Case Study #1

45-year-old man was found to have a 6-cm descending colon mass, diagnosed as invasive moderately differentiated adenocarcinoma with nodal metastasis (pT3, pN1b) following a left colectomy. The neoplasm showed typical adenocarcinoma morphology with gland formation with retained nuclear expression of mismatch repair proteins MLH1, PMS2, MSH2, and MSH6 and negative for mutations in *KRAS, BRAF,* and *NRAS*. The patient received adjuvant Capecitabine with Oxiplatin (CAPEOX) for 4 cycles.

After chemotherapy, surveillance imaging identified an enlarging segment 8 liver lesion measuring 3.6 cm which increased rapidly to 7.6 cm one month later. Core needle biopsy of the liver lesion showed a poorly differentiated malignancy characterized by epithelioid neoplastic cells being arranged in solid sheets and islands with complete lack of glandular formation and no particular growth pattern, with focal squamoid cytologic features. MLH1, PMS2, and MSH2 loss was present by IHC, with no other specific IHC findings on extensive workup. What diagnostic approach should be considered for therapy planning?

A) Comprehensive NGS of both neoplasms
B) Comprehensive NGS of the liver lesion + 22c3 IHC
C) Comprehensive NGS of the colon cancer + 22c3 IHC
D) Referral to surgery for partial hepatectomy and genetic counseling with paired tumor-normal NGS analysis

Case Study #2

Metastatic Melanoma : Choice of Immunotherapy

A 75-year-old man presents with pulmonary nodules diagnosed incidentally on a chest X-ray done for another reason. He had a h/o primary melanoma on the L-arm skin diagnosed 5 years back, which was treated with a WLE and SLNB of L-axilla; initial TNM Stage was IIB (T3b, pN0, M0).

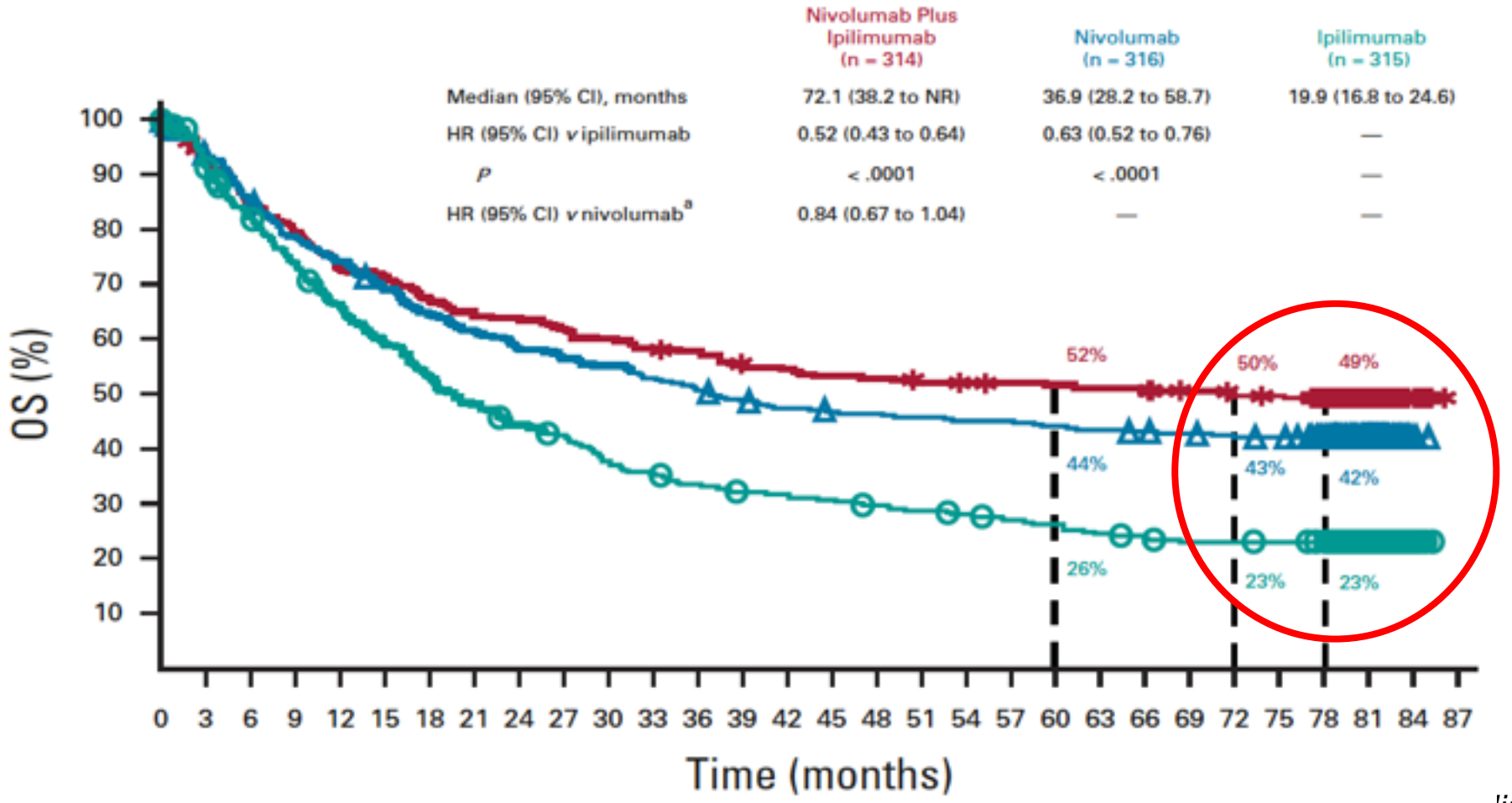
Patient denies having any symptoms; ECOG score is 0.

