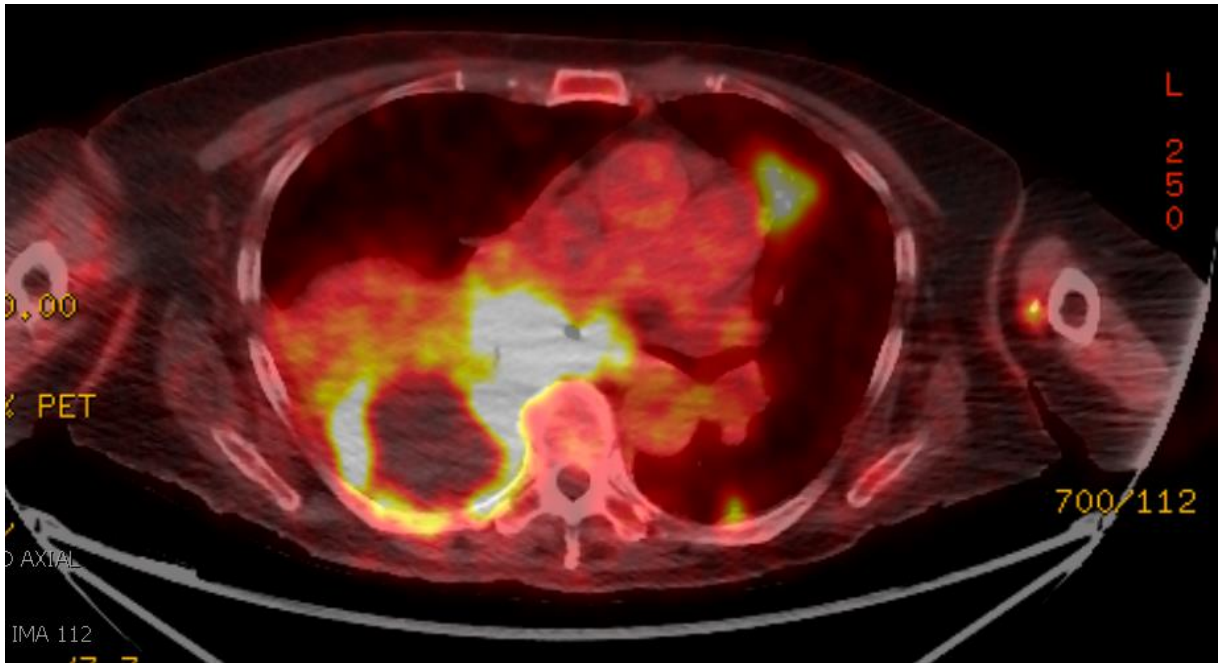
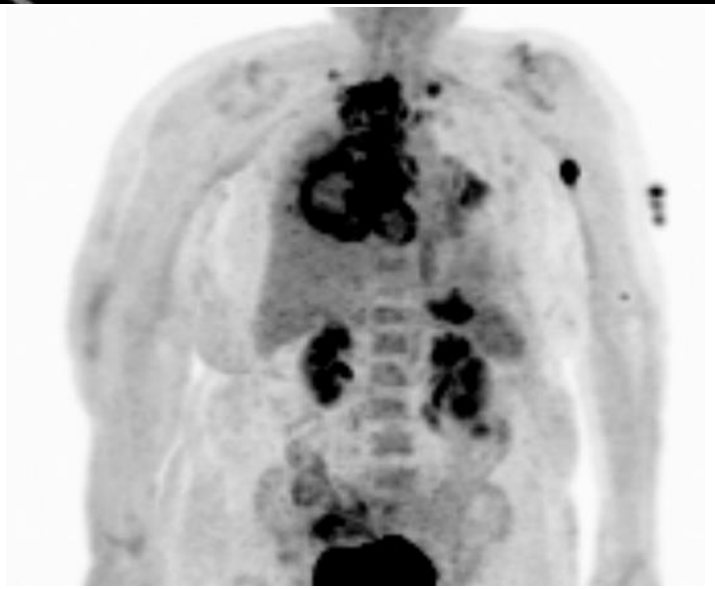
First-Line Immunotherapy, Advanced Stage

Case*

- 66-year-old woman presents with dyspnea
- Former smoker (20 pk/years)
- PS=0
- PET/CT: FDG avid bilateral lung lesions with RLL primary, 8.3 cm, SUV=13
- Mediastinal and hilar adenopathy + pleural implants
- Brain MRI: negative for metastatic disease
- Biopsy of RLL mass positive for squamous cell carcinoma
- PD-L1 (22C3) is <1%





*Cases may have been modified for educational purposes

Question

Stage IVA NSCLC-squamous cell carcinoma and PD-L1 TPS = <1%, former tobacco use of 20 pack years

Question 1: Would you do molecular testing?

