022. Abstr 973MO. 2. Socinski. J Thorac Oncol. 2021;16:1909. 3. Socinski. ASCO 2018. Abstr 9002. 4. West. Lancet Oncol. 2019;20:924. , Novellow S et al ESMO 2022

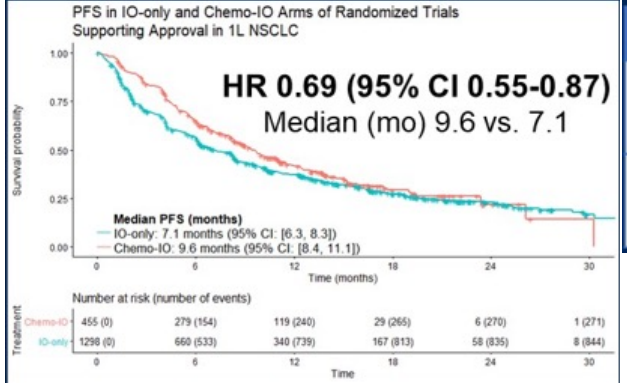
FDA Pooled Analysis of First Line Treatment Setting in PD-L1 High Disease (≥ 50%)

- **Randomized Clinical Trials supporting FDA approved IO-based regimens**
  - **Chemo-IO (6 trials, n=455):** Platinum-Chemo + Pembrolizumab, Atezolizumab (+/- bevacizumab), or Nivolumab/Ipilimumab
  - **IO (6 trials, n=1298):** Nivolumab, Pembrolizumab, Atezolizumab, Cemiplimab, Nivolumab/Ipilimumab
- **Biomarkers[1]: PD-L1 ≥ 50% TPS and *EGFR/ALK* WT**

OS – no difference



PFS – favor chemo-IO

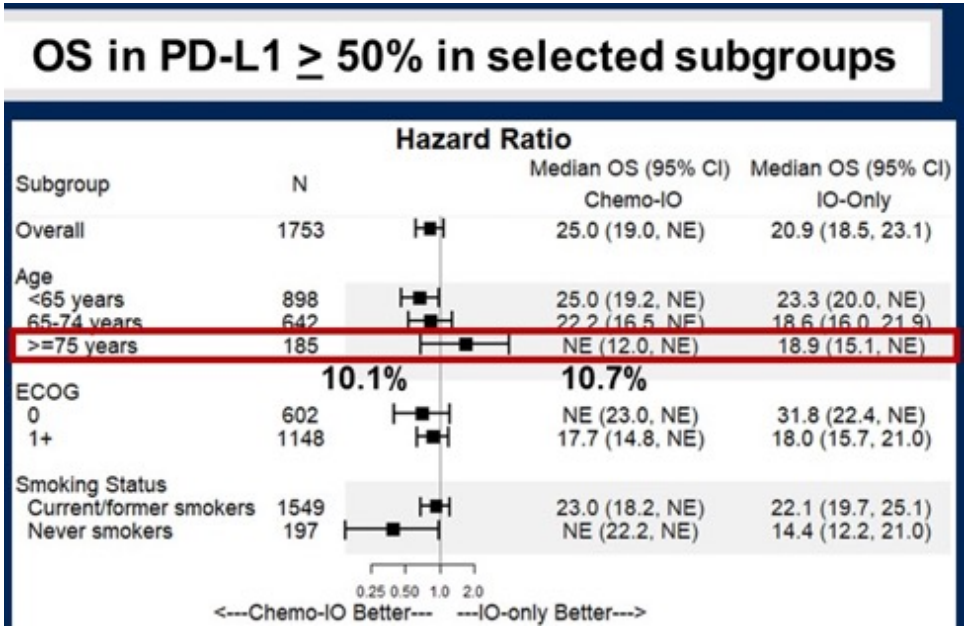


ORR – favor chemo-IO

	Chemo-IO	IO
% (95% CI)	61 (56, 66)	43 (41, 46)
Odds ratio (95% CI)	**1.2** (1.1, 1.3)	

Akinboro O. et al ASCO 2022

FDA Pooled Analysis of First Line Treatment Setting in PD-L1 High Disease (≥ 50%)



- The decision between single agent IO versus IO-chemotherapy is a per patient decision.
- The right sequence or combination is unclear.

PD-L1 "High" Disease Across Histologies

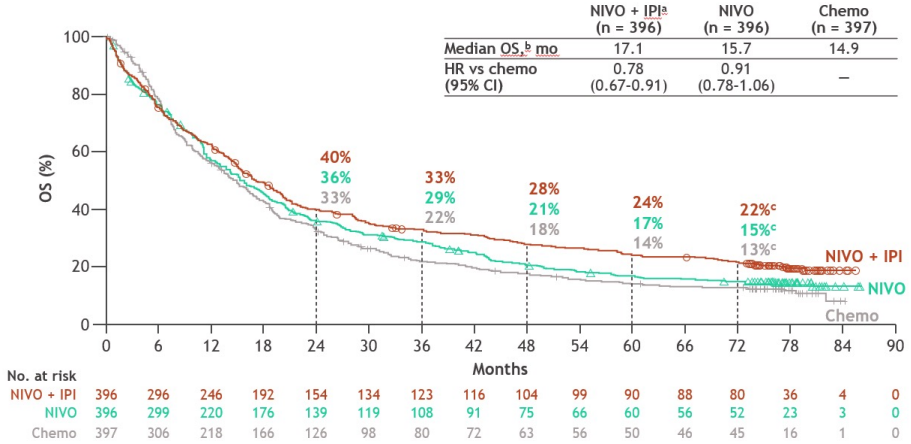
	Pembro KN 024	Atezo IMpower 110	Cemiplimab EMpower	Ipi/Nivo CM-227	Ipi/Nivo /Chemo CM9LA
OS median (mo)	26.3 (HR-0.62)	20.2 (HR-0.59)	22.1 (HR-0.68) or NR (HR-0.57)	21.2 (HR-0.66)	18.9 (HR-0.67)
PFS median (mo)	7.7 (HR-0.5)	8.1 (HR-0.63)	6.2 or 8.2 in confirmed PD-L1 (HR-0.54)	6.7 (HR-0.60)	7.5 (HR-0.59)
ORR	46%	38.3%	36.5% or 39.2%	45.4%	38%