Staging CT-CAP shows **multiple pulmonary nodules** (largest 2 cm) and a **liver mass** (2 cm) with appearance suggestive of metastases. Brain MRI is WNL. LDH is WNL. Biopsy of a peripheral pulmonary nodule has confirmed **metastatic melanoma**.

BRAF V600E mutation was not detected. **PD-L1 score on the biopsy sample was 5%.**

Patient states his treatment goals to have the best chance of long-term survivorship while balancing QoL.

Checkmate-067 LTFU (6.5 yrs)



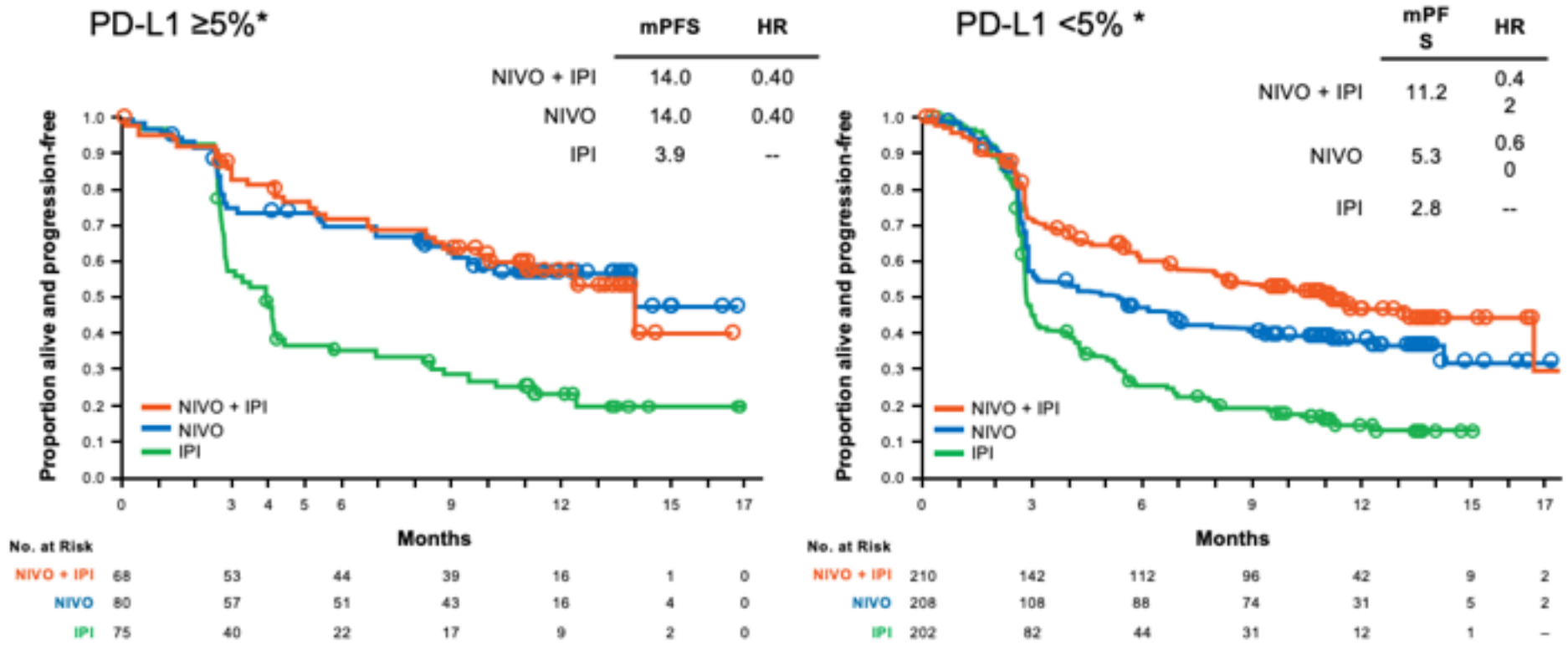
{Wolchok JD et al. *J Clin Oncol* 2022}