1. **Yes**
2. **No**

Question

Molecular testing shows a p53 mutation and TMB 32 mt/Mb (high). PD-L1 was <1%.

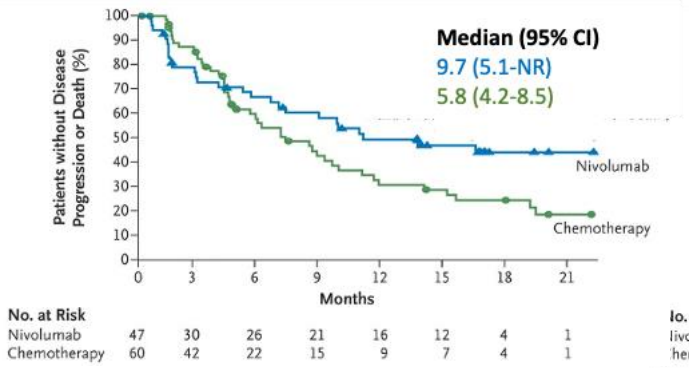
Question 2: Does the TMB-high affect your treatment recommendations for this patient with Stage IVA NSCLC-squamous cell carcinoma with PS 0 and PD-L1 <1%?

1. **Yes**
2. **No**

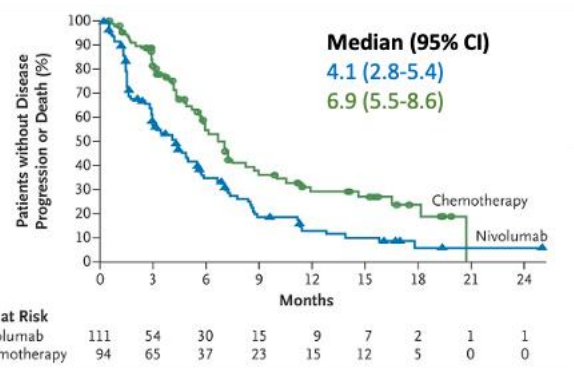
TMB Association with PFS in NSCLC

CM026: Nivolumab in First-line NSCLC

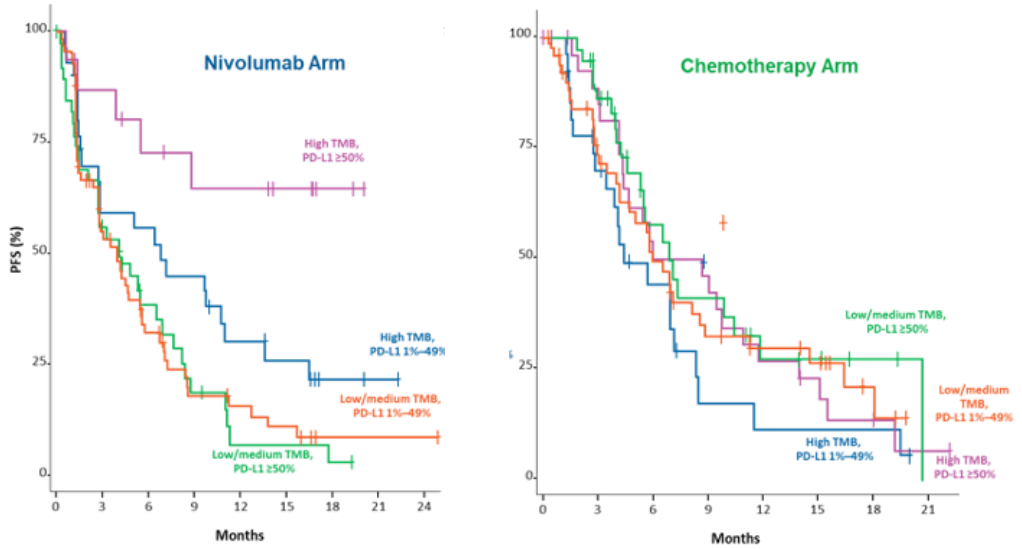
PFS in High TMB