Reck M et al JCO 2021, Herbst R et al NEJM 2020, Sezer A Ann Oncol 2020 LBA52, Paz-Ares L et al ASCO 2021 #9016, Reck M et al ASCO 2021 #9000

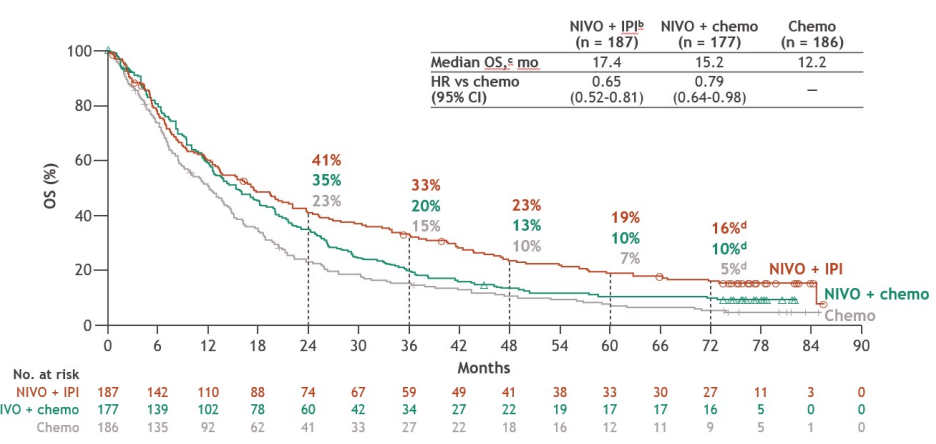
What about in PD-L1 Positive vs Negative Disease?

Nivolumab plus Ipilimumab - CM 227 Overall Survival

OS in patients with tumor PD-L1 ≥ 1%



OS in patients with tumor PD-L1 < 1%



No data available that separates out the 1-49% group.

	PD-L1 ≥ 1%			PD-L1 ≥ 50%			PD-L1 < 1%		
	NIVO + IPI (n = 396)	NIVO (n = 396)	Chemo (n = 397)	NIVO + IPI (n = 205)	NIVO (n = 214)	Chemo (n = 192)	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
ORR, %	36.4	27.5	30.0	45.4	36.9	35.4	27.3	37.9	23.1
Median PFS, months (95% CI)	5.1 (4.07-6.31)	4.2 (3.02-5.32)	5.6 (4.63-5.82)	6.7 (4.53-11.1)	5.6 (4.17-8.34)	5.6 (4.57-6.60)	5.1 (3.52-6.37)	5.6 (4.63-6.90)	4.7 (4.21-5.59)
HR vs chemo (95% CI)	0.81 (0.68-0.96)	0.98 (0.83-1.15)	–	0.60 (0.47-0.76)	0.72 (0.57-0.90)	–	0.74 (0.58-0.94)	0.72 (0.57-0.91)	–
4-year PFS rates, %	14	10	4	20	14	1	12	7	NA

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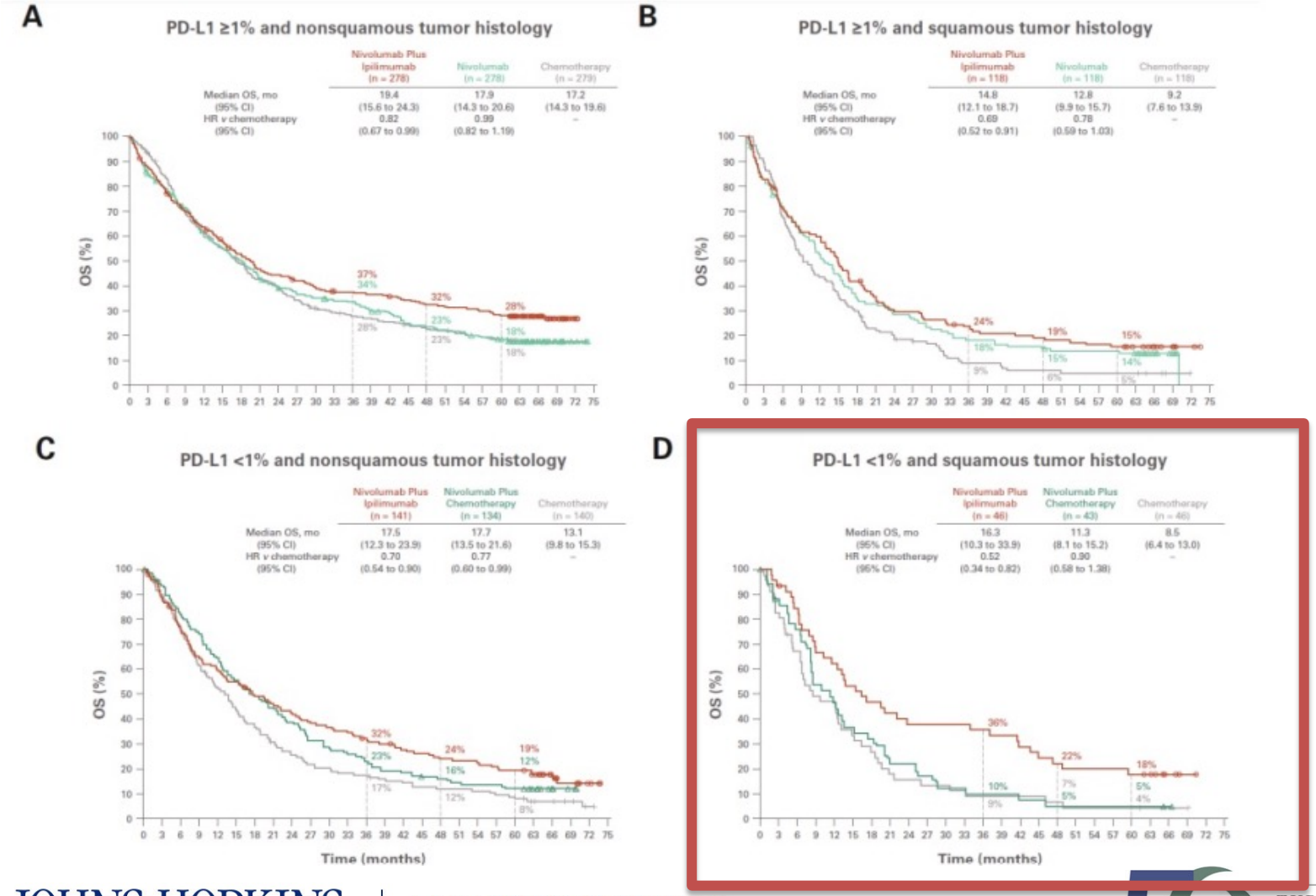
Ramalingham S et al WCLC 2023 Paz-Ares L et al ASCO 2021, #9016

