

**A Definitive First-Line
& Subsequent Therapy
Clinical Decision Tree**

Systemic Therapy for Stage IV NSCLC Without Driver Alterations

Navigating the ASCO Living Guideline
(2026.3.1 Update)

The 2026.3.1 Addition

Retifanlimab

PD-1 inhibitor

Action: Added as a **Conditional** first-line option.

Population: Nonsquamous NSCLC, Any PD-L1 Expression.

Regimen: Retifanlimab + platinum-based chemotherapy (4 cycles).

Reviewed, Not Added

Trial: HARMONi-6

Drug: Ivonescimab

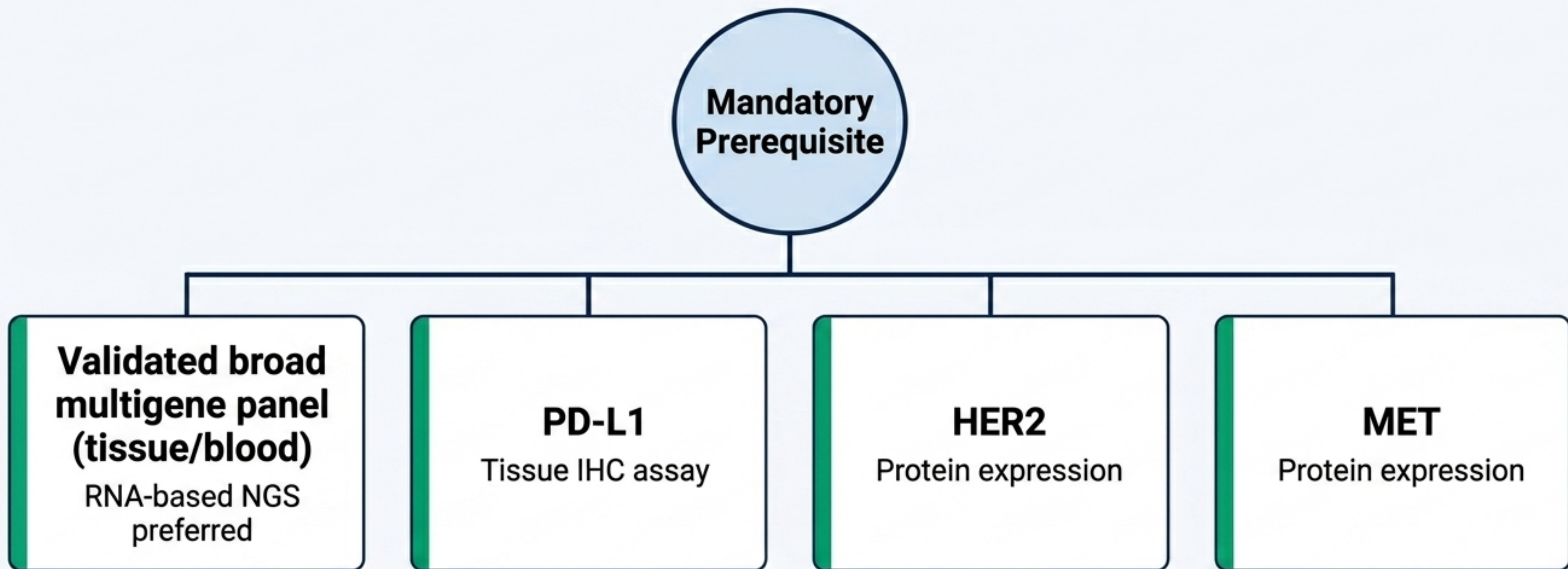
Status: Requires multiregional validation due to short median follow-up (10.3 months).

Trial: BAP BRAIN

Drug: Bevacizumab + chemo

Status: Limited relevance; trial lacked first-line immunotherapy comparator.

The Diagnostic Foundation: Universal Testing (Recommendation 1.0)



CLINICAL WARNING: PD-L1 IHC alone should not be used to guide treatment decisions. Tissue testing has the advantage of histologic assessment; always consider the false-negative rate of liquid biopsies.