PFS in Low-Medium TMB



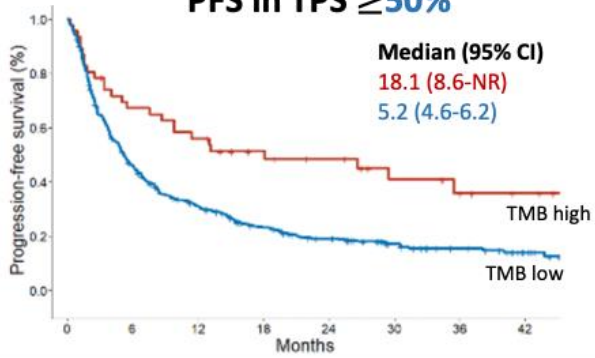
PFS by TMB and PD-L1



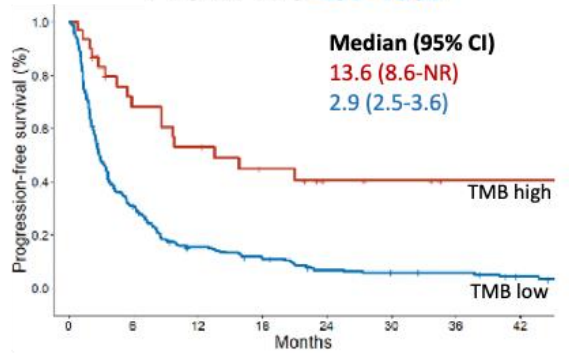
Carbone et al. NEJM 2017

N=1552 patients with advanced NSCLC treated with PD(L)1 inhibition alone

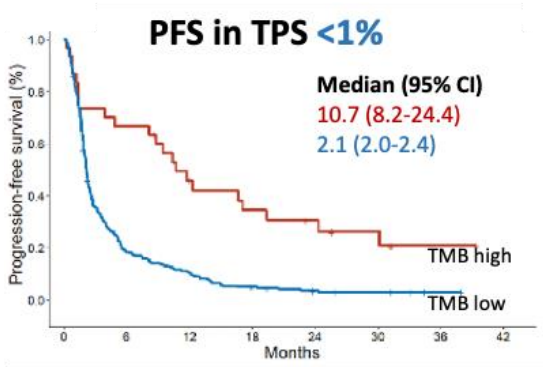
PFS in TPS ≥50%



PFS in TPS 1%-49%



PFS in TPS <1%

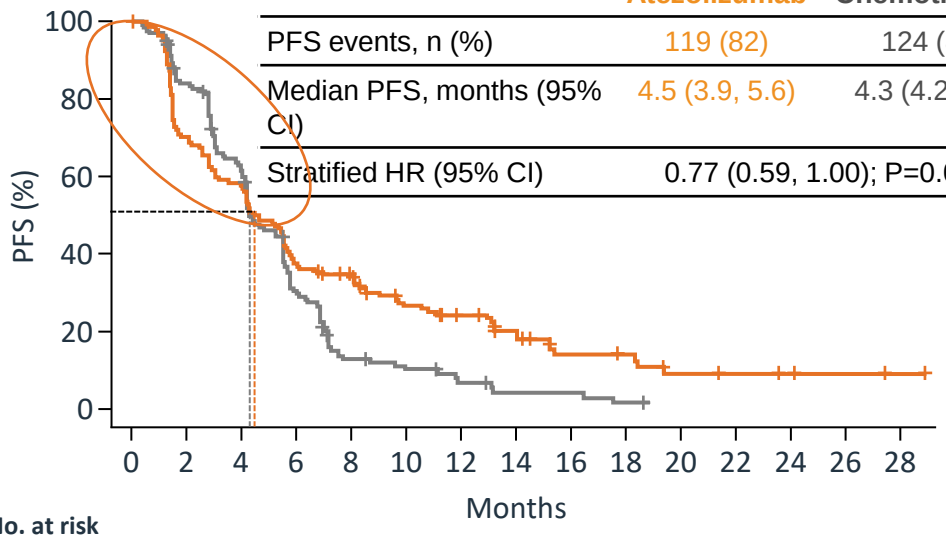


Ricciuti et al. JAMA Oncology 2022

Phase III BFAST Trial: Atezolizumab vs Platinum Chemotherapy in bTMB high (≥16)