CM-227 – Histology and PD-L1



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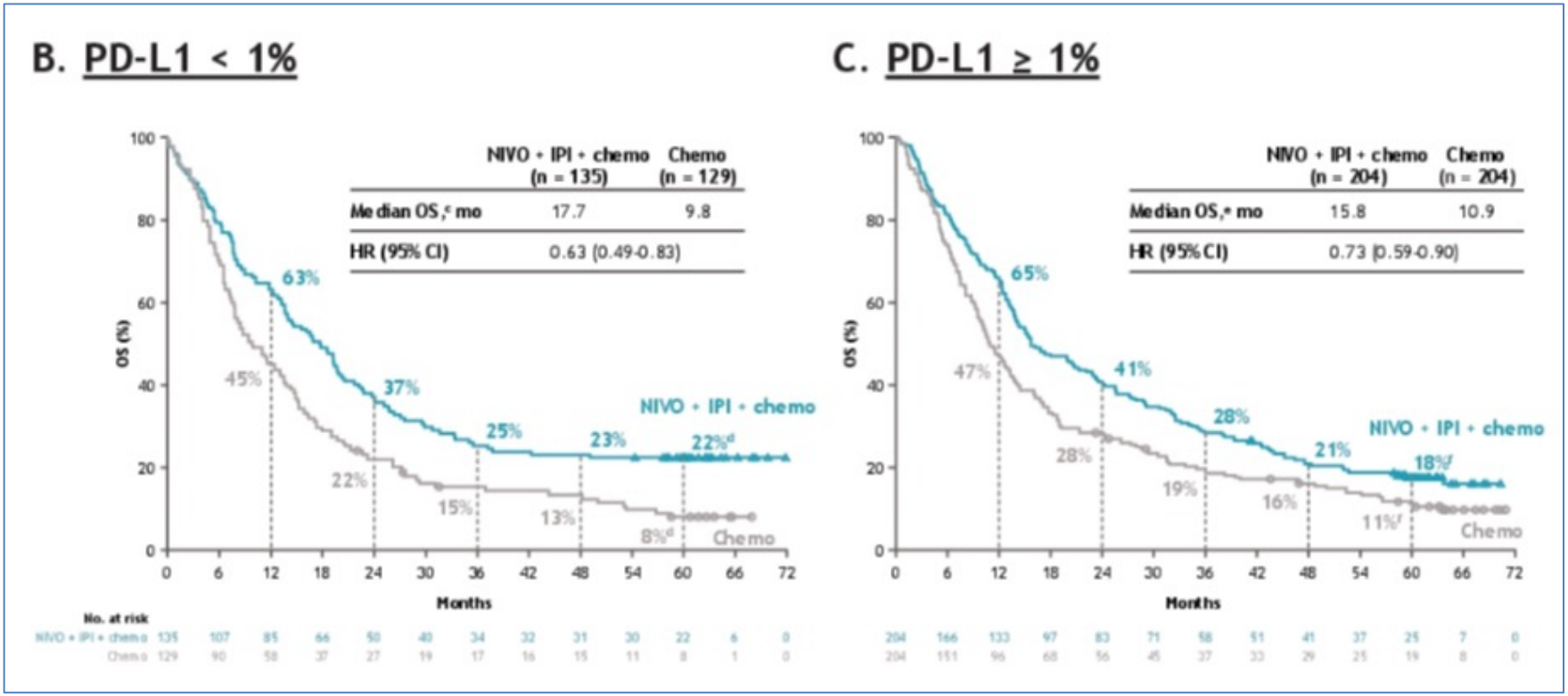
Brahmer J et al ASCO 2022, JCO 2022

