Role of Immune Checkpoint Inhibition in the Front-line Setting

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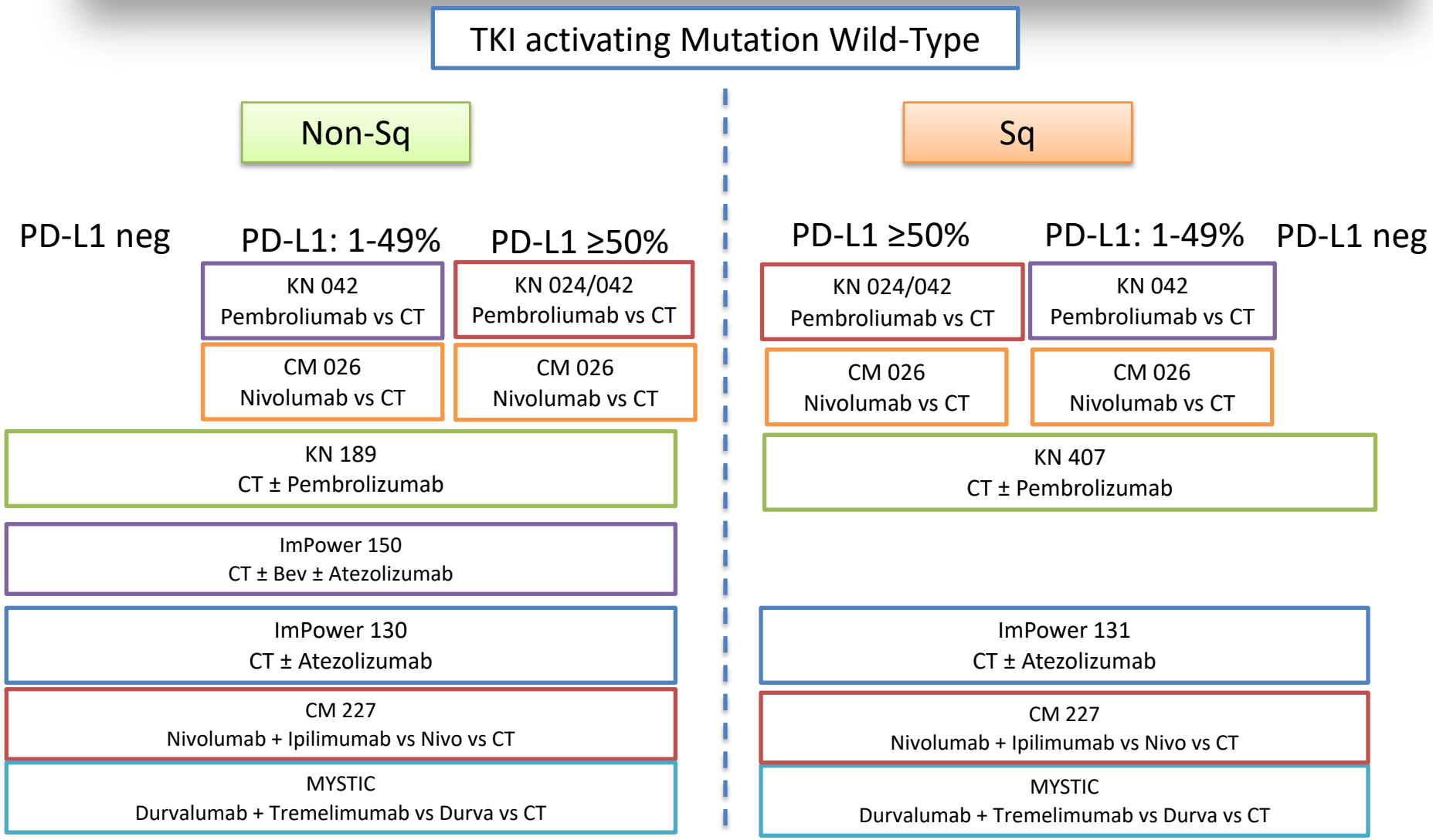
Front-line ImmunoTx Strategies in Advanced NSCLC

- IO vs CT
- Combinations
  - IO + CT
  - IO + CT + Biologic agents
  - IO + IO
  - Other immunotherapy strategies
    - Cancer vaccines
    - Adaptive T cell therapy

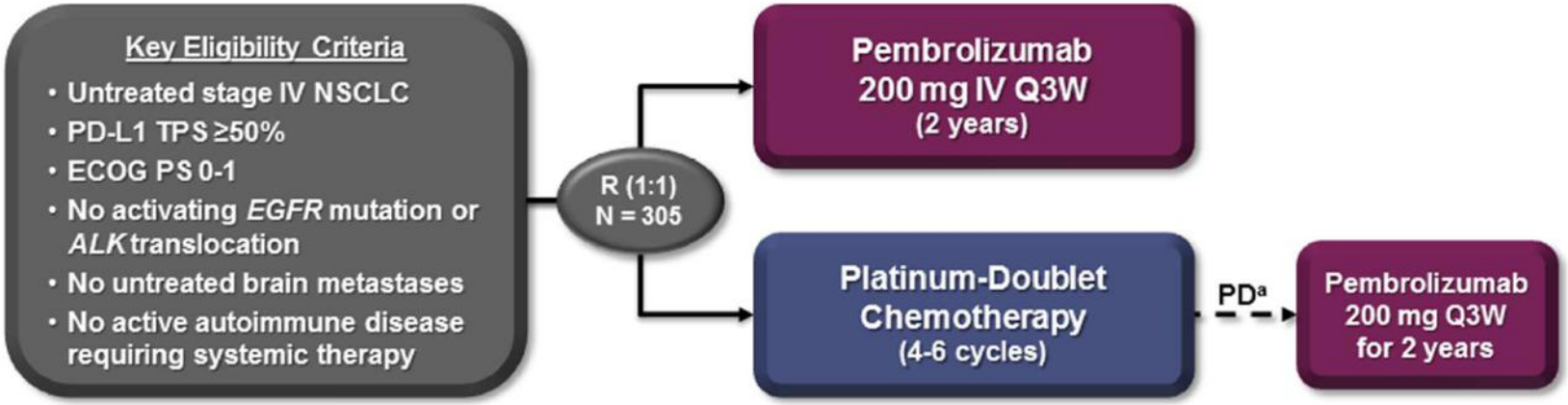
Front-line ImmunoTx Landscape in 2019



IO VS CT

KEYNOTE 024 / 042	Pembro vs CT
CHECKMATE 026	Nivo vs CT

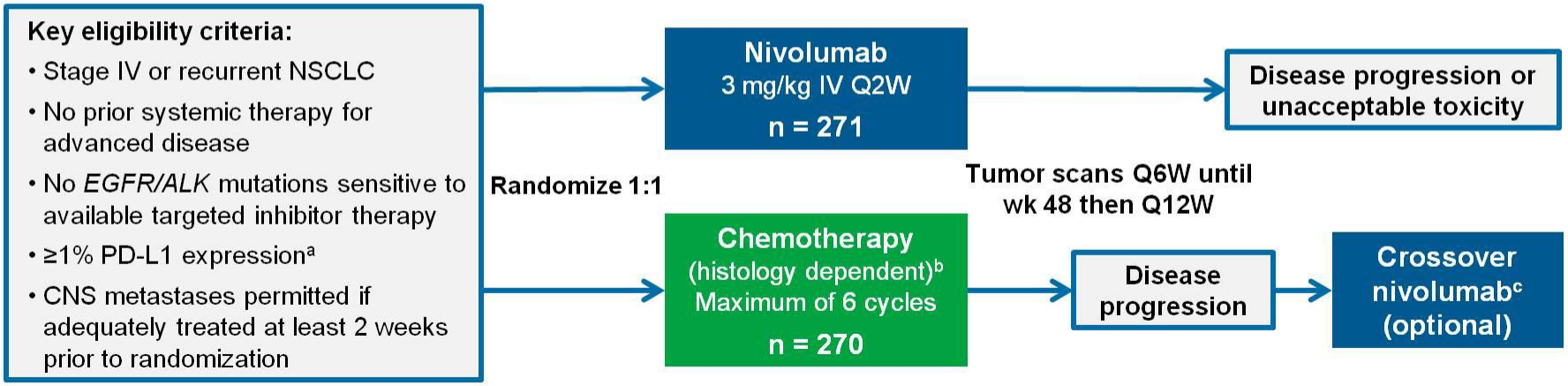
KEYNOTE-024 Study Design (NCT02142738)