PFS in the total ITT (all histologies) group

	Atezolizumab	Chemotherapy
PFS events, n (%)	119 (82)	124 (85)
Median PFS, months (95% CI)	4.5 (3.9, 5.6)	4.3 (4.2, 5.5)
Stratified HR (95% CI)	0.77 (0.59, 1.00); P=0.053	

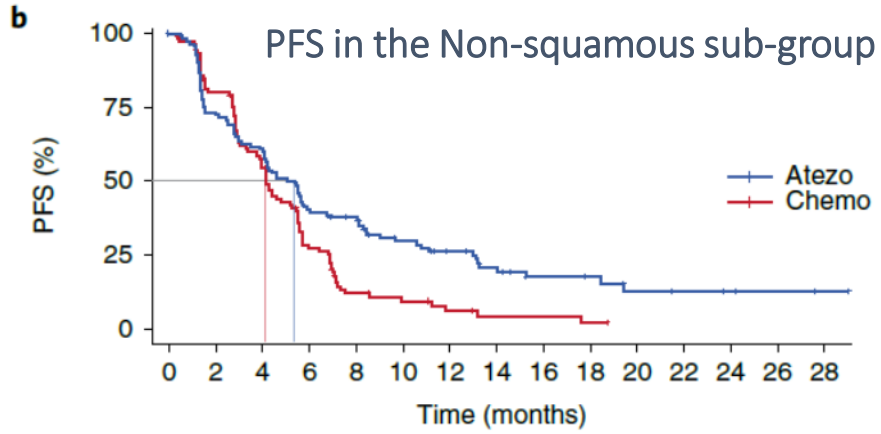


No. at risk

Atezo	145	101	83	54	46	32	25	18	10	9	5	4	3	2	1
Chemo	146	113	81	38	15	11	6	3	3	1	0	0	0	0	0

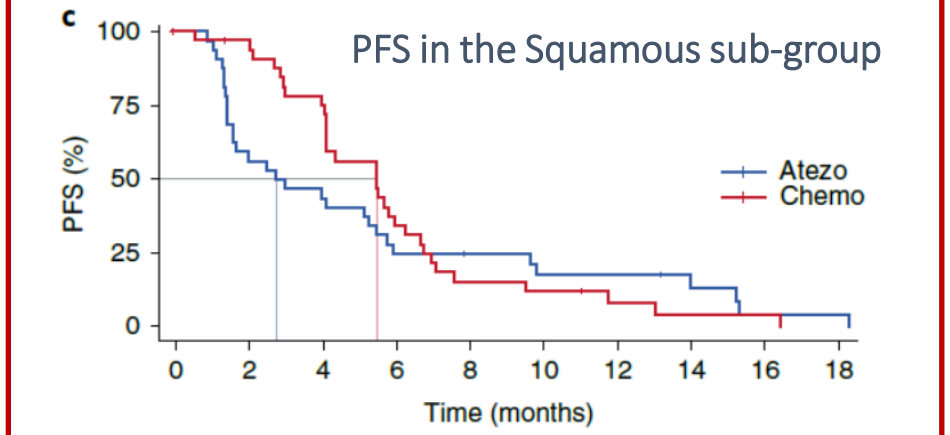
Initial PFS "KM Gap" as seen in prior IO monotherapy trials.
Although progression rates were initially greater in the atezolizumab vs chemotherapy arm, PFS benefit was seen with atezolizumab after 4 months.

Confirmed ORR for bTMB ≥16 was 25.5% (95% CI: 18.7, 33.4) for atezolizumab vs 17.8% (95% CI: 12.0, 25.0) for chemotherapy
OS: median 13.3 mos for ≥ bTMB 16 (6.6-18.4) and 10.3 mos (8.5-13.8) for bTMB low.