CheckMate 9LA – by PD-L1



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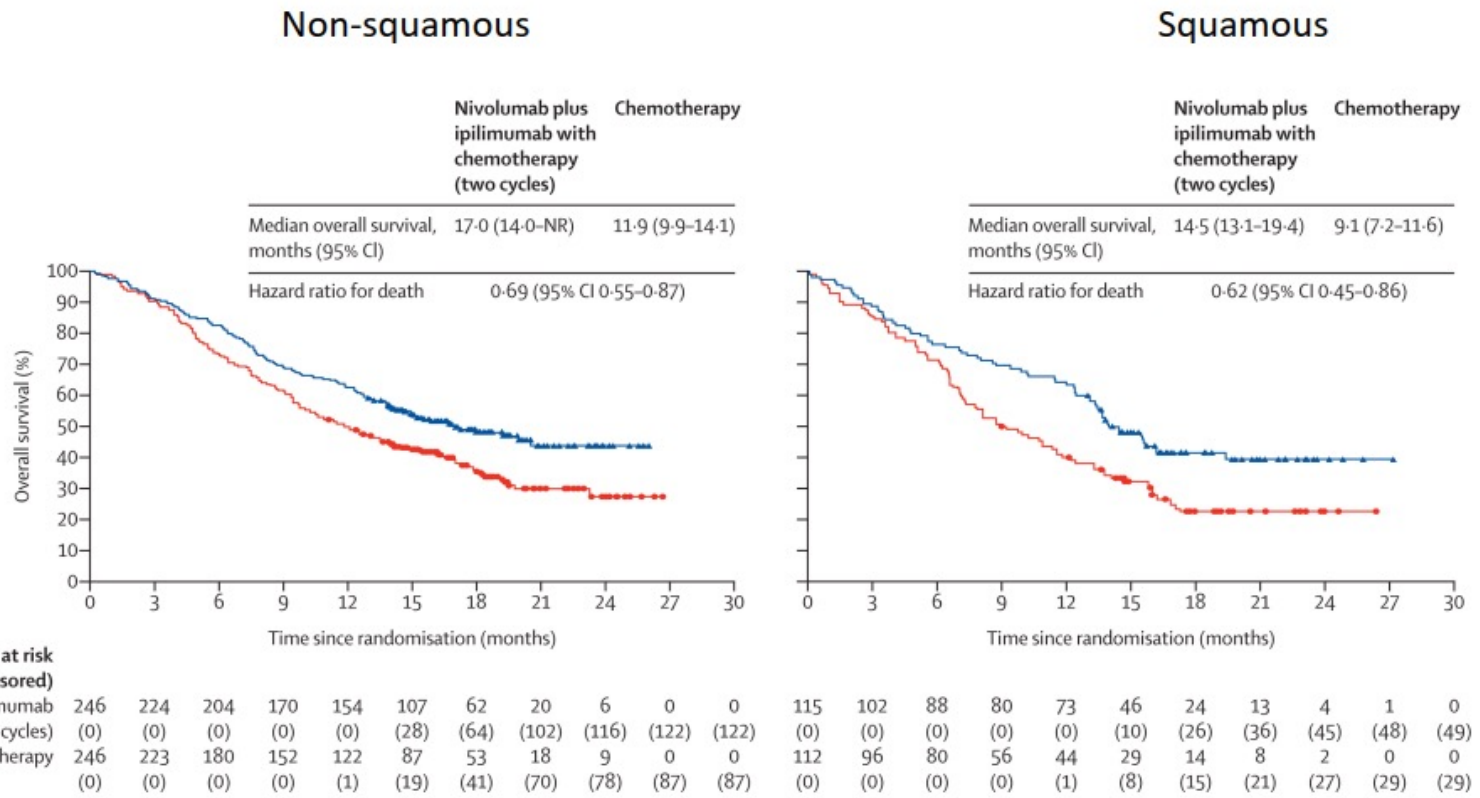
Reck M et al ASCO 2024

CM-9LA - Histology



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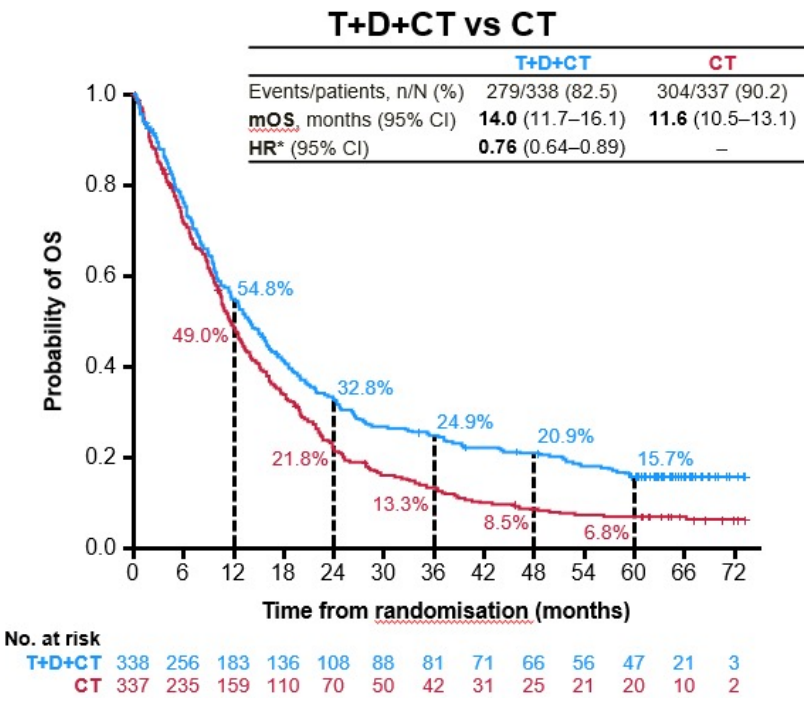
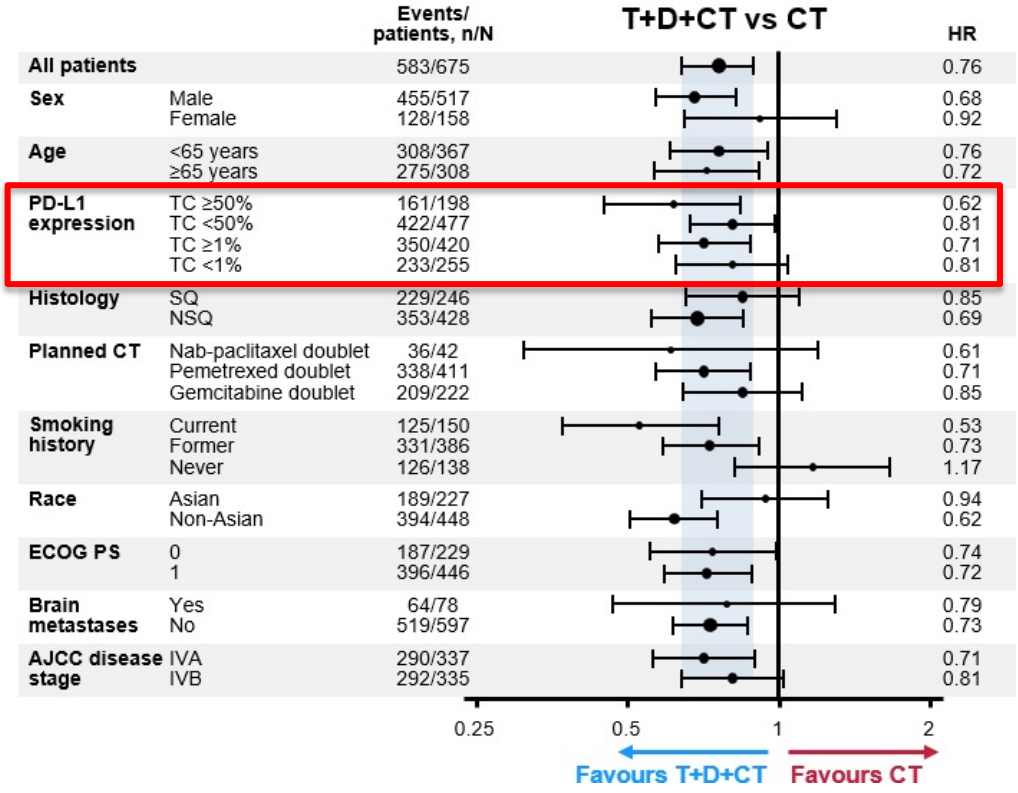
TURNING RESEARCH INTO RESULTS 1973–2023