Key End Points

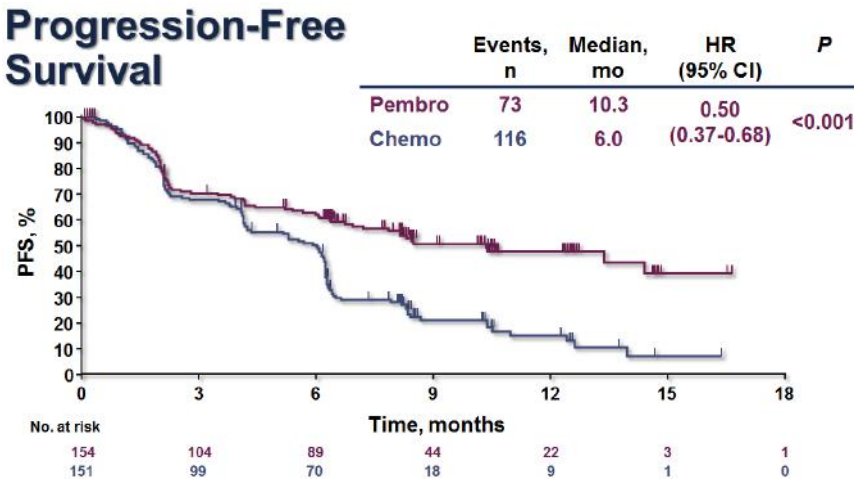
Primary: PFS (RECIST v1.1 per blinded, independent central review)

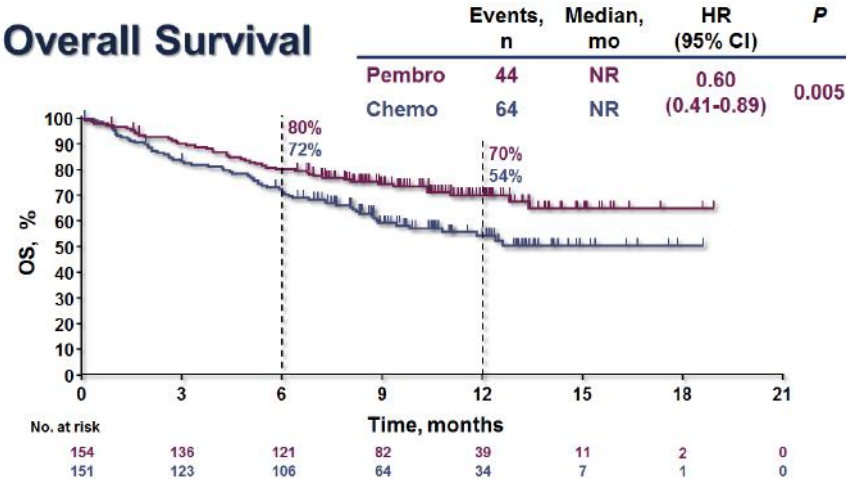
Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC



Anti PD-1 Agents vs CT: 1st L Treatment

Study	Line	Agents	PD-L1	Result	HR
CheckMate 026	1st	Nivo vs Chemo	≥1%	No difference in PFS, OS	1.15, 1.02
KEYNOTE-024	1st	Pembro vs Chemo	>50%	Improved OS, improved QoL	0.60





cross-over (+)

Barlesi et al. ESMO 2016 LBA44. Socinski et al. ESMO 2016
Reck et al. N Engl J Med 2016; 375: 1823 - 33

KEYNOTE-042 Study Design: Pembrolizumab vs. chemotherapy

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 tumor proportion score (TPS) ≥1%[a]
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1

Stratification Factors

- Region (east Asia vs rest of the world)
- PD-L1 TPS (≥50% vs 1-49%)

R (1:1)

N = 637 → Pembrolizumab 200 mg Q3W for up to 35 cycles

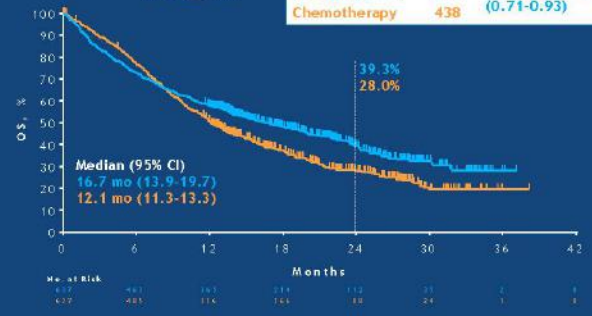
N = 637 → Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m^2 Q3W[b] OR Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m^2 Q3W[b] for up to 6 cycles

NO CROSSOVER ALLOWED!

Keynote 042:

TPS ≥ 1%

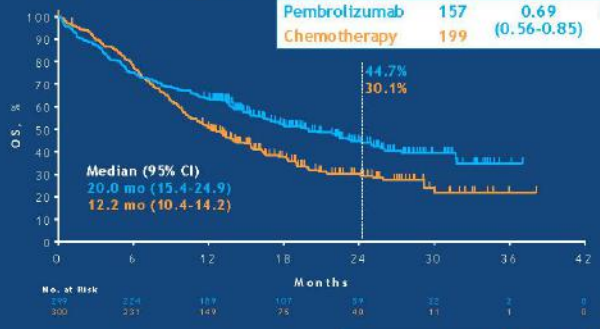
	Events	HR (95% CI)	P
Pembrolizumab	371	0.81 (0.71-0.93)	0.0018
Chemotherapy	438		



Benefit driven by High PD-L1 subgroup

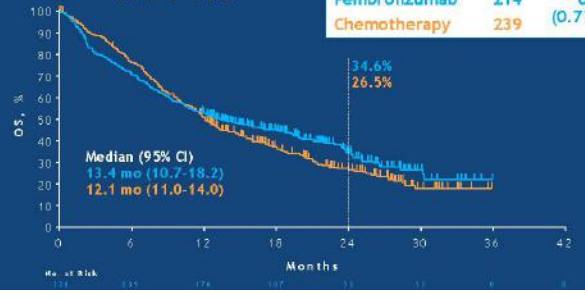
TPS ≥50%

	Events	HR (95% CI)	P
Pembrolizumab	157	0.69 (0.56-0.85)	0.0003
Chemotherapy	199		



TPS 1-49%

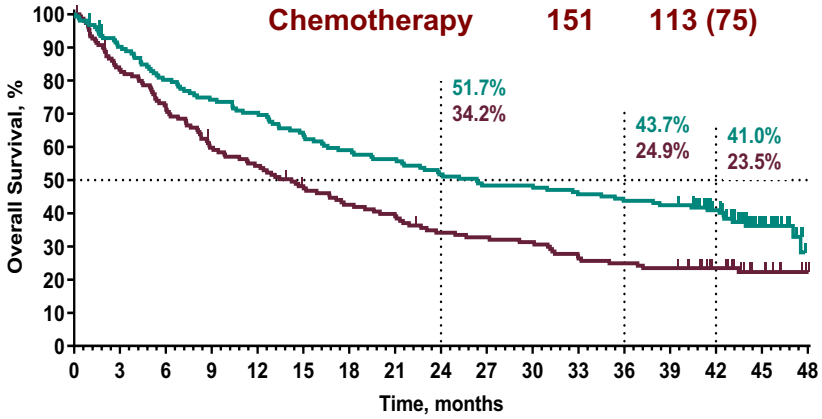
	Events	HR (95% CI)
Pembrolizumab	214	0.92 (0.77-1.11)
Chemotherapy	239	



KEYNOTE 024

	Pembrolizumab N = 154	Chemotherapy N = 151
Men, n (%)	92 (60)	95 (63)
Enrolled in east Asia	21 (14)	19 (13)
ECOG PS 1, n (%)	99 (64)	98 (65)
Squamous histology, n (%)	29 (19)	27 (18)
Smoking status,[a] n (%)		
Current	34 (22)	31 (21)
Former	115 (75)	101 (67)
Never	5 (3)	19 (13)

	N	Events, n (%)	HR (95% CI)
Pembrolizumab[a]	154	97 (63)	0.65 (0.50–0.86) *P* = 0.001[b]
Chemotherapy	151	113 (75)	