No. at risk

Atezo	113	82	68	45	39	27	20	14	9	8	5	4	3	2	1
Chemo	111	82	56	26	10	7	4	2	2	1					



No. at risk

Atezo	32	19	15	9	7	5	5	4	1	1
Chemo	35	31	25	12	5	4	2	1	1	

Peters et al. Nat Med 2022

Question

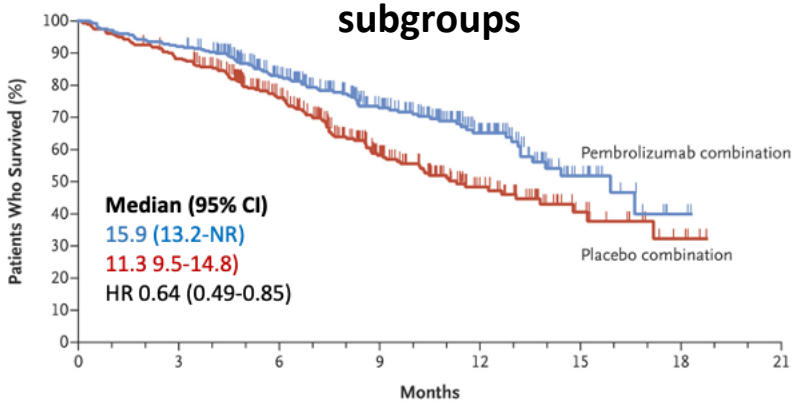
Stage IVA NSCLC-squamous cell carcinoma, PS 0, PD-L1 TPS <1%, TMB 32 mt/Mb (high) and p53 mutation

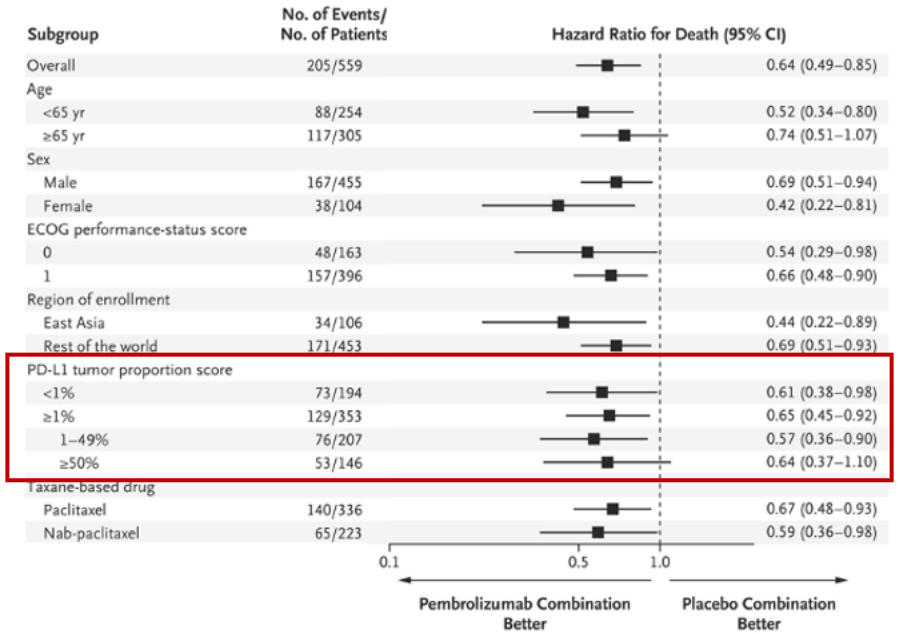
Question 3: Which do you recommend for first-line systemic therapy?

1. **Carboplatin/pemetrexed/pembrolizumab (KN 189)**
2. **Carboplatin/paclitaxel/pembrolizumab (KN 407)**
3. **Carboplatin/paclitaxel/bevacizumab/atezolizumab (IM 150)**
4. **Nivolumab + ipilimumab (CM 227)**
5. **Platinum chemotherapy X 2 cycles + nivolumab/ipilimumab (CM 9LA)**

First-line treatment in advanced squamous cell with PD-L1<1%:
Overall Survival

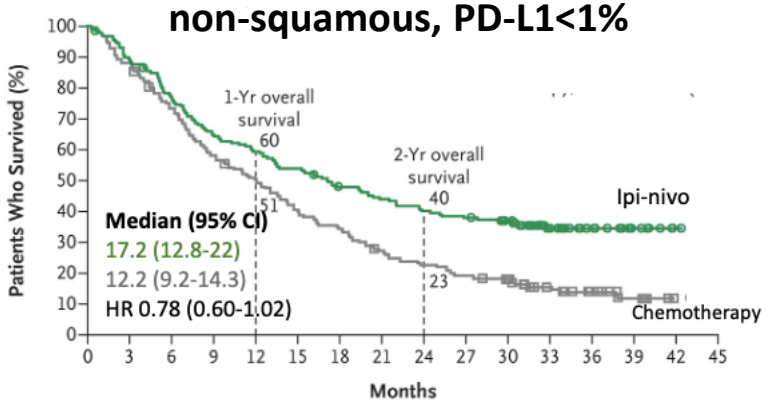
KN407: Pembro-Chemo in Squamous, all TPS subgroups