Paz-Ares et al, *Lancet Oncology*, 2021

Poseidon - Overall Survival by PD-L1





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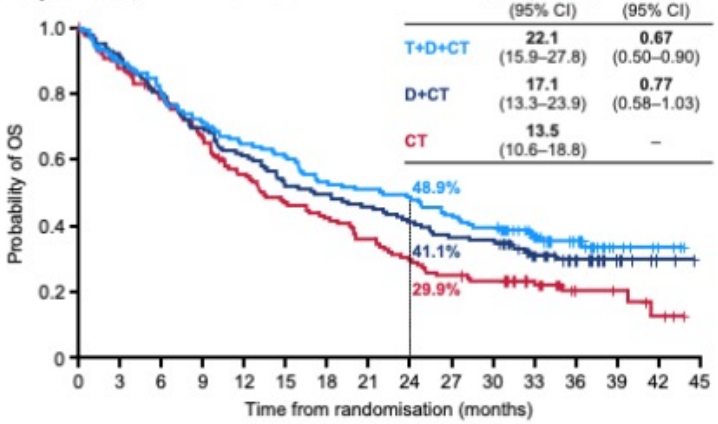
Peters S et al ESMO 2023

Poseidon – Histology and PD-L1

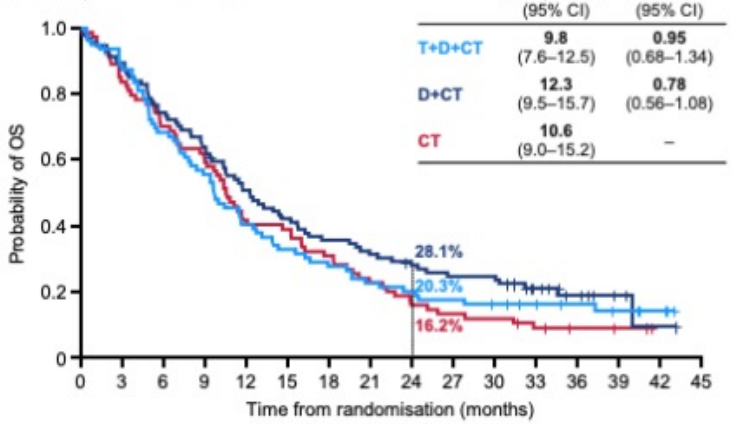
Non-squamous, PD-L1 TC ≥1%

	mOS, months (95% CI)	HR vs CT (95% CI)
T+D+CT	22.1 (15.9–27.8)	0.67 (0.50–0.90)
D+CT	17.1 (13.3–23.9)	0.77 (0.58–1.03)
CT	13.5 (10.6–18.8)	–



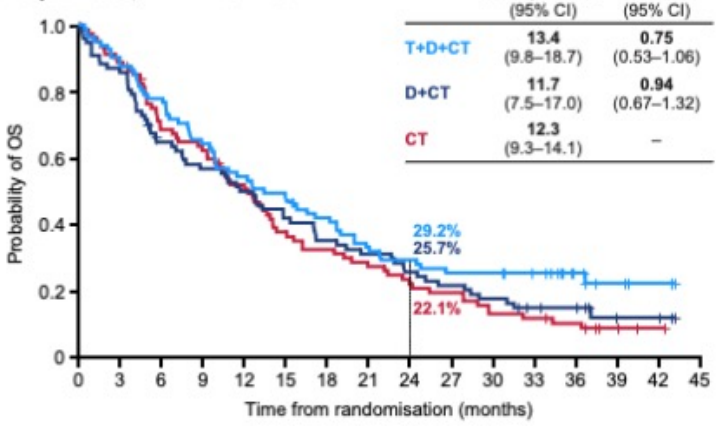
Squamous, PD-L1 TC ≥1%

	mOS, months (95% CI)	HR vs CT (95% CI)
T+D+CT	9.8 (7.6–12.5)	0.95 (0.68–1.34)
D+CT	12.3 (9.5–15.7)	0.78 (0.56–1.08)
CT	10.6 (9.0–15.2)	–



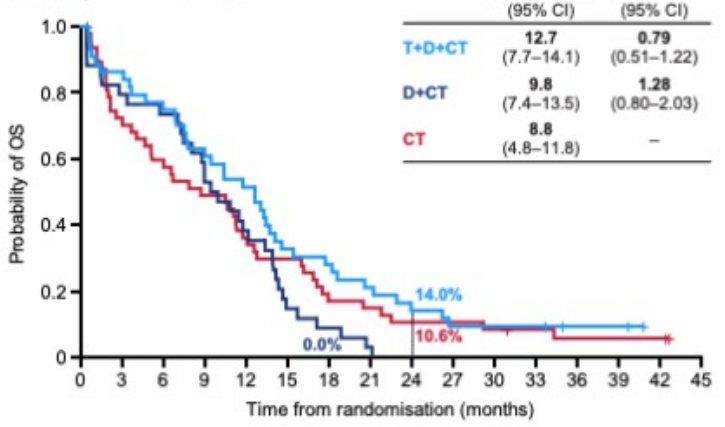
Non-squamous, PD-L1 TC <1%

	mOS, months (95% CI)	HR vs CT (95% CI)
T+D+CT	13.4 (9.8–18.7)	0.75 (0.53–1.06)
D+CT	11.7 (7.5–17.0)	0.94 (0.67–1.32)
CT	12.3 (9.3–14.1)	–