Median (95% CI)
26.3 mo (18.3–40.4 mo)
14.2 mo (9.8–18.3 mo)

No. at risk

brolizumab	154	136	121	112	106	96	89	85	78	73	73	69	66	64	50	24	5
emotherapy	151	124	108	88	80	69	61	56	48	46	44	37	35	33	24	14	6

KEYNOTE 042

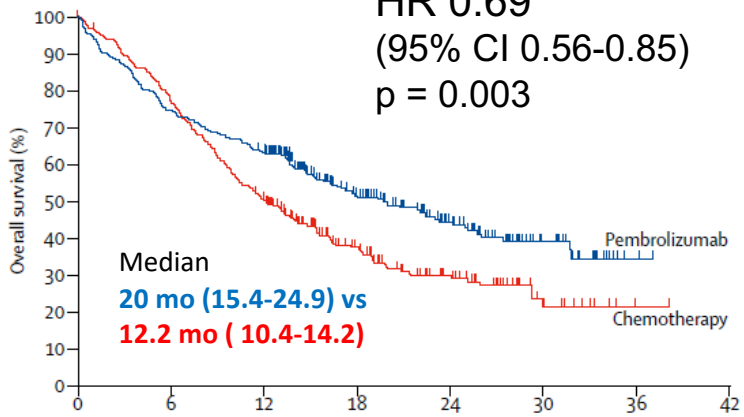
Baseline Characteristics: TPS ≥1%

	Pembrolizumab (N = 637)	Chemotherapy (N = 637)
Men	450 (71)	452 (71)
Enrolled in east Asia	185 (29)	185 (29)
ECOG PS 1	438 (69)	445 (70)
Squamous histology	242 (38)	249 (39)
PD-L1 TPS ≥50%[a]	299 (47)	300 (47)
Smoking status		
Current/former	495 (78)	497 (78)

19.8% in CT arm had subsequent ICI

PD-L1 TPS ≥ 50%

HR 0.69
(95% CI 0.56-0.85)
p = 0.003



Number at risk (censored)

Pembrolizumab group	299 (0)	224 (0)	189 (1)	107 (55)	59 (91)	22 (122)	2 (140)	0 (142)
Chemotherapy group	300 (0)	231 (2)	149 (4)	75 (46)	40 (67)	11 (90)	1 (100)	0 (101)

Cross trial comparison:

OS and HR are quite similar despite 65% (KN 024) vs. no (KN 042) crossover

Reck, Journal of Clinical Oncology 2019 37:7; Mok Lancet 2019

Front-line IO

- Pembrolizumab received FDA approval as 1st L monotherapy;
  - Oct 24, 2016: advanced NSCLC in pts with PD-L1 **≥** 50% **PD-L1** staining by the 22C3 assay
  - Apr 11, 2019: advanced or stage III NSCLC not amenable to curative therapy in pts with TPS **≥ 1% PD-L1** staining by an FDA approved assay

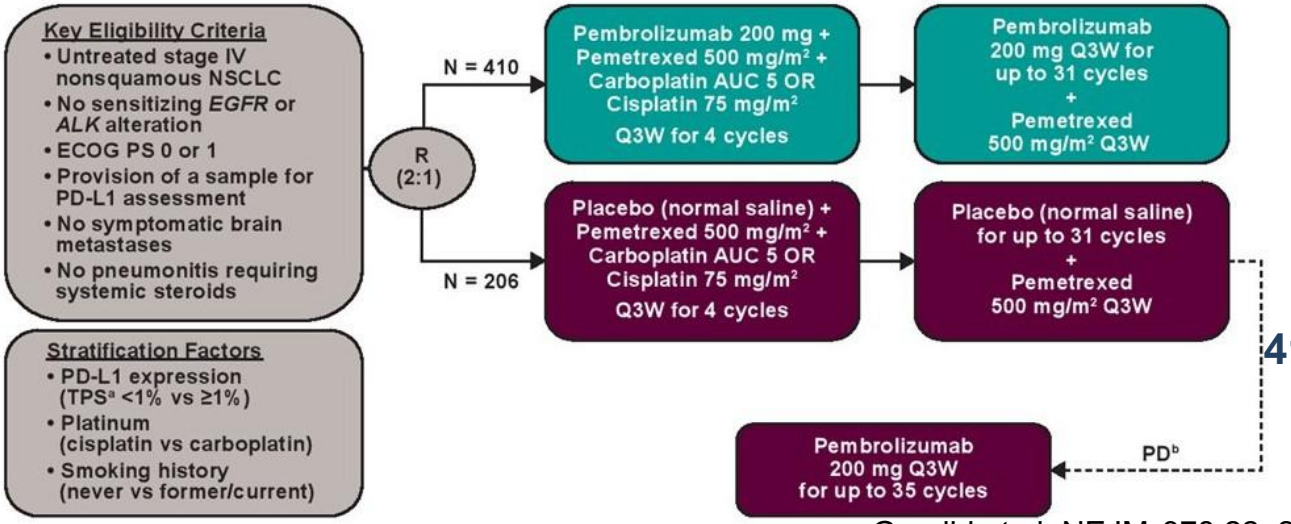
Combinations:
CT & Biologic Agents + IO's