First-Line Biomarker Matrix

Note: Displays Strong Recommendations only. Conditional alternatives follow in detailed pathway maps.

		X-Axis		
		PD-L1 $\geq 50\%$	PD-L1 1%-49%	PD-L1 $< 1\%$
Y-Axis	Nonsquamous	Pembro, Cemi, or Atezo (monotherapies)	Pembro or Cemi + carbo + pemetrexed	[None - Conditional Only]
	Squamous	Pembro, Cemi, or Atezo (monotherapies)	Pembro or Cemi + carbo + paclitaxel	[None - Conditional Only]

The Efficacy Data: POD1UM-304 Trial Snapshot

583 untreated stage IV patients without driver alterations. Retifanlimab + Chemo vs. Placebo + Chemo.

Overall Survival (OS)

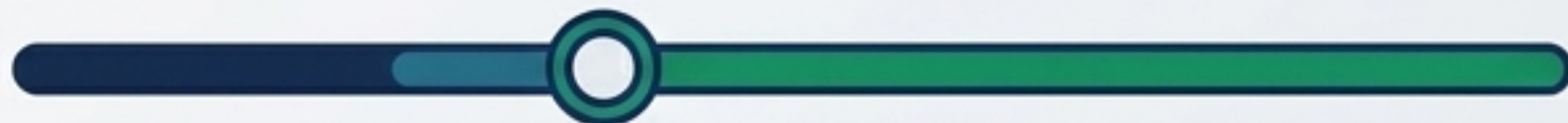
18.1 mos vs 13.4 mos



HR: 0.75

Progression-Free Survival (PFS)