Squamous, PD-L1 TC <1%

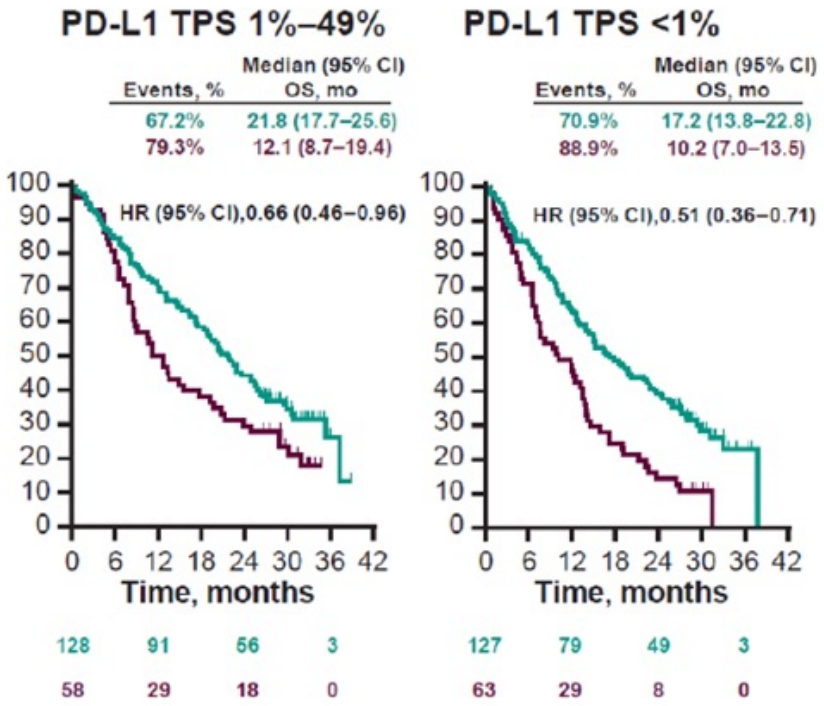
	mOS, months (95% CI)	HR vs CT (95% CI)
T+D+CT	12.7 (7.7–14.1)	0.79 (0.51–1.22)
D+CT	9.8 (7.4–13.5)	1.28 (0.80–2.03)
CT	8.8 (4.8–11.8)	–