KEYNOTE 021 / 189 Pembro + CT vs CT

IMPower 150 Atezo + Bev + CT vs Bev + CT vs Atezo + CT

IMPower 130 / 131 Atezo + CT vs CT

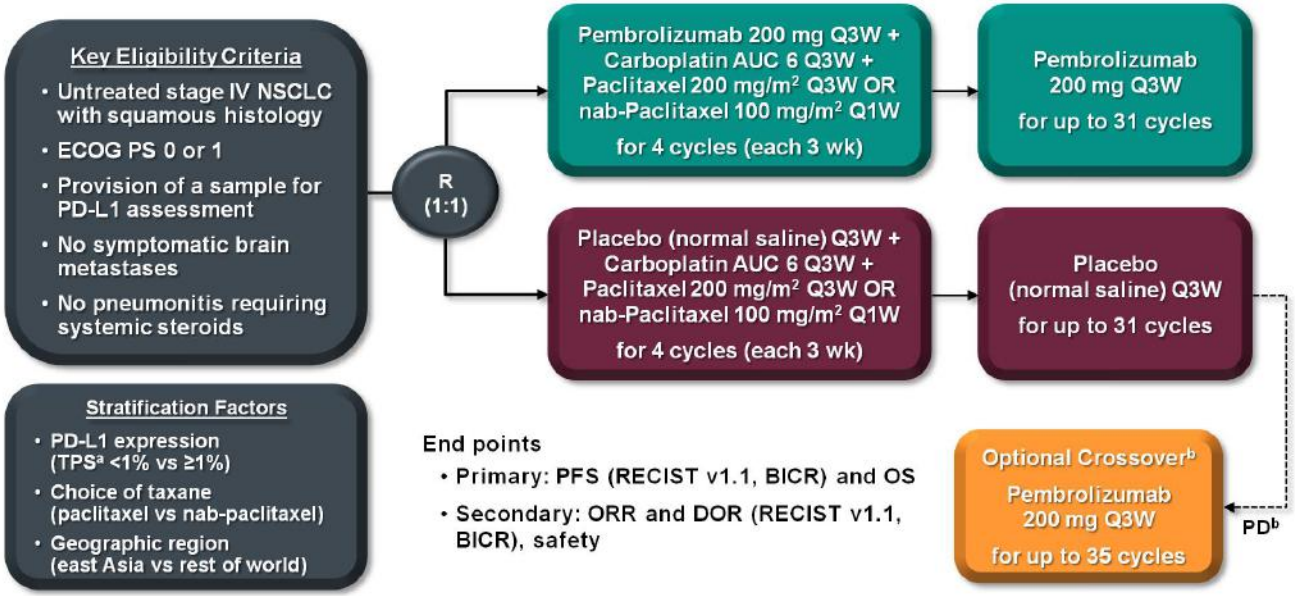
KEYNOTE 189: Non-Sq



41.3% Cross-over

Gandhi et al. NEJM 378;22. 2018. , Gadgeel et al. ASCO 2019

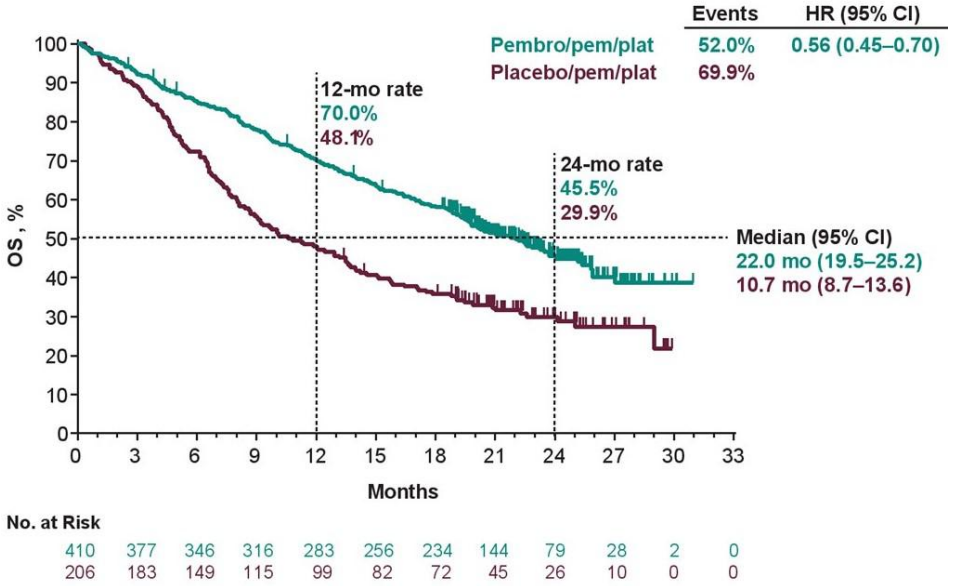
KEYNOTE-407 Study Design (NCT02775435)



42.5% Cross-over

Paz-Ares L, N Engl J Med 2018; 379:2040-2051

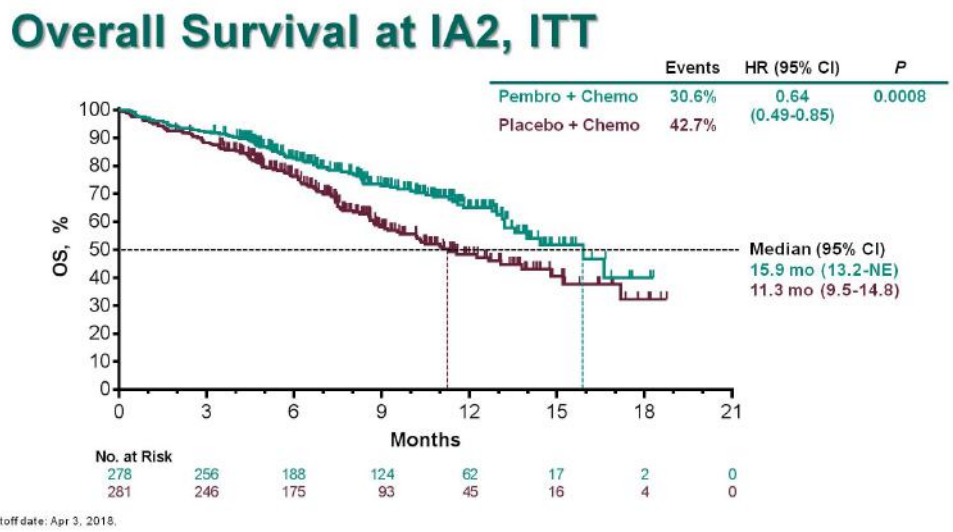
KEYNOTE 189: Non-Sq



Pembro + CT vs CT
HR: 0.56 (0.45-0.7); p<0.00001
Med OS: 22.0 vs 10.7 mo

Gadgeel et al. ASCO 2019

KEYNOTE 407: Sq



Pembro + CT vs CT
HR: 0.64 (0.49-0.85); p: 0.0008
Med OS: 15.9 vs 11.3 mo

Luis Paz-Ares, ASCO 2018

KEYNOTE 189: Pembrolizumab + Chemotherapy
Summary of OS, PFS, ORR, and PFS2 (ITT)[a,b]

End Point	Total N = 616	TPS ≥50% n = 202	TPS 1-49% n = 186	TPS <1% n = 190
OS, HR (95% CI)	0.56 (0.45–0.70)	0.59 (0.39–0.88)	0.62 (0.42–0.92)	0.52 (0.36–0.74)
PFS, HR (95% CI)	0.48 (0.40–0.58)	0.36 (0.26–0.51)	0.51 (0.36–0.73)	0.64 (0.47–0.89)
ORR, pembro/pem/plat vs chemo/pem/plat	48.0% vs 19.4%	62.1% vs 24.3%	49.2% vs 20.7%	32.3% vs 14.3%
PFS2, HR (95% CI)	0.49 (0.40–0.59)	0.47 (0.33–0.69)	0.59 (0.41–0.86)	0.46 (0.33–0.66)

Gadgeel et al. ASCO 2019

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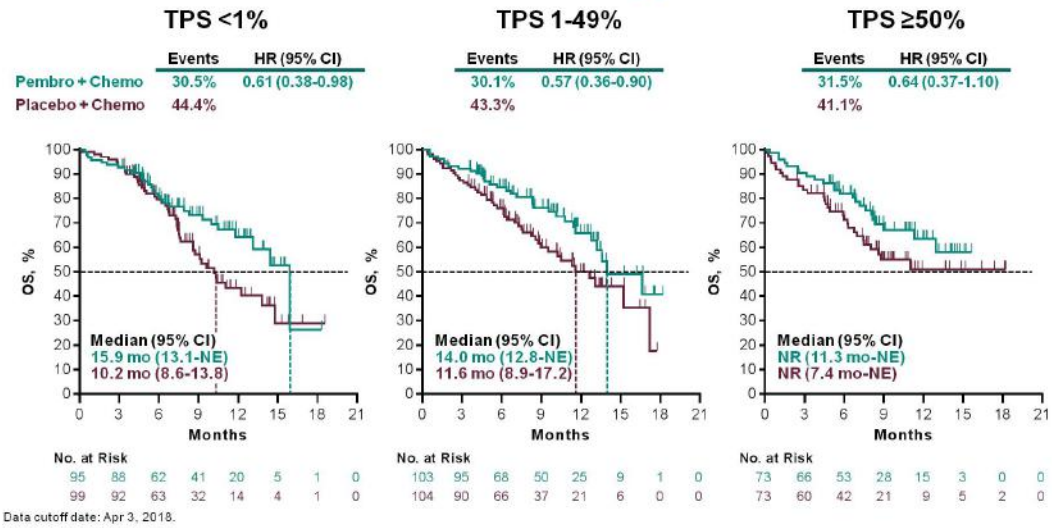
Gadgeel et al. ASCO 2019

KEYNOTE 407: Sq

Overall Survival at IA2 by PD-L1 TPS



Pembro + CT vs CT

<1%:

HR: 0.61 (0.38-0.98); 15.9 vs 10.2 mo

1-49%:

HR: 0.57 (0.36-0.9); 14.0 vs 11.6 mo

>50%:

HR: 0.64 (0.37-1.10); NR vs NR

Luis Paz-Ares, ASCO 2018

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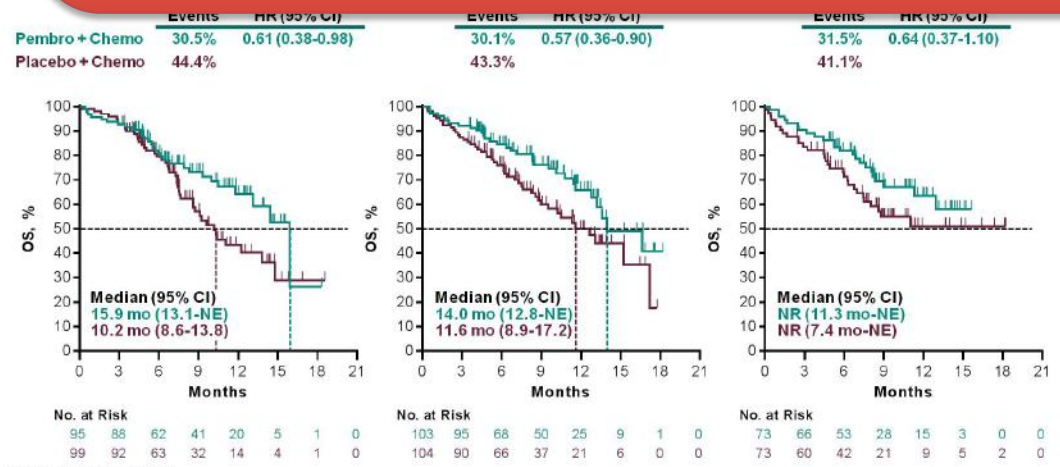
PF				0.66)