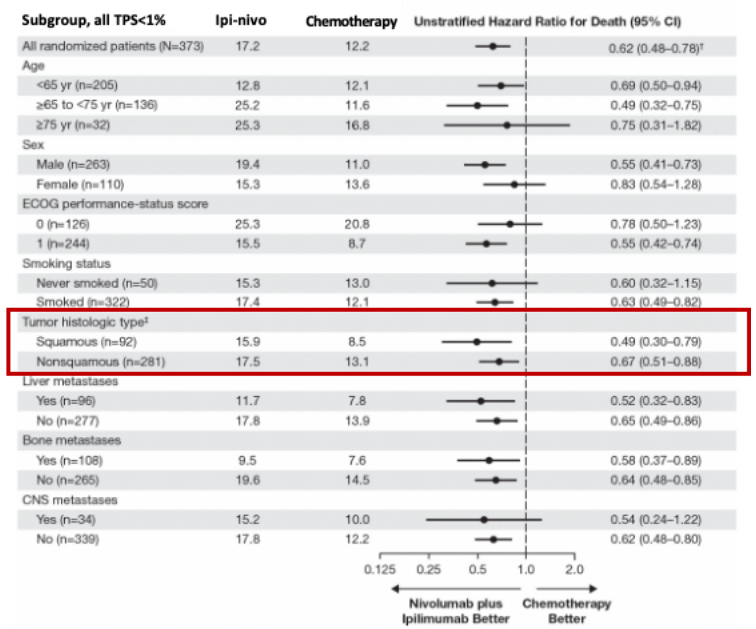




Paz-Ares et al. NEJM 2018

CM227: Ipi-nivo in squamous and non-squamous, PD-L1<1%

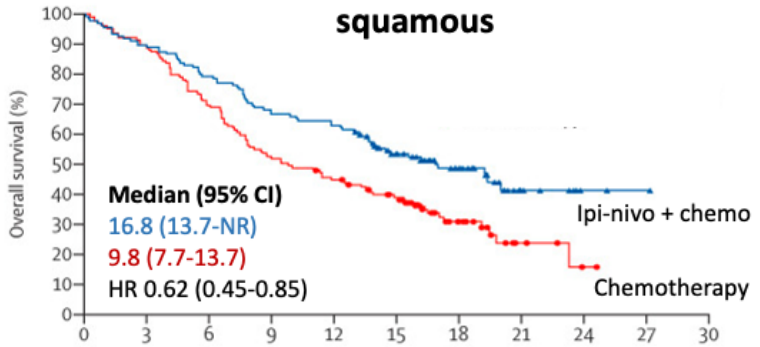




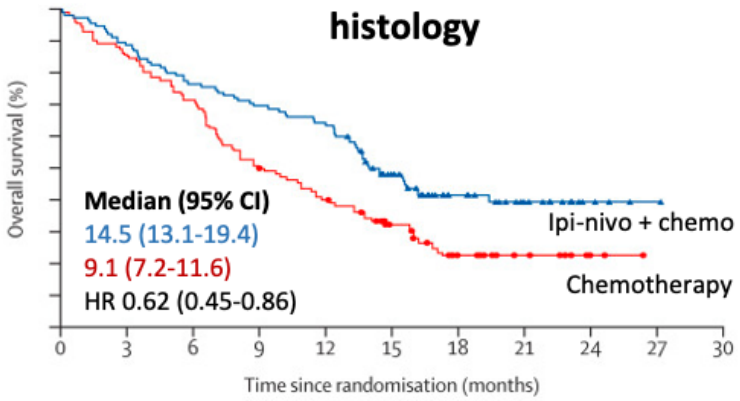
Hellmann et al. NEJM 2019

CM9LA: Ipi-nivo + chemo

PD-L1 <1%, both squamous and non-squamous



All PD-L1 subgroups, squamous histology



Paz-Ares et al. Lancet Oncology 2021

Question

The patient desires to avoid chemotherapy and starts ipilimumab-nivolumab (CM 227). About 8 months into treatment, the patient develops abdominal pain and new diarrhea (>4 bowel movements per day). Treatment is held, IV fluids are given, stool cultures and clostridium difficile screen are negative. She is given prednisone 1mg/kg/day and referred to gastroenterology.

5 days later, she reports increased stool output to roughly 7 watery bowel movements per day. She has been taking the prednisone daily without missed doses. Her gastroenterology appointment has not yet been scheduled.

