Selection of 1st line Immunotherapy in PDL1 negative and non driver mutations- mNSCL ca

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Real world prevalence of PDL1 expression

Multicenter Study > Lung Cancer. 2019 Aug;134:174-179. doi: 10.1016/j.lungcan.2019.06.012.
Epub 2019 Jun 12.

Real-world prevalence of programmed death ligand 1 expression in locally advanced or metastatic non-small-cell lung cancer: The global, multicenter EXPRESS study

M Dietel [1], N Savelov [2], R Salanova [3], P Micke [4], G Bigras [5], T Hida [6], J Antunez [7], B Guldhammer Skov [8], G Hutarew [9], L F Sua [10], H Akita [11], O S H Chan [12], B Piperdi [13], T Burke [14], S Khambata-Ford [13], A C Deitz [14]

Affiliations + expand

PMID: 31319978 DOI: 10.1016/j.lungcan.2019.06.012

Prevalence of PDL1 negative

Approximately 50% patients are usually PDL1 >1%

Approximately 48% patients are usually PDL1 <1%

Prevalence of PDL1 expression was similar across all geographic area (Asia pacific, Europe, USA)

Role of TMB in PDL1 negative

Role of TMB in PDL1 negative

MSI-H (3%)

TMB-high(7.7%)

Discrepancy between MSI, TMB, PDL1 are there.

In 2020, the NCCN Panel removed TMB as an emerging immune biomarker for patients with metastatic NSCLC based on clinical trial data, concerns about variable TMB measurements (NCCN 2022)

Prognosis of PDL1 negative patients

- PDL1 negative, non driver mutation positive patients do behave aggressively compared to PDL1 positive and driver mutation positive counterparts and overall prognosis is poignant.

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What options available for PDL1 negative, driver mutation negative, mNSCL ca?

1stline IO in PDL1 negative, driver mutation negative mNSCL ca

Pembrolizumab +Chemo

Atezolizumab +Chemo

Nivolumab+Ipilimumab with or without Chemo

Pembro+ chemo

Pembrolizumab with chemotherapy

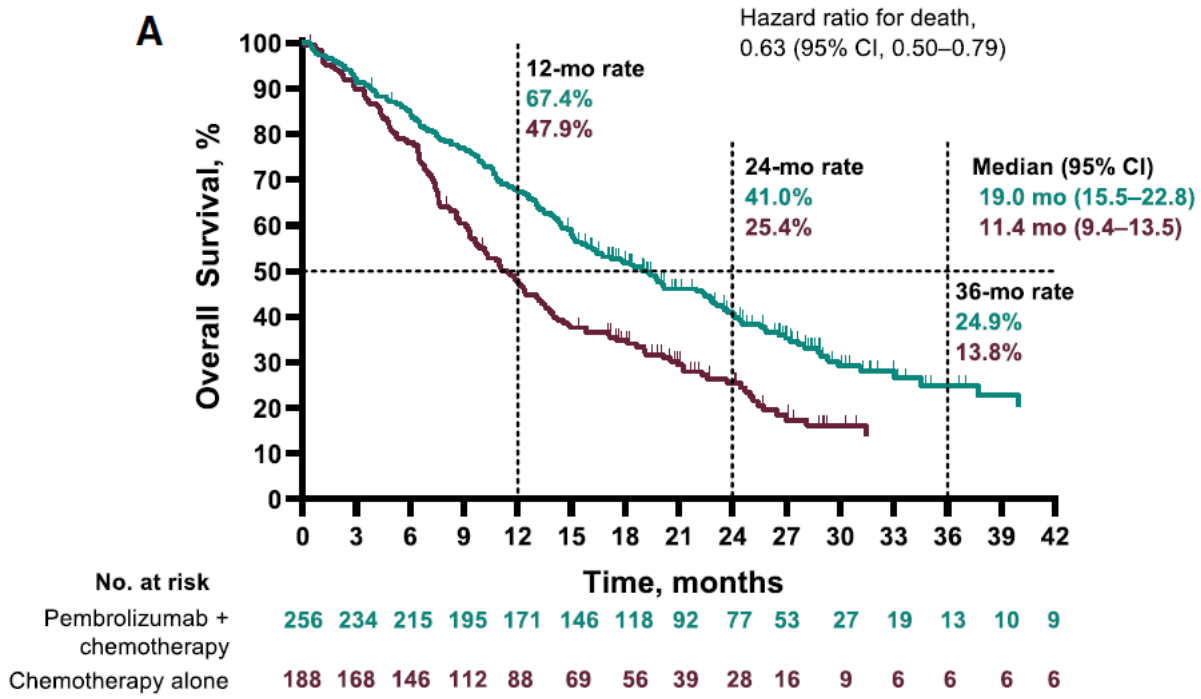
- KN 407:squamous histology, chemo (carbo+pacli or nab pacli)
  - PDL1 negative patients subset: median OS 15.9M vs 10.2 month (HR 0.61)(5 year data published in Sept 22)