019

Pembro + CT improves OS in all subgroups regardless of PD-L1 expression



<1%:
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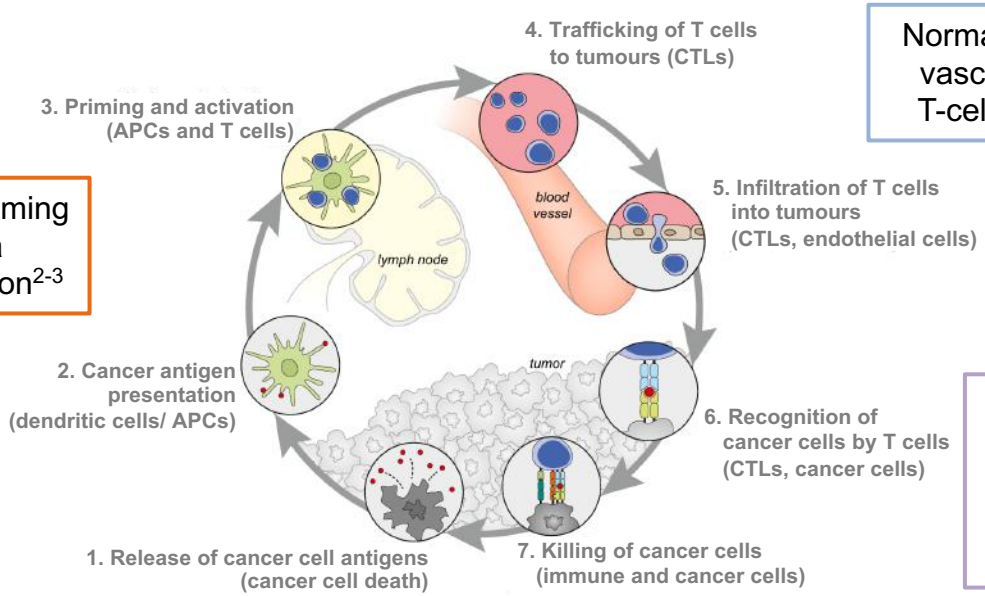
1-49%:
HR: 0.57 (0.36-0.9); 14.0 vs 11.6 mo
>50%:
HR: 0.64 (0.37-1.10); NR vs NR

Luis Paz-Ares, ASCO 2018

Rationale for combining IO + bevacizumab

- Inhibition of VEGF has immune modulatory effects



Normalisation of the tumour vasculature for increased T-cell tumour infiltration[4-7]

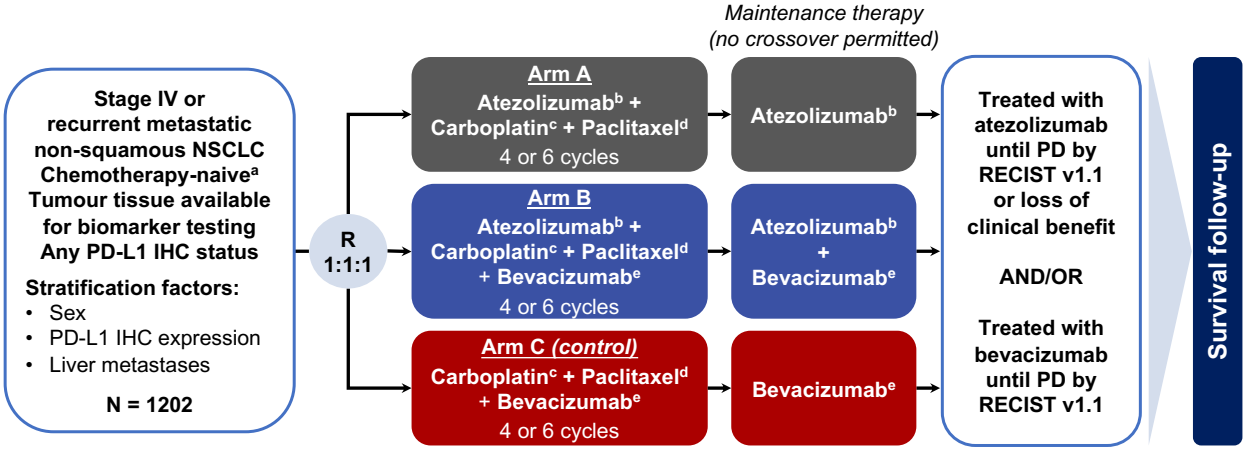
Promotion of T-cell priming and activation via dendritic cell maturation[2-3]

Establishing an immune-permissive tumour microenvironment by decreasing MDSC and Treg populations[7-11]

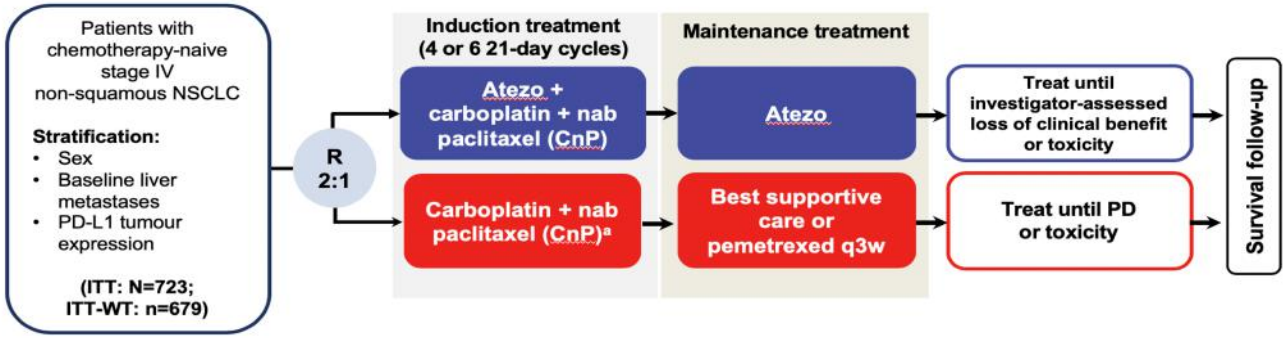
- T-cell mediated cancer cell killing by IO's may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression

1. Ferrara N, et al. *Nat Rev Drug Discov*, 2004. 2. Gabrilovich DI, et al. *Nat Med*, 1996. 3. Oyama T, et al. *J Immunol*, 1998. 4. Goel S, et al. *Physiol Rev*, 2011.
5. Motz GT, et al. *Nat Med*, 2014. 6. Hodi FS, et al. *Cancer Immunol Res*, 2014. 7. Wallin JJ, et al. *Nat Commun*, 2016. 8. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*, 2009. 9. Roland CL, et al. *PLoS One*, 2009. 10. Facciabene A, et al. *Nature*, 2011. 11. Voron T, et al. *J Exp Med*, 2015.
Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.