Question 4: What would you do next?

1. **Give IV hydration in infusion center, increase prednisone to 3mg/kg/day**
2. **Admit to the hospital, consult gastroenterology, and give 500mg IV methylprednisolone**
3. **Admit to the hospital, consult gastroenterology, and give infliximab**
4. **Admit to the hospital, consult gastroenterology, and await colonoscopy in 3 days before escalating treatment**

Question

The patient is admitted to the hospital and given a single dose of infliximab. She rapidly improves and is discharged from the hospital 5 days later with a prednisone taper.

She is seen in clinic about 5 weeks after discharge and has completed her prednisone taper. Her diarrhea has resolved, and she has returned to her baseline functional status. At this point, she has has completed 8 months of treatment. Repeat scans show that most sites of disease that have slightly reduced in size.

Question 5: What do you recommend at this point?

1. **Observation and close monitoring with repeat scans**
2. **Ipilimumab and nivolumab**
3. **Nivolumab alone**
4. **Carboplatin/paclitaxel**
5. **Carboplatin/paclitaxel/pembrolizumab**

Decision to resume immune checkpoint inhibitor after an immune event

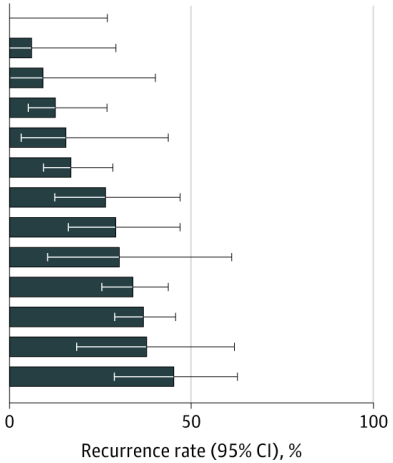
ASCO 2018 Guidelines: When to permanently discontinue ICI

Grade	Endocrine	MSK	Skin	Ocular	Nervous System	Heme	Renal	GI	Lung	CV
1	Continue	Continue	Continue	Continue	NA	Continue	Consider hold	Consider hold	Hold	Consider hold
2	Consider hold	Hold	Consider hold	Hold	Hold	Consider permanently discontinue	Hold	Hold	Hold	Permanently discontinue
3	Hold	Hold	Hold	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue CTLA-4; hold PD-1/PDL-1	Permanently discontinue	Permanently discontinue
4	Hold	Hold	Hold	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue	Permanently discontinue

Adapted from ***Brahmer et al. ASCO Guidelines 2018***

Rate of recurrence according to initial event

Adverse drug reaction	No. of cases	Recurrence rate (95% CI), %
Diabetes	13	0 (0-27)
Neurologic	17	6 (0-29)
Uveitis	11	9 (0-40)
Adrenal	40	12 (5-27)
Pancreatitis	13	15 (3-43)
Thyroiditis	60	17 (9-28)
Hypophysitis	23	26 (12-47)
Hepatitis	31	29 (16-47)
Hematologic	10	30 (10-61)
Pneumonitis	101	34 (25-43)
Colitis	123	37 (29-45)
Skin	16	38 (18-61)
Arthritis	29	45 (28-62)



Dolladille et al. JAMA Oncology 2020

Factors associated with recurrence of the same immune-related adverse event

Initial irAE	No. (%) Recurrence after ICI rechallenge (n = 130)	No. (%) No recurrence after ICI rechallenge (n = 322)	Reporting OR (95% CI) Multivariate analysis
ICI			
Anti-PD-1 or anti-PD-L1 alone	105 (80.8)	265 (82.3)	NA
Anti-CTLA-4 alone	7 (5.4)	15 (4.7)	3.5 (1.05-11.64)
Combination therapy	18 (13.8)	42 (13.0)	NA

Initial irAE	No. (%) Recurrence after ICI rechallenge (n = 130)	No. (%) No recurrence after ICI rechallenge (n = 322)	Reporting OR (95% CI) Multivariate analysis
Type of initial irAE[a]			
Colitis	47 (36.2)	78 (24.2)	2.99 (1.60-5.59)
Hepatitis	11 (8.5)	22 (6.8)	3.38 (1.31-8.74)
Nephritis	4 (3.1)	4 (1.2)	4.92 (0.94-25.64)
Pneumonitis	36 (27.7)	67 (20.8)	2.26 (1.18-4.32)