- KN 189: non squamous histology
  - PDL1 negative patients subset: median OS 15.2M vs 12 month (HR 0.61)(P= 0.009, HR 0.59)(5 year data published in Sept 22)

- KN 021 cohort G: non squamous histology, phase2 data, chemo (Peme +carbo)

Pooled analysis of KN trials(407,189,021)

Pooled analysis from KN 407, KN 189, KN 021



Pooled analysis from KN 407, KN 189, KN 021

TABLE 2. Summary of Confirmed ORRs Assessed According to RECIST Version 1.1 by Blinded, Independent, Central Review in a Pooled Analysis of Patients With a PD-L1 TPS < 1%

	Pembrolizumab + Chemotherapy (n = 256)	Chemotherapy Alone (n = 188)
ORR[a]		
No. of patients	128	56
% (95% CI)	50.0 (43.7-56.3)	29.8 (23.4-36.9)
Best overall response, No. (%)		
Complete response	2 (0.8)	5 (2.7)
Partial response	126 (49.2)	51 (27.1)
Stable disease	90 (35.2)	79 (42.0)
Progressive disease	20 (7.8)	32 (17.0)
Not evaluable[b]	11 (4.3)	12 (6.4)
No assessment[c]	7 (2.7)	9 (4.8)
Time to response, median (range), mo	1.6 (1.2-26.3)	1.4 (1.2-26.9)
DOR, median (range), mo[d]	8.5 (1.1+ to 46.0)	6.9 (1.4+ to 30.1+)
Ongoing response, No. (%)[e]	20 (15.6)	9 (16.1)

Pooled analysis from KN 407, KN 189, KN 021

TABLE 3. All-Cause Adverse Events in Patients With a PD-L1 TPS < 1%

	Pembrolizumab + Chemotherapy (n = 255), No. (%)		Chemotherapy Alone (n = 186), No. (%)	
	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Any event	253 (99.2)	182 (71.4)	184 (98.9)	134 (72.0)
Event leading to discontinuation of study drug	93 (36.5)	64 (25.1)	31 (16.7)	24 (12.9)
Event leading to death	27 (10.6)	27 (10.6)	12 (6.5)	12 (6.5)
Event leading to treatment-related death	13 (5.1)	13 (5.1)	3 (1.6)	3 (1.6)
Event occurring in ≥20% of patients in either group				
Anemia	132 (51.8)	41 (16.1)	105 (56.5)	41 (22.0)
Nausea	131 (51.4)	5 (2.0)	88 (47.3)	5 (2.7)
Fatigue	98 (38.4)	15 (5.9)	56 (30.1)	6 (3.2)
Diarrhea	88 (34.5)	9 (3.5)	48 (25.8)	6 (3.2)
Constipation	82 (32.2)	1 (0.4)	59 (31.7)	3 (1.6)
Decreased appetite	86 (33.7)	2 (0.8)	57 (30.6)	0
Neutropenia	72 (28.2)	38 (14.9)	52 (28.0)	37 (19.9)
Cough	59 (23.1)	1 (0.4)	48 (25.8)	0
Thrombocytopenia	65 (25.5)	22 (8.6)	46 (24.7)	15 (8.1)
Vomiting	61 (23.9)	6 (2.4)	31 (16.7)	4 (2.2)
Alopecia	55 (21.6)	1 (0.4)	43 (23.1)	1 (0.5)
Asthenia	53 (20.8)	11 (4.3)	36 (19.4)	9 (4.8)
Rash	53 (20.8)	1 (0.4)	23 (12.4)	2 (1.1)
Dyspnea	40 (15.7)	3 (1.2)	38 (20.4)	1 (0.5)

Abbreviations: PD-L1, programmed death ligand 1; TPS, tumor proportion score.