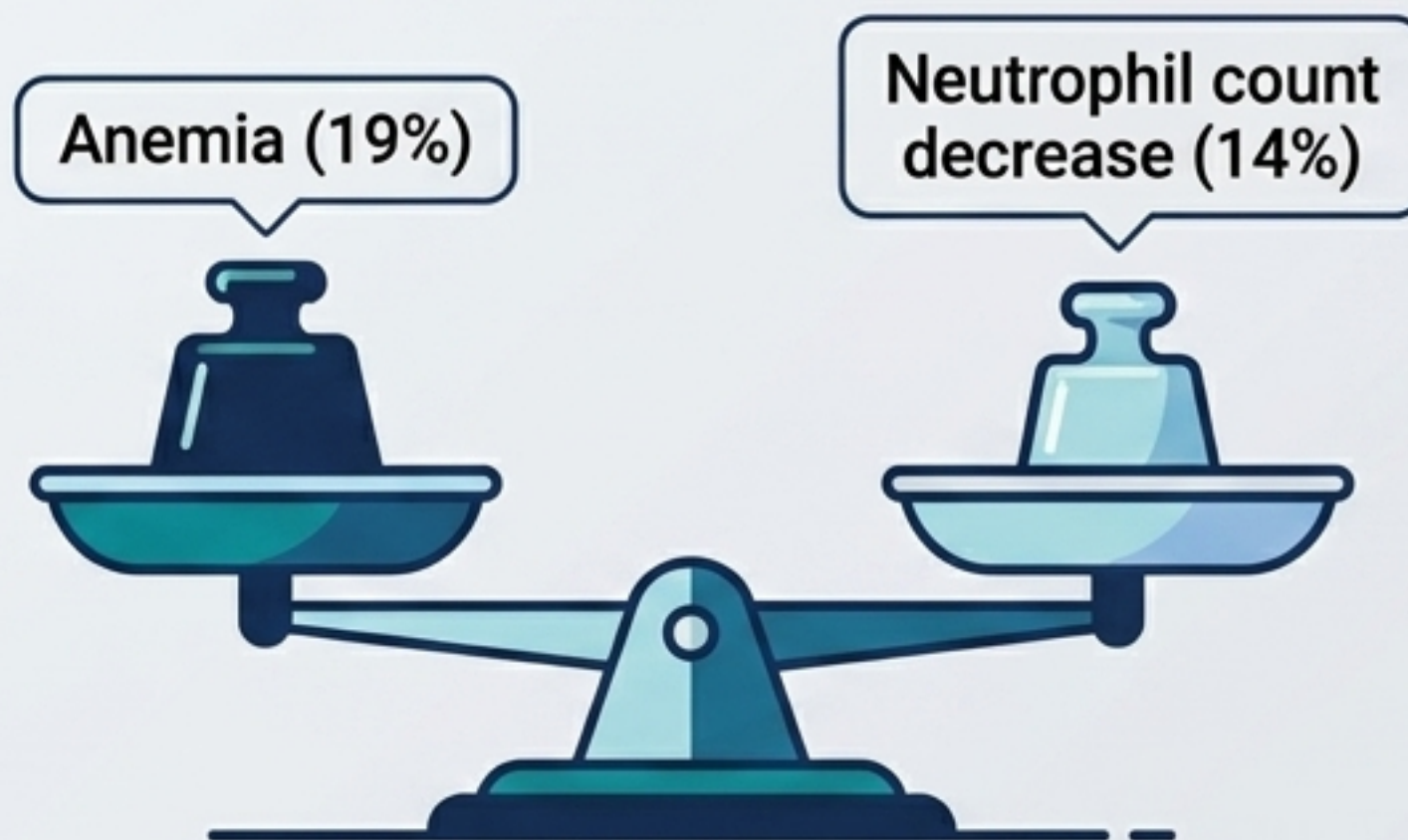
7.7 mos vs 5.5 mos



HR: 0.64

ORR: 52% vs 39%

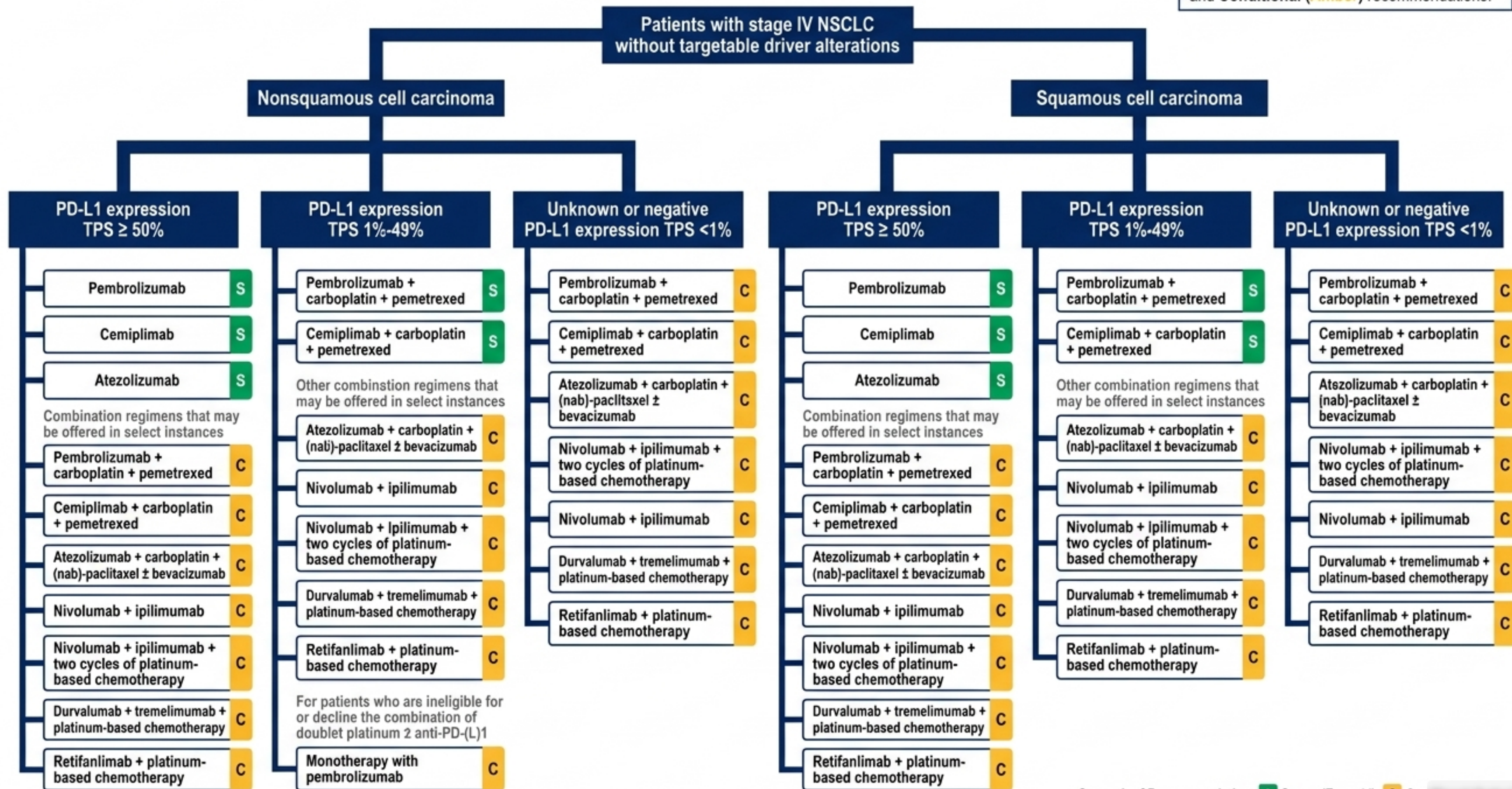
Weighing Grade ≥ 3 AEs



Verdict: No new safety concerns. Retifanlimab provides a new treatment option, confirming a class effect.

Algorithmic Flow: Stage IV Without Targetable Driver Alterations

Select a pathway track below to view specific regimen options mapped by **Strong (Emerald)** and **Conditional (Amber)** recommendations.



Nonsquamous Cell Carcinoma | PD-L1 $\geq 50\%$

Primary Options (Strong)

Single-Agent Checkpoint Inhibitors

- Pembrolizumab
- Cemiplimab
- Atezolizumab

} OR

Alternative Regimens (Conditional)

Combination Regimens (Select Instances)

- Pembro or Cemi + carbo + pemetrexed
- Atezo + carbo + (nab)-paclitaxel \pm bevacizumab
- Nivo + Ipi (with or without 2 cycles platinum chemo)
- Durva + Treme + platinum chemo
- **NEW:** Retifanlimab + platinum chemo

Nonsquamous Cell Carcinoma | PD-L1 1%–49%

Primary Options (Strong)

Combination Checkpoint + Chemotherapy

- Pembrolizumab + carbo + pemetrexed

OR

- Cemiplimab + carbo + pemetrexed

Alternative Regimens (Conditional)

Alternative Combinations & Monotherapy

- Atezo + carbo + \pm carbo + pemetrexed
- Atezo + carbo + (nab)-paclitaxel \pm bevacizumab
- Nivo + Ipi (with or without 2 cycles platinum chemo)
- Durva + Treme + platinum chemo

Exception Node

Pembrolizumab monotherapy (Only for patients ineligible for or declining combination therapy).

Nonsquamous Cell Carcinoma | PD-L1 <1% (Negative/Unknown)

Primary Options (Strong)

No Strong Recommendations
for this cohort.