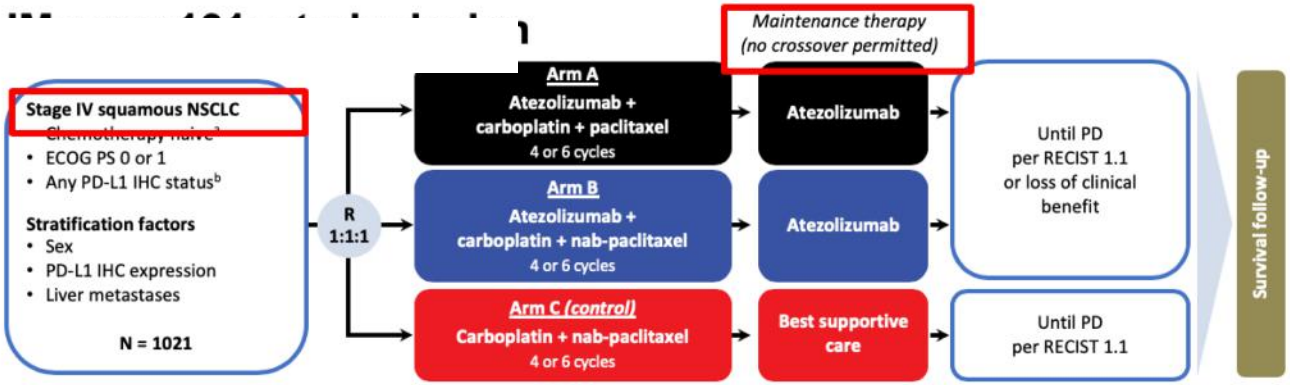
First line atezolizumab plus chemotherapy nsq & sq NSCLC



IMpower 150



IMpower 130/132



IMpower 131

Socinsky N Engl J Med 2018, West Lancet Oncol 2019

The Introduction of Immunotherapy Combinations

Trial	Patients	PFS	OS
KN 407 (Pembro/Carb/Pac or nab-Pac vs Carb/Pac or nab-Pac)	559	**6.4 vs 4.8 m HR 0.56, P<0.001**	**15.9 vs 11.3 HR 0.64, p=0.0008**
IMpower 131 (Atezo/Carb/nab-Pac vs Carb/nab-Pac)	684	**6.3 vs 5.6 m HR 0.71, p=0.001**	14.0 vs 13.9* HR 0.96, p=0.69
KN 189 (Pembro/Cis or Carb/Pem vs Cis or Carb/Pem)	616	**5.6 vs 4.9 m HR 0.52, p<0.00001**	**Nr vs 11.3 m HR 0.49, p<0.00001**
IMpower 132 (Atezo/Cis or Carb/Pem vs Cis or Carb/Pem)	578	**7.6 vs 5.2 m HR 0.6, p<0.0001**	18.1 vs 13.6 m** HR 0.81, p=0.0797
IMpower 130 (Atezo/Carbo/nab-Pac vs Carbo/nab/Pac)	723	**7.0 vs 5.5 m HR 0.64, P<0.0001**	**18.6 vs 13.9 m HR 0.79, P=0.033**
IMpower 150 Atezo/Bev/Carb/Pac vs Bev/Carb/Pac	800	**8.3 vs 6.8 m HR 0.59, p<0.0001**	**19.2 vs 14.7 m HR 0.78, p=0.016**

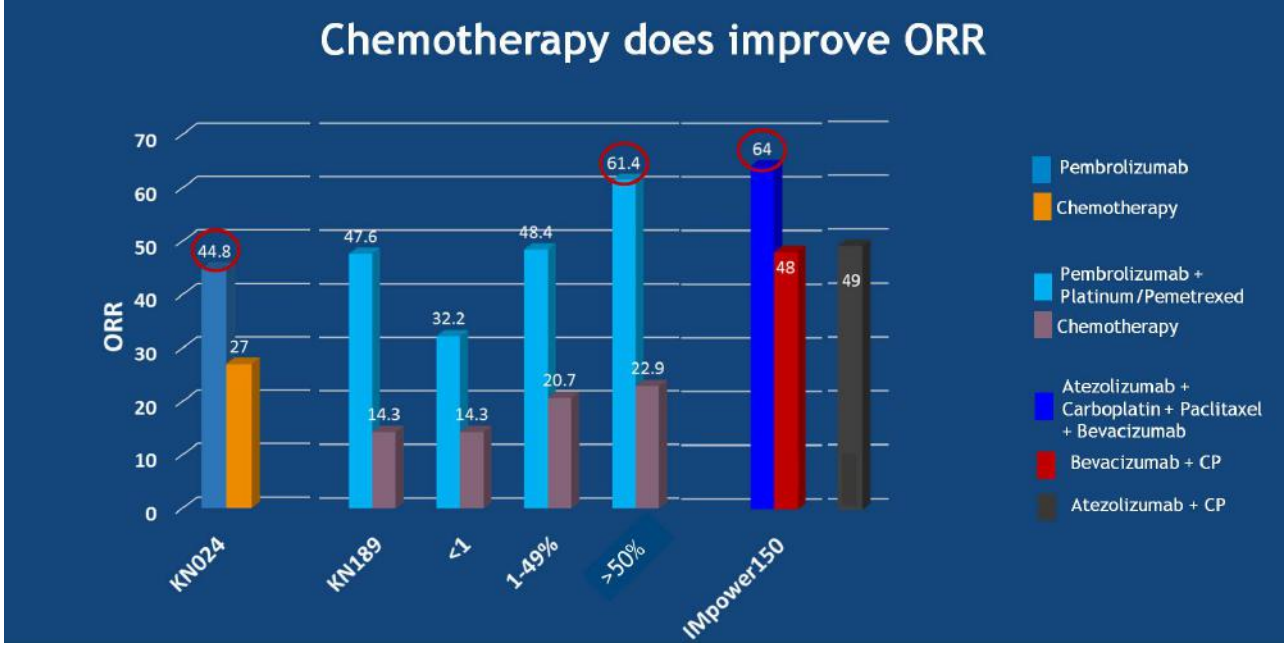
*: median OS in the subgroup of patients with a high tumor expression of PD-L1 was significantly higher for those patients receiving atezolizumab (23.4 months vs 10.2 months; HR, 0.48; 95% CI, 0.29-0.81).

**: interim analysis

Ghandi L et al, NEJM 2018; Socinski MA, et al. NEJM 2018; Papadimitrakopoulos V et al, WCLC 2018, Cappuzzo F et al, ESMO 2018, Jotte RM et al, ASCO 2018, Paz-Ares L et al, NEJM 2018

What is the best front line treatment for patients with advanced NSCLC, no driver alterations and PD-L1 TPS =/> 50%?

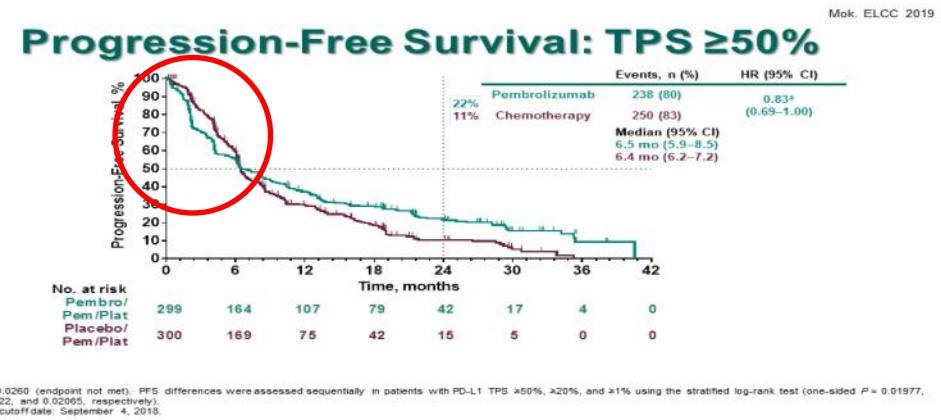
IO VS IO + CT ??



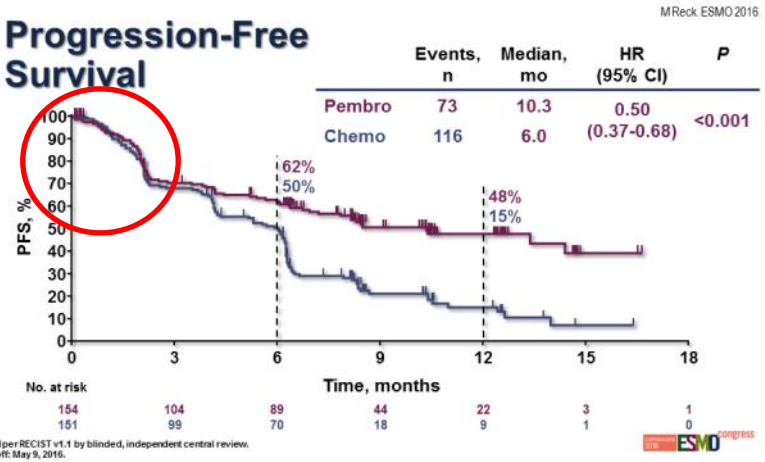
But increases toxicity as well….