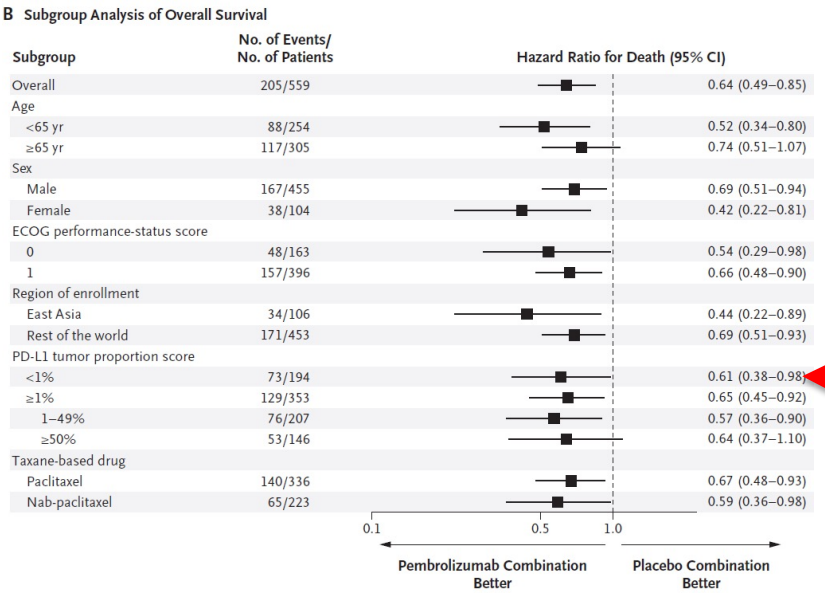
Garon E et al WCLC 2022

Chemo-IO Combinations for PD-L1 1-49% or Negative Disease

KN189 - OS



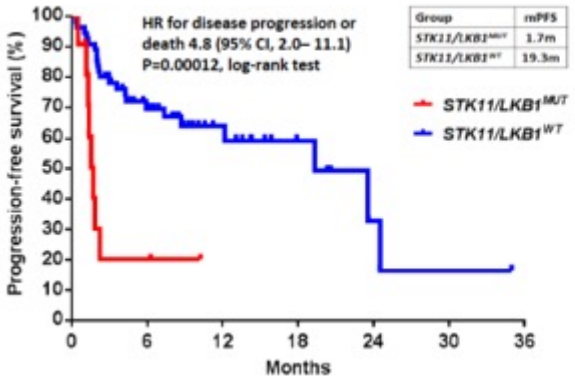
KN407 - OS

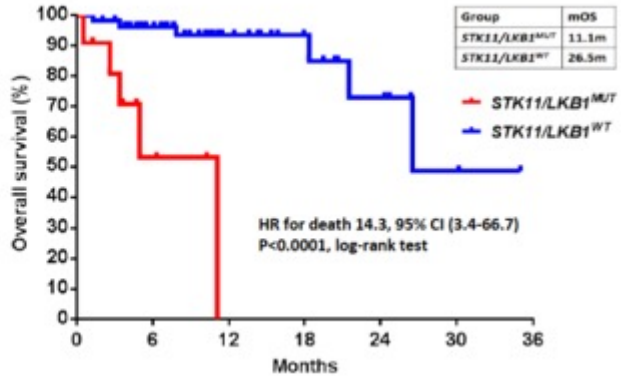


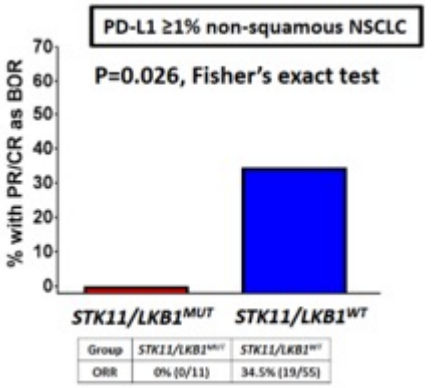
Gandhi L 2018; Gadghel S ASCO 2019; Rodriguez-Abreu ASCO 2020., Paz-Ares L et al JTO 2020

Using Molecular Subsets to Guide Therapy

STK11 mutations and PD-1 ICI Outcomes







KN189

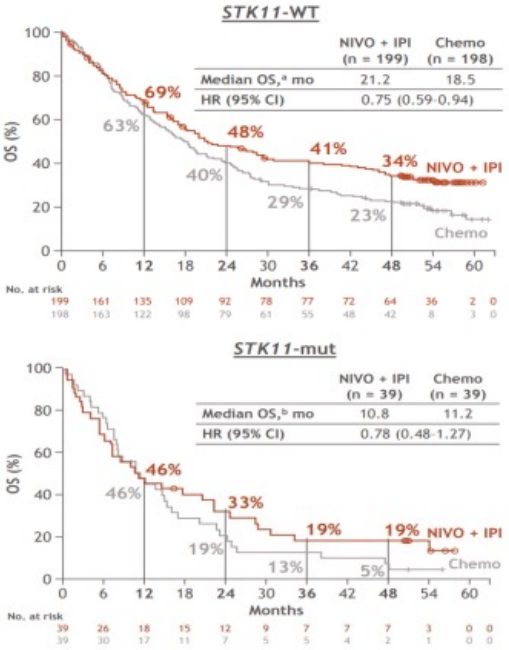
	STK11				*KEAP1*			
	With Mutation		**Without Mutation**		**With Mutation**		**Without Mutation**	
	Pembro + Chemo (n = 36)	**Placebo + Chemo (n = 18)**	**Pembro + Chemo (n = 168)**	**Placebo + Chemo (n = 67)**	**Pembro + Chemo (n = 45)**	**Placebo + Chemo (n = 23)**	**Pembro + Chemo (n = 159)**	**Placebo + Chemo (n = 62)**
ORR, % (95% CI)	31 (16-48)	17 (4-41)	49 (41-57)	16 (8-27)	36 (22-51)	17 (5-39)	48 (40-56)	16 (8-28)
PFS, median, mo (95% CI)	6 (4-9)	5 (5-9)	10 (8-14)	5 (5-5)	5 (4-11)	5 (5-9)	10 (8-14)	5 (5-5)
PFS, HR (95% CI)	0.81 (0.44-1.47)		0.38 (0.27-0.52)		0.65 (0.38-1.12)		0.38 (0.28-0.53)	
OS, median, mo (95% CI)	17 (5-NR)	8 (7-NR)	23 (20-NR)	12 (8-25)	13 (7-NR)	9 (7-NR)	24 (20-NR)	12 (8-NR)
OS, HR (95% CI)	0.75 (0.37-1.50)		0.59 (0.41-0.85)		0.81 (0.44-1.49)		0.57 (0.39-0.84)	

R

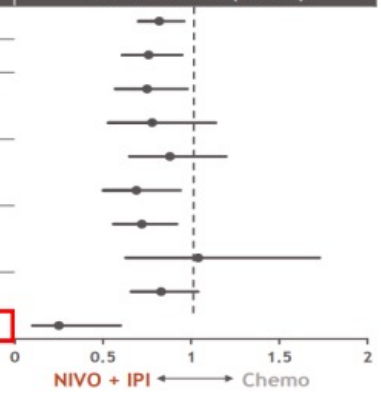
TURNING RESEARCH INTO RESULTS 1973–2023

Skoulidis et al Cancer Discovery 2018, Gadgeel SM et al, AACR 2020

Molecular Subsets: CM 227



Subgroup, n[b]	4-y PFS rate, %		Median PFS, mo		Unstratified HR
	NIVO + IPI	Chemo	NIVO + IPI	Chemo	
NSQ (n = 419, 419)	14	3	5.2	5.6	0.82
Mut-eval (n = 238, 237)	14	3	5.6	5.6	0.76
KRAS-WT (n = 150, 162)	19	6	5.6	5.6	0.75
KRAS-mut (n = 88, 75)	17	2	5.4	5.8	0.78
TP53-WT (n = 111, 106)	10	5	5.4	5.6	0.88
TP53-mut (n = 127, 131)	24	7	5.8	6.6	0.69
STK11-WT (n = 199, 198)	19	6	8.1	6.1	0.72
STK11-mut (n = 39, 39)	13	0	2.8	4.3	1.04
KEAP1-WT (n = 218, 219)	16	6	5.5	5.8	0.83
KEAP1-mut (n = 20, 18)	41	0	11.1	2.9	0.25



