OVERCOMING IMMUNOTHERAPY RESISTANCE IN NSCLC

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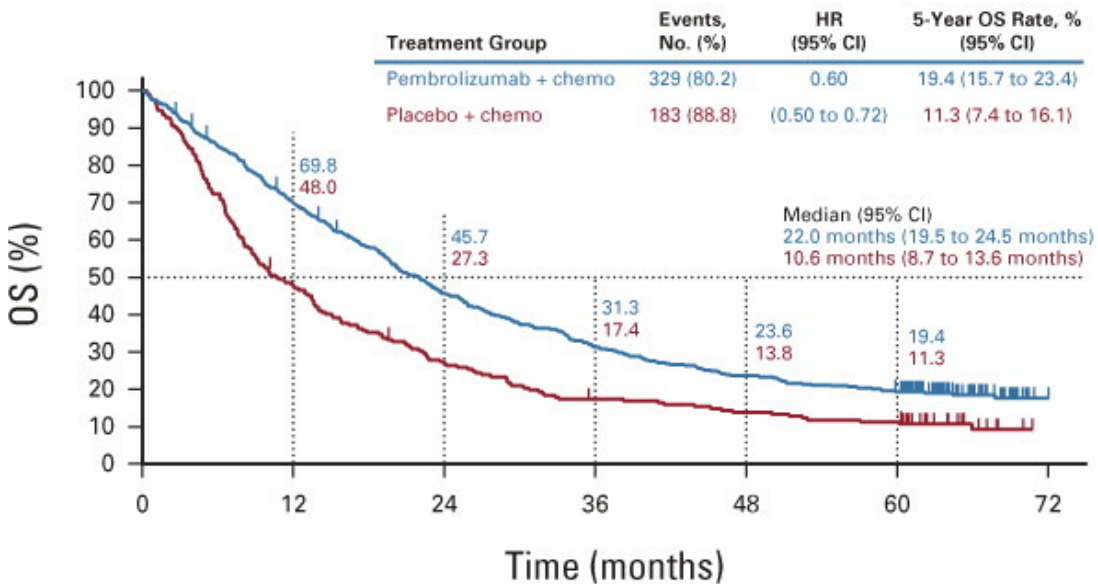
Goals for today's talk

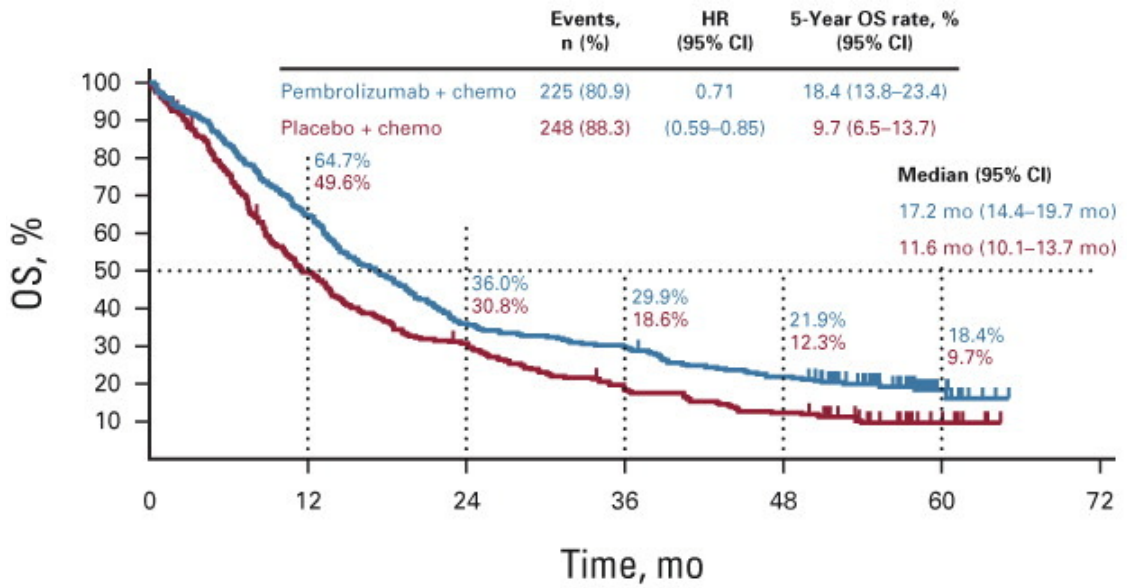
- Briefly review definitions and key mechanisms of immunotherapy resistance

- Highlight promising approaches under study for overcoming immunotherapy resistance in advanced NSCLC, including strategies targeting the VEGF axis and TAM receptors

Despite survival and clinical benefits of immunotherapy in NSCLC, resistance unfortunately develops in most patients