	Keynote 042 Pembrolizumab (n=636)	Keynote 189 Pembrolizumab/pemetrexed/platinum (n=405)
Treatment related AEs	**63%**	**100%**
Grade 3-5	18%	66%
Led to death	2%	7%
Led to discontinuation	9%	14%
Immune related AEs	**28%**	**23%**
Grade 3-5	8%	9%
Led to death	0.2%	0.7%

KN 042: Prembrolizumab alone

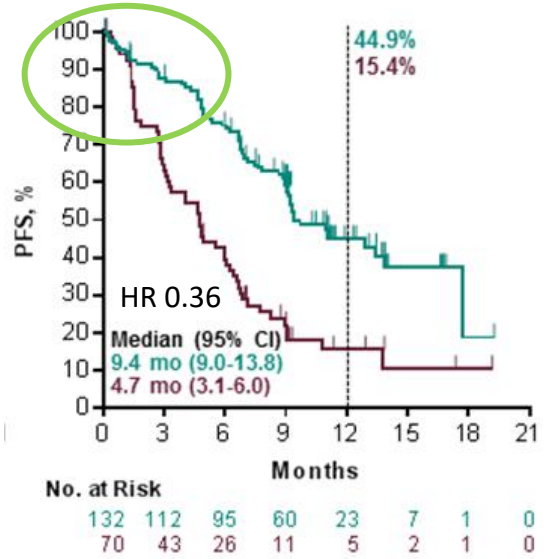


KN 024: Prembrolizumab alone



KN 189: Prembrolizumab plus chemo

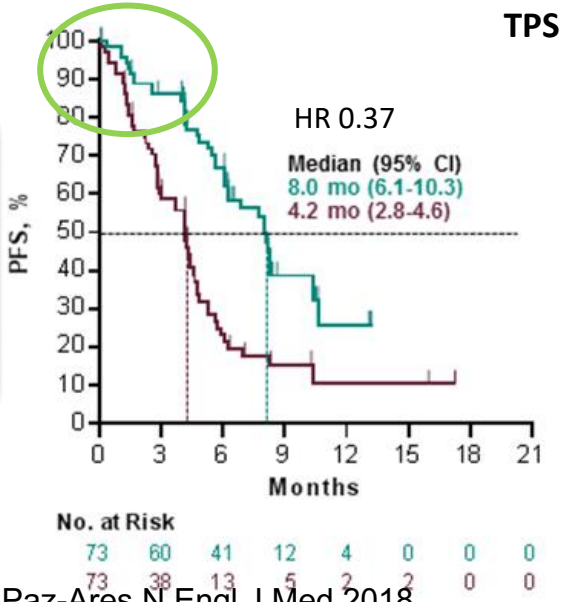
TPS ≥ 50%



Early PFS advantage may indicate higher efficacy favoring the combined regimen

KN 407: Prembrolizumab plus chemo

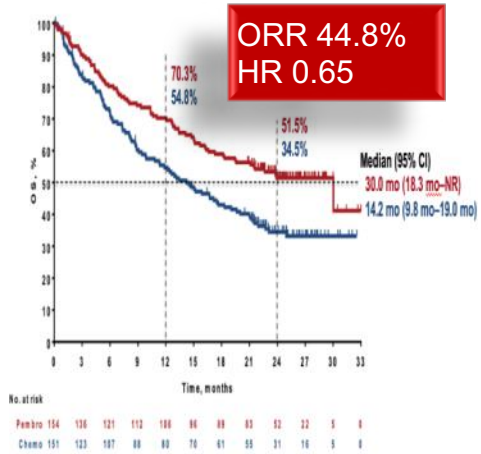
TPS ≥ 50%

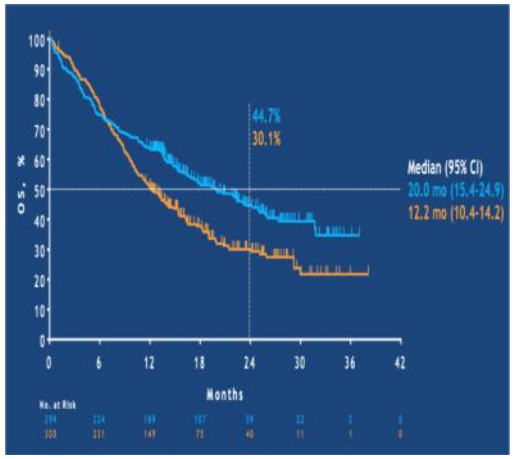


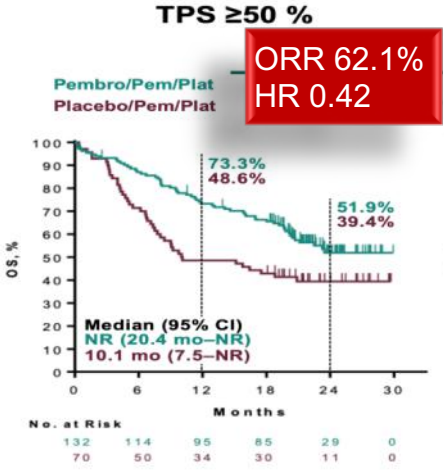
Reck N Engl J Med 2016, Mok Lancet 2019, Ghandi N Engl J Med 2018, Paz-Ares N Engl J Med 2018

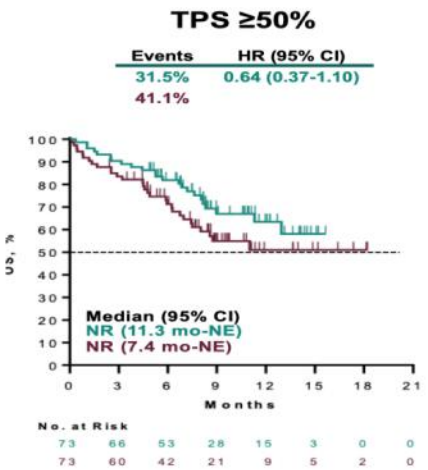
Overall Survival

KN-24	KN-42	KN-189	KN-407









65 % cross-over

No cross-over (20% subs ICI)

41.3% cross-over

42.5% cross-over

Med OS: 30.0 vs 14.2 m 2 year OS: 51.5% vs 34.5% HR: 0.63 (0.50-0.86)	Med OS: 20.0 vs 12.2 m 2 year OS: 44.7% vs 30.1% HR: 0.69 (0.56-0.85)	Med OS: NR vs 10.1 m 2 year OS: 51.9% vs 39.4% HR: 0.59 (0.39-0.88)	Med OS: NR vs NR NR HR: 0.64 (0.37-1.10)

Gandhi et al. NEJM 378;22. 2018.*Reck M et al, NEJM 2016; Mok T et al, Lancet 2019; Gadgeel S et al, Abstract #9013, ASCO 2019; Paz-Ares L et al, NEJM 2018*

IO & CT Combination

Monotherapy-Pro

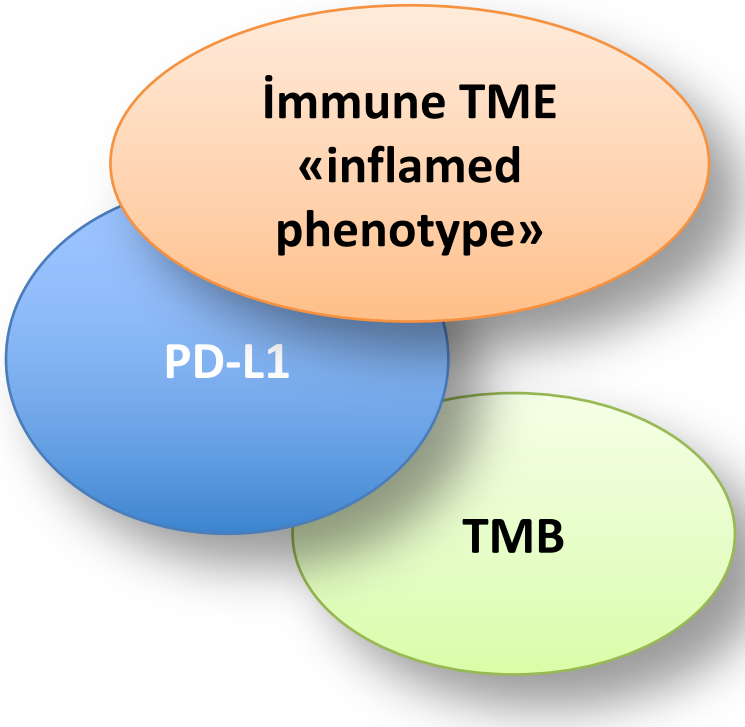
- Non-inferior in high PD-L1 expressing sub-groups
- Better toxicity profile
- Benefit seen for OS only (HR:0.81)
  - Similar ORR & PFS
- Which option after progression on combinations?
- Lower cost