Alternative Regimens (Conditional)

Available Combination Regimens

- Pembro + carbo + pemetrexed
- Cemi + carbo + pemetrexed
- Atezo + carbo + (nab)-paclitaxel ± bevacizumab
- Nivo + Ipi (with or without 2 cycles platinum chemo)
- Durva + Treme + platinum chemo
- NEW: Retifanlimab + platinum chemo

Squamous Cell Carcinoma | PD-L1 $\geq 50\%$

Primary Options (Strong)

Single-Agent Checkpoint Inhibitors

- Pembrolizumab

OR

- Cemiplimab

OR

- Atezolizumab

Alternative Regimens (Conditional)

Combination Regimens

- Pembro or Cemi + carbo + paclitaxel (or *nab*-paclitaxel)
- Nivo + Ipi (with or without 2 cycles platinum chemo)
- Durva + Treme + platinum chemo

Squamous Cell Carcinoma | PD-L1 1%–49%

Primary Options (Strong)

Combination Regimens

- Pembro or Cemi + carbo + paclitaxel (or nab-paclitaxel)

Alternative Regimens (Conditional)

Alternative Combinations & Monotherapy

- Nivo + Ipi (with or without 2 cycles platinum chemo)
- Durva + Treme + platinum chemo

Exception Node

Pembrolizumab monotherapy (Only for patients ineligible for or declining combination therapy).

Squamous Cell Carcinoma | PD-L1 <1% (Negative/Unknown)

Primary Options (Strong)

No Strong Recommendations
for this cohort.

Alternative Regimens (Conditional)

Available Combination Regimens

- Pembro or Cemi + carbo + paclitaxel (or *nab*-paclitaxel)
- Nivo + Ipi (with or without 2 cycles platinum chemo)
- Durva + Treme + platinum chemo

General Approaches & Critical Contraindications

Interdisciplinary Palliative Care (Strong Action)

Refer early alongside active treatment for both inpatient and outpatient care.

Non-ICI Candidates (Strong Action)

Offer platinum-doublet combination therapy (assuming preserved performance status).

Bevacizumab Strict Contraindications (**WARNING**)

MUST AVOID IF: Squamous cell histology, significant hemoptysis, inadequate organ function, ECOG PS > 1, uncontrolled hypertension, or significant cardiovascular disease.

Clinical Note: Maintenance bevacizumab + pemetrexed offers no survival advantage and increases toxicity.

Subsequent Therapies (Preserved Performance Status)

IF: Previously treated with Immune Checkpoint Therapy **WITHOUT** Chemotherapy.

THEN:
Offer platinum-doublet chemotherapy.

IF: Previously treated with Chemotherapy **AND** Immune Checkpoint Therapy.

THEN (Primary):
Docetaxel ± ramucirumab.

THEN (Alternative):
Pemetrexed, nab-paclitaxel, or gemcitabine.

Specialty Nodes (Conditional)

MET Overexpressing (IHC 3+ in ≥50%):
Telisotuzumab vedotin (Teliso-V)

HER2 Overexpressing (IHC 3+):
Trastuzumab deruxtecan

On the Horizon: Promising Signals Pending Validation

Trial & Intervention	Primary Efficacy Signal	ASCO Panel Verdict
HARMONi-6 Trial Ivonescimab (PD-1/VEGF bispecific) vs. Tislelizumab.	Impressive PFS HR of 0.60 (11.1 vs 6.9 mos).	Verdict: Requires Broader Validation. Follow-up is only 10.3 mos; control arm had higher brain mets/never-smokers. Awaiting global HARMONi-3 results.
BAP BRAIN Trial Bevacizumab + Chemo for brain metastases.	Improved iPFS (HR 0.494) and increased intracranial ORR (69.9% vs 32.4%).	Verdict: Limited Relevance. Conducted before 1L immunotherapy became standard. May be considered only for patients ineligible for immunotherapy.

Synthesis: The Evolving Checkpoint Landscape

The addition of Retifanlimab marks a pivotal shift in the stage IV NSCLC landscape.

With pembrolizumab, cemiplimab, atezolizumab, and now retifanlimab populating the guidelines, the ASCO panel signals a new era:

New additions are no longer required to prove superior efficacy. They are confirming a fundamental Class Effect.

The saturation of PD-1/PD-L1 inhibitors is expanding treatment access. Clinical decisions in the first line are now increasingly guided by drug availability, cost-effectiveness, and local formulary access without compromising patient survival.