Pooled analysis from KN 407, KN 189, KN 021

TABLE 4. Immune-Mediated Adverse Events and Infusion Reactions in Patients With a PD-L1 TPS < 1%

	Pembrolizumab + Chemotherapy (n = 255), No. (%)		Chemotherapy Alone (n = 186), No. (%)	
	Any Grade	Grade 3-5[a]	Any Grade	Grade 3-5[a]
Any event	74 (29.0)	31 (12.2)	23 (12.4)	6 (3.2)
Hypothyroidism	19 (7.5)	1 (0.4)	6 (3.2)	0
Pneumonitis	18 (7.1)	11 (4.3)	4 (2.2)	2 (1.1)
Hyperthyroidism	14 (5.5)	0	5 (2.7)	0
Infusion reactions	12 (4.7)	3 (1.2)	4 (2.2)	0
Colitis	5 (2.0)	3 (1.2)	1 (0.5)	1 (0.5)
Nephritis	5 (2.0)	4 (1.6)	1 (0.5)	1 (0.5)
Hepatitis	5 (2.0)	4 (1.6)	0	0
Severe skin reactions	4 (1.6)	2 (0.8)	3 (1.6)	3 (1.6)
Hypophysitis	3 (1.2)	1 (0.4)	0	0
Thyroiditis	2 (0.8)	0	0	0
Adrenal insufficiency	2 (0.8)	0	0	0
Encephalitis	1 (0.4)	1 (0.4)	0	0
Guillain-Barre syndrome	1 (0.4)	1 (0.4)	0	0
Pancreatitis	1 (0.4)	1 (0.4)	0	0
Myositis	1 (0.4)	0	0	0

Abbreviations: PD-L1, programmed death ligand 1; TPS, tumor proportion score.
Events are included regardless of attribution to the study drug or immune relatedness by the investigator.
[a]Two patients in the pembrolizumab plus chemotherapy group had events of pneumonitis that led to death. There were no immune-mediated adverse events or infusion reactions leading to death in the chemotherapy group.

Summary for Pembro as 1stline IO in PDL1 negative, driver mutation negative mNSCL ca

Pembro+ chemo can be used in metastatic squamous as well as adeno carcinoma patients in 1st line according to KN 407, KN 189, KN 021 cohort G and pooled analysis.

Atezo + chemo

Atezo+ chemo

- IMPOWER 130: non squamous histology, Chemo(carbo+ nab pacli)
  - Median OS for PDL1 negative patients: 15.2 M(Atezo+ chemo arm) vs 12 M(Chemo arm)(HR 0.81)

- IMPOWER 150:non squamous histology, liver mets, Atezo+chemo vs Bev +chemo vs ABCP
  - Median OS for PDL1 negative patients: 15.2 M (ABCP) vs 12 M (Chemo+ Bev)(HR 0.82)

Summary for Atezo as 1stline IO in PDL1 negative, driver mutation negative mNSCL ca

ABCP or Atezo+chemo can be used in 1st line mNSCL ca (ONLY ADENO ca)

This combination is preferable if liver metastasis present

Nivolumab+Ipilimumab with or without chemo

Nivolumab+Ipilimumab with or without chemo

- Checkmate 227:Nivo+ipili vs Nivo +Chemo vs Chemo, both squamous and adeno ca
  - PDL1 negative patients- Median OS for PDL1 negative patients: 19% vs 7% , median DOR 19.4M vs 4.8 M

- Checkmate 9LA: Nivo+ipili+2 cycles of chemo vs Chemo, both squamous and adeno ca
  - PDL1 negative patients- Median OS : 17.7 M vs 9.8 M, HR 0.67;Median PFS 6.4 M vs 5.3 M, HR 0.7

Summary for Nivo+ipili as 1stline IO in PDL1 negative, driver mutation negative mNSCL ca

Dual IO (Nivo+ipili) with(CM-9LA) or without chemo(CM-227) can be used in mNSC lung ca in both squamous and adeno ca histology

No extra safety concern with dual IO.

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NCCN 22

Systemic therapy for metastatic Adeno carcinoma NCCN 2022

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred

- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,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]

Systemic therapy for metastatic Squamous cell carcinoma NCCN 2022

SQUAMOUS CELL CARCINOMA (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred

- **Pembrolizumab/carboplatin/paclitaxel (category 1)[34,e]**
- **Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[34,e]**

Other recommended

- **Nivolumab/ipilimumab[5,e]**
- **Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e]**

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Determining Factors

Determining factors for Chemo+ IO

Histology (Squamous vs adeno)

Apprehension regarding side effects (Alopecia/pre existing neuropathy)

Disease burdon (low/high)