KEAP1^{MUT}(N=38)
Ipi/Nivo: mOS 24.4m
Chemo: mOS 8.9m

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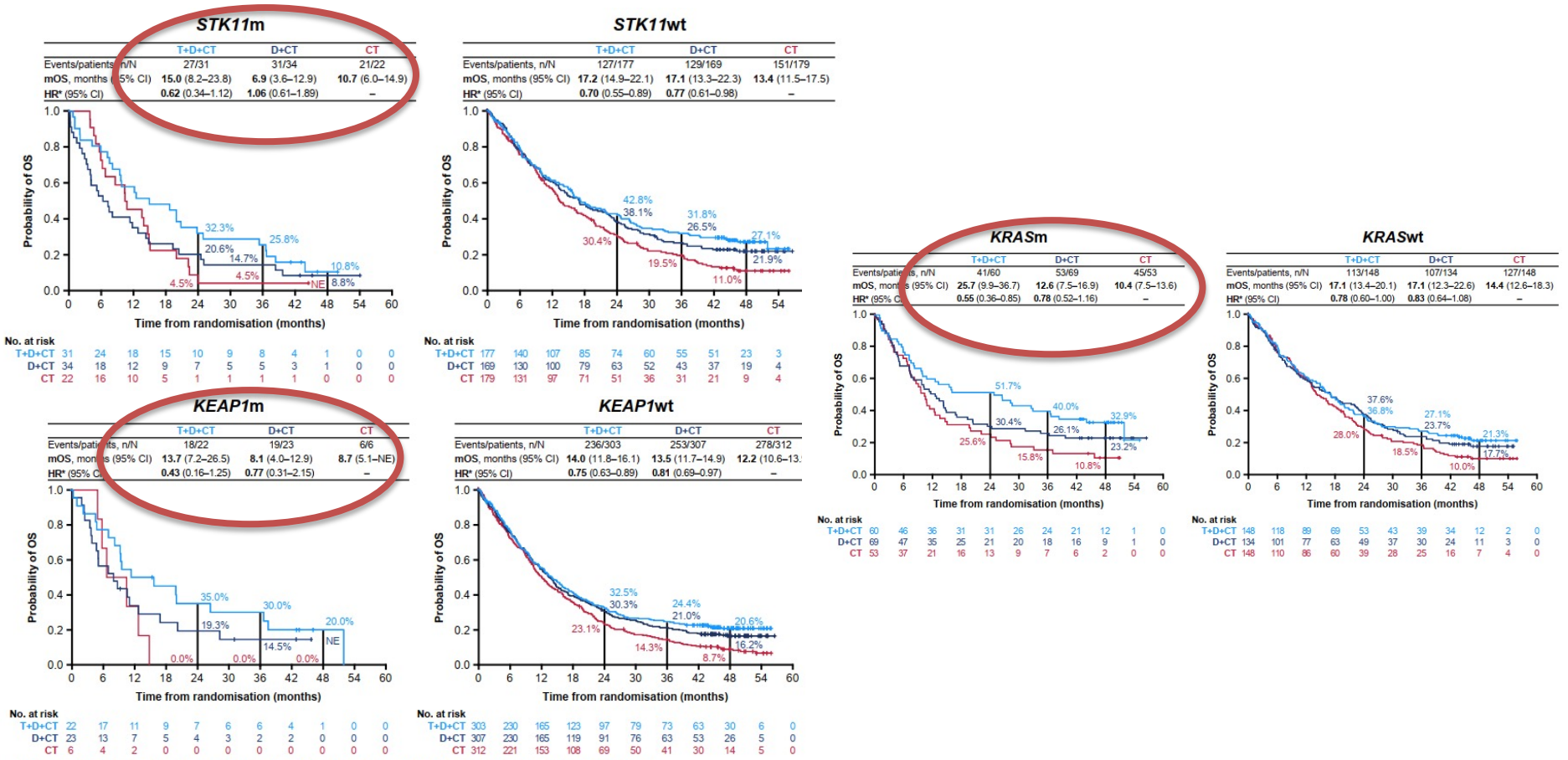
Ramalingam S et al., ESMO Immuno-Oncology Congress,2021

Poseidon– OS by Molecular Subtype



In NSQ *KEAP1*m, HR (95% CI) vs CT was 0.33 (0.10–1.15) with T+D+CT and 0.67 (0.23–2.17) with D+CT

Johnson M et al ESMO 2022

Advanced NSCLC: PD-L1 ≥50%

First-line Treatment in Patients Without Molecularly Driven Tumors

ADENOCARCINOMA

Preferred
- Pembrolizumab (category 1)[49,50]
- (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)[51,52]
- Atezolizumab (category 1)[53]
- Cemiplimab-rwlc (category 1)[54]
- Cemiplimab-rwlc + pemetrexed + (carboplatin or cisplatin) (category 1)[55]

Other Recommended
- Carboplatin + paclitaxel + bevacizumab[c,e] + atezolizumab (category 1)[56]
- Carboplatin + albumin-bound paclitaxel + atezolizumab[57]
- Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin) (category 1)[58]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[59]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + pemetrexed (category 2B)[59]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[60]

Most Preferred Regimens: Immune Checkpoint Inhibitors (ICIs) as Monotherapy

SQUAMOUS CARCINOMA

Preferred
- Pembrolizumab (category 1)[49,50]
- Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[61]
- Atezolizumab (category 1)[53]
- Cemiplimab-rwlc (category 1)[54]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[55]

Other Recommended
- Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[58]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[59]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine (category 2B)[59]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[60]

NCCN Guidelines. NSCLC v2.2024.

Advanced NSCLC: PD-L1 <1%, ≥1%-49%

First-line Treatment in Patients Without Molecularly-driven Tumors

ADENOCARCINOMA

Preferred
- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]
- Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin) (category 1)[7,e]

Other Recommended
- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1)[6,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e] (category 1)
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[8,e] (category 1)

- ICI + CT
- ICI/ICI +/- CT

SQUAMOUS CARCINOMA

Preferred
- Pembrolizumab/carboplatin/paclitaxel (category 1)[36,e]
- Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[36,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]

Other Recommended
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e] (category 1)
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine[8,e] (category 1)

Useful in Certain Circumstances • PD-L1 ≥1%
Pembrolizumab (category 2B)g,49,50

NCCN Guidelines. NSCLC v2.2024.

So Many Choices for Advanced Stage NSCLC…

The choice of immunotherapy is based on the following:

- **Histology (squamous versus nonsquamous)**
- **PD-L1 expression**
- **Molecular subsets**
- **Patient preference about their goals of their lung cancer treatment**
- **Overall health of patient (performance status)**
- **Whether the patient has a history of an autoimmune disease or transplant**

Thank You!

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