Systemic immunotherapy: Outcomes in melanoma

	Response rate (%)	Grade 3 or higher IRAE (%)
Ipilimumab	19	27
Nivolumab	44	16
Ipi plus Nivo	58	**55**

[*Larkin J et al* NEJM *2015*]

Ipi plus Nivo: PFS by PD-L1 Expression Level



*Per validated PD-L1 immunohistochemical assay with expression defined as ≥5% of tumor cells showing PD-L1 staining in a section of at least 100 evaluable tumor cells.

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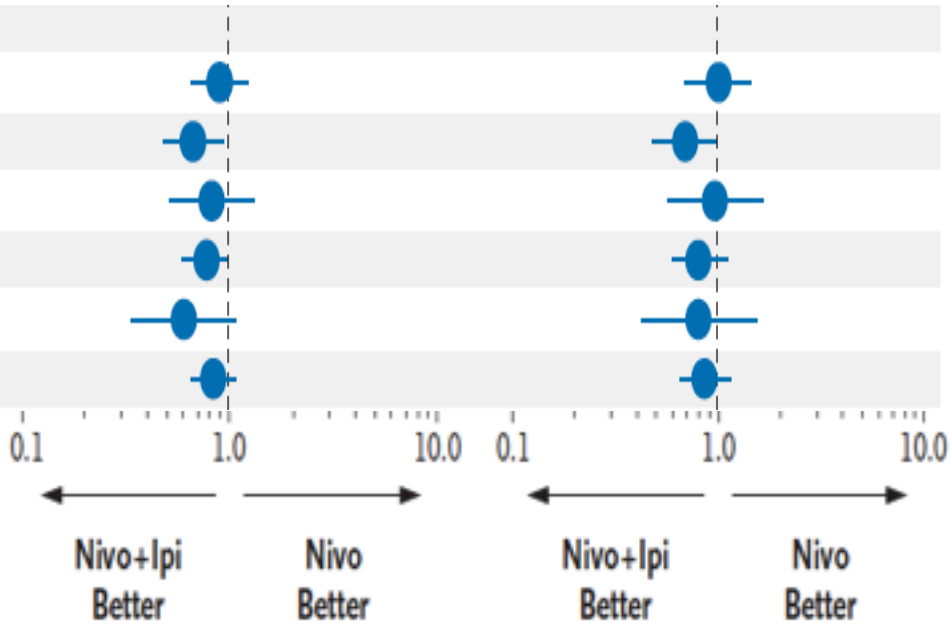
What will you recommend next?

- Anti-PD-1 monotherapy (Pembrolizumab or Nivolumab)
- Combination Immunotherapy with Ipilimumab plus Nivolumab

Checkmate-067: Outcomes by PD-L1

Subgroup	No. of Patients		3-Yr Progression-free Survival Rate		3-Yr Overall Survival Rate		Unadjusted Hazard Ratio	
	Nivo+ Ipi	Nivo	Nivo+ Ipi	Nivo	Nivo+ Ipi	Nivo	Progression-free Survival	Overall Survival
PD-L1 expression level								
≥1%	155	171	43	39	62	60	0.90	1.02
<1%	123	117	35	26	54	42	0.67	0.70
≥5%	68	80	49	41	65	61	0.83	0.99
<5%	210	208	36	31	56	50	0.78	0.82
≥10%	46	59	58	39	67	58	0.61	0.82
<10%	232	229	35	32	57	51	0.84	0.87



[*Wolchok J et al* NEJM *2017*]

Checkmate-067 Subgroup Analyses

Subgroup	No. of Patients		3-Yr Progression-free Survival Rate		3-Yr Overall Survival Rate		Unadjusted Hazard Ratio	
	Nivo+ Ipi	Nivo	Nivo+ Ipi	Nivo	Nivo+ Ipi	Nivo	Progression-free Survival	Overall Survival
			%		%			
All patients	314	316	39	32	58	52	0.79	0.85
Age								
<65 yr	185	198	39	31	61	51	0.73	0.78
≥65 yr	129	118	37	34	54	52	0.90	0.96
Geographic region								
United States	64	68	45	31	70	57	0.71	0.59
Europe	177	170	34	28	53	49	0.77	0.91
BRAF mutation								
Yes	102	98	40	22	68	56	0.59	0.69
No	212	218	38	36	53	50	0.89	0.94
ECOG performance-status score								
0	230	237	39	33	64	58	0.80	0.85
1	83	79	37	27	43	32	0.75	0.81
Metastasis stage								
M0, M1a, or M1b	129	132	50	39	72	64	0.67	0.79
M1c	185	184	31	27	48	42	0.87	0.88
LDH level								
≤ULN	199	197	45	37	66	61	0.75	0.86
>ULN	114	112	28	21	44	34	0.79	0.83
>2×ULN	37	37	17	11	31	14	0.69	0.73
PD-L1 expression level								
<1%	123	117	35	26	54	42	0.67	0.70
≥5%	68	80	49	41	65	61	0.83	0.99
<5%	210	208	36	31	56	50	0.78	0.82
<10%	232	229	35	32	57	51	0.84	0.87
Tumor burden								
≤31 mm	78	85	45	38	72	69	0.72	0.96
>31 mm and ≤97 mm	154	150	38	30	59	48	0.76	0.74
>97 mm	82	80	33	29	41	39	0.89	0.92
No. of lesion sites								
1	89	80	47	37	70	65	0.65	0.88
2 or 3	166	176	38	28	57	48	0.74	0.80
>3	59	59	27	36	42	44	1.25	1.06

[*Wolchok J et al* NEJM *2017*]

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Case Study #3

The patients is a 62 year old man with stage IVB metastatic colon cancer. His tumor is KRAS mutated, BRAFT WT, NRAS WT with a TMB of 14. The patient has received FOLFOX Bevacizumab as first line therapy and after 4 months of therapy moved on to maintenance therapy. After 4 months of maintenance therapy progression was detected on CT scan and FOLFOX Bevacizumab was resumed. However, after 6 months progression was again detected. During this time NGS was performed and determined the tumor was Microsatellite Stable (MSS, MSI Low) but the TMB was 14. POL-D was NOT mutated.

What is the next best treatment?

A. Pembrolizumab

B. Nivolumab + Ipilimumab

C. FOLFIRI +/- VEGF Inhibition

D. Trifluridine/Tipiracil