Combination-Pro

- Preclinical rationale
  - Enhanced antigen presentation & immunogenic cell death
  - Cytotoxic agents disrupt immune evasion in the TME
  - Pemetrexed induces PD-L1 expression
- Strong clinical evidence favoring combinations
  - ORR, PFS & OS benefit
- Efficacy regardless of PD-L1 benefit
- Poor outcomes for early progressors by monotherapy (primary resistance)
  - 50% of pts will not receive 2L Tx
- Preferable in CNS mets requiring steroids or symptomatic pts with higher tm burden

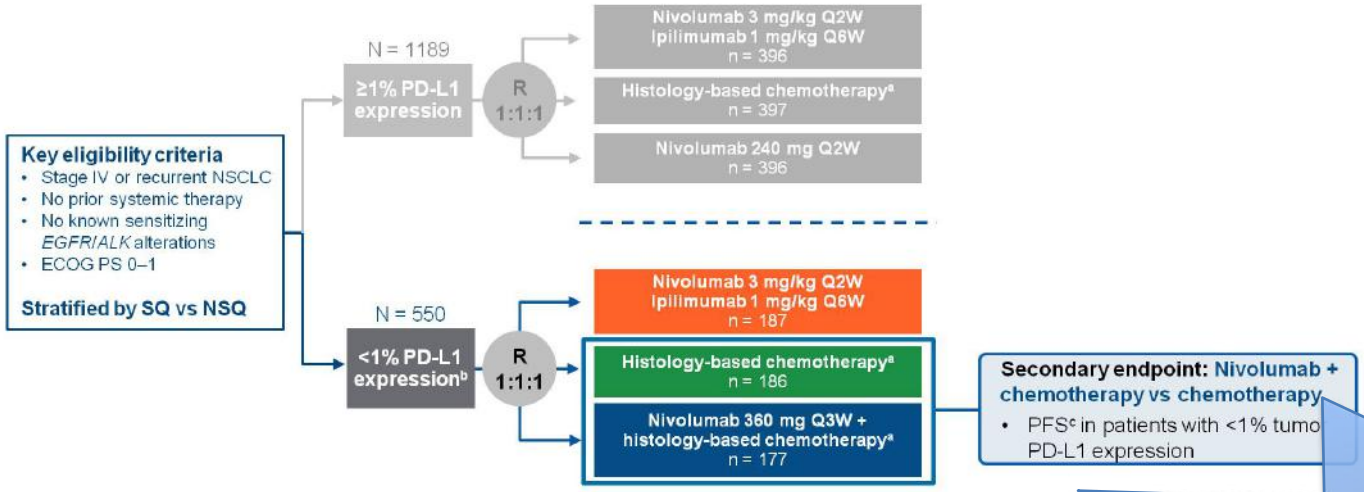
No randomized study of 1L IO vs. chemo/ IO in PD-L1 ≥50% !!

Refining patient selection…



- Emerging biomarkers..
  - **TIL's**
  - **Other immune cell populations**
  - **Microsatellite instability**
  - **RNA sequencing**
  - **Immune gene expression signatures (IFN-gamma etc)**
  - **Circulating biomarkers**

CM 0227 & OS wrt PD-L1 expression



Median OS (PD-L1 <1%)

- nivolumab/ipilimumab 17.2 mo,
- nivolumab/CT 15.2 mo,
- CT: 12.2 mo,
- HR nivolumab/ipilimumab vs chemotherapy, 0.62; 95% CI, 0.48-0.78; p<0.05

Exploratory benefit in TMB≥10

Median OS; 1 yr & 2 yr OS rates (PD-L1≥ 1%)

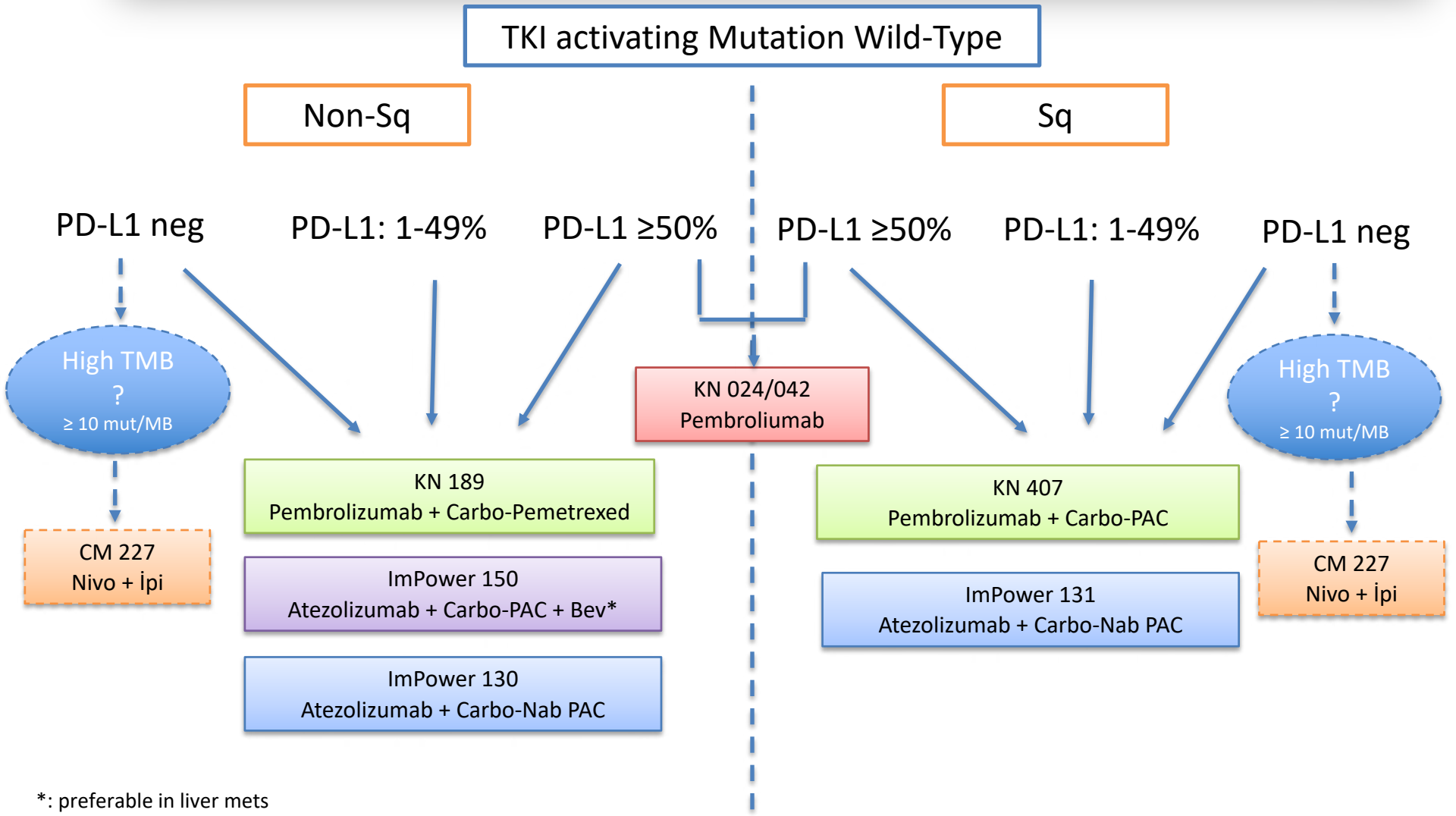
- Nivo + Ipi: 17.1 months, 63%; 40%
- Nivo: 15.7 months; 57%; 36%
- CT:14.9 months; 56%; 33%

HR:

- Nivolumab/ipilimumab vs chemo, 0.79; 97.72% CI, 0.65-0.96; p:0.007
- Nivolumab vs chemotherapy, 0.88; 97.72% CI, 0.75-1.04; NS

S. Peters, ESMO 2019

Front-line ImmunoTx Landscape in 2019



*: preferable in liver mets