KEYNOTE-189: ITT population



KEYNOTE-407: ITT population

Garassino et al., J Clin Oncol 2023; Novello et al., J Clin Oncol 2023

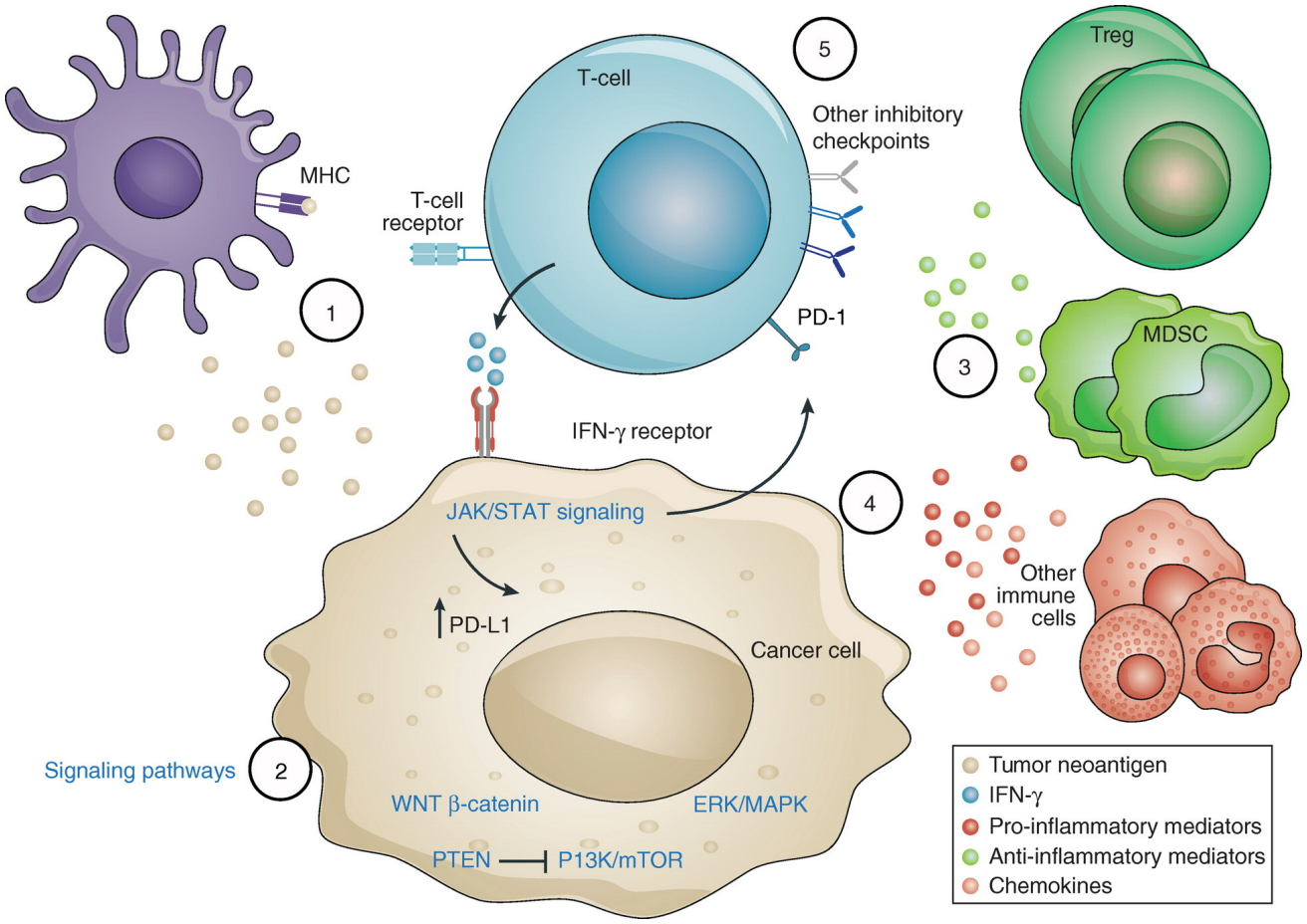
Definitions of immunotherapy resistance are not standardized and may vary among clinical trials

SITC definitions of IO resistance in advanced disease setting

Resistance phenotype	Drug exposure requirement	Best response
Primary resistance	≥6 weeks	PD; SD for <6 months
Secondary (acquired) resistance	≥6 months	CR, PR, SD for >6 months

Kluger HM et al., J Immunother Cancer 2020

Mechanisms of IO resistance are complex and multifactorial



1 – Changes in tumor neoantigen presentation

2 – Alterations in oncogenic signalling pathways

3 and 4 – Changes towards immunosuppressive TME via decrease in pro-inflammatory mediators and/or increase in anti-inflammatory mediators

5 – Dependence on alternate immune checkpoints