Age and Performance status

Pre existing pneumonitis

Any contra indications of Immunotherapy/Active auto immune disease

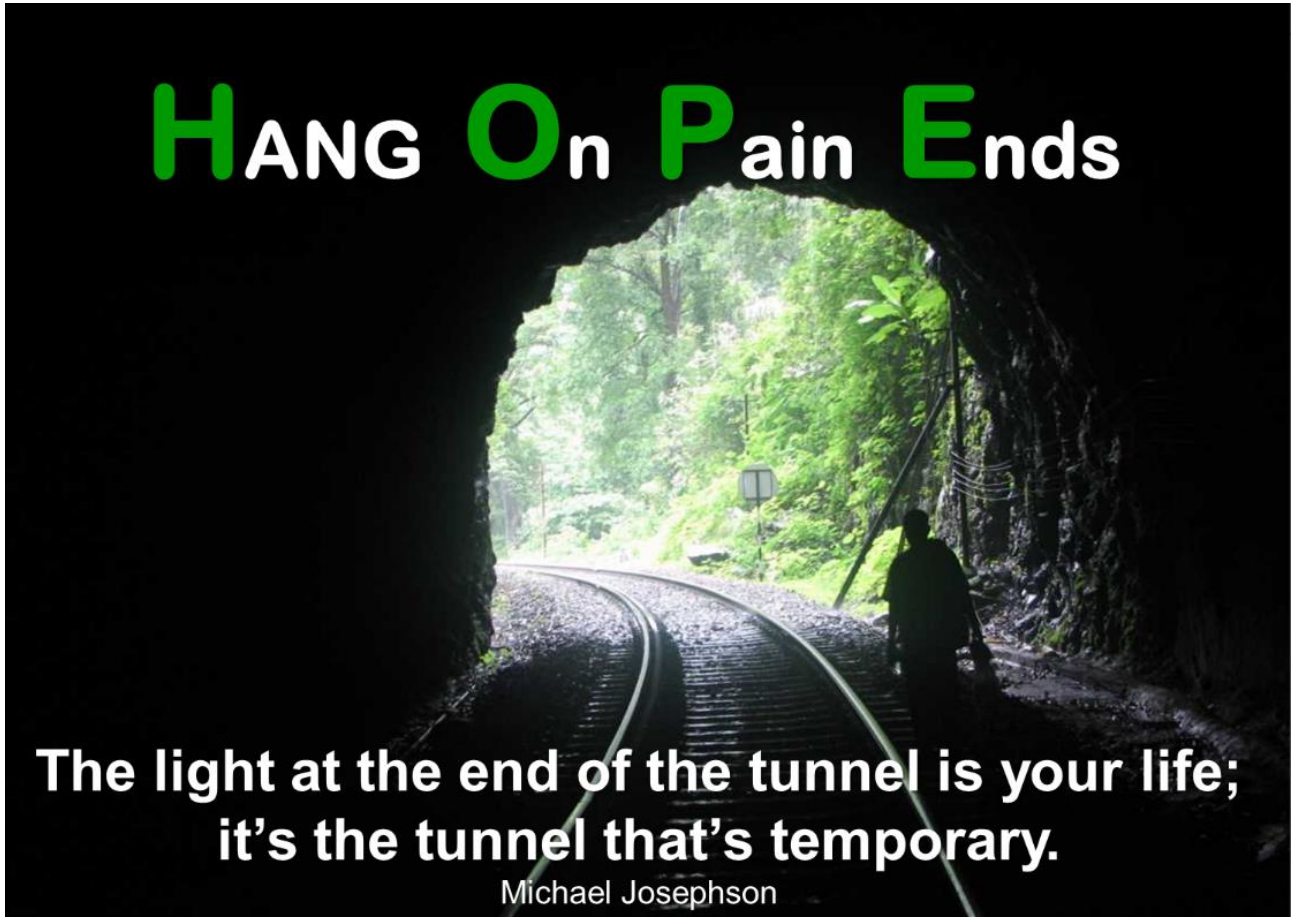
My take on…

PDL1 negative, driver mutation negative, mNSC Lung ca

Squamous histology: Pembro(KN-407), Dual IO with or without chemo(CM-227, CM-9LA)

Adeno histology: Pembro(KN 021, KN 189), Atezo (IMPOWER 130, 150), Dual IO with or without chemo (CM-227, CM-9LA)

Thank you


HANG On Pain Ends
The light at the end of the tunnel is your life;
it's the tunnel that's temporary.
Michael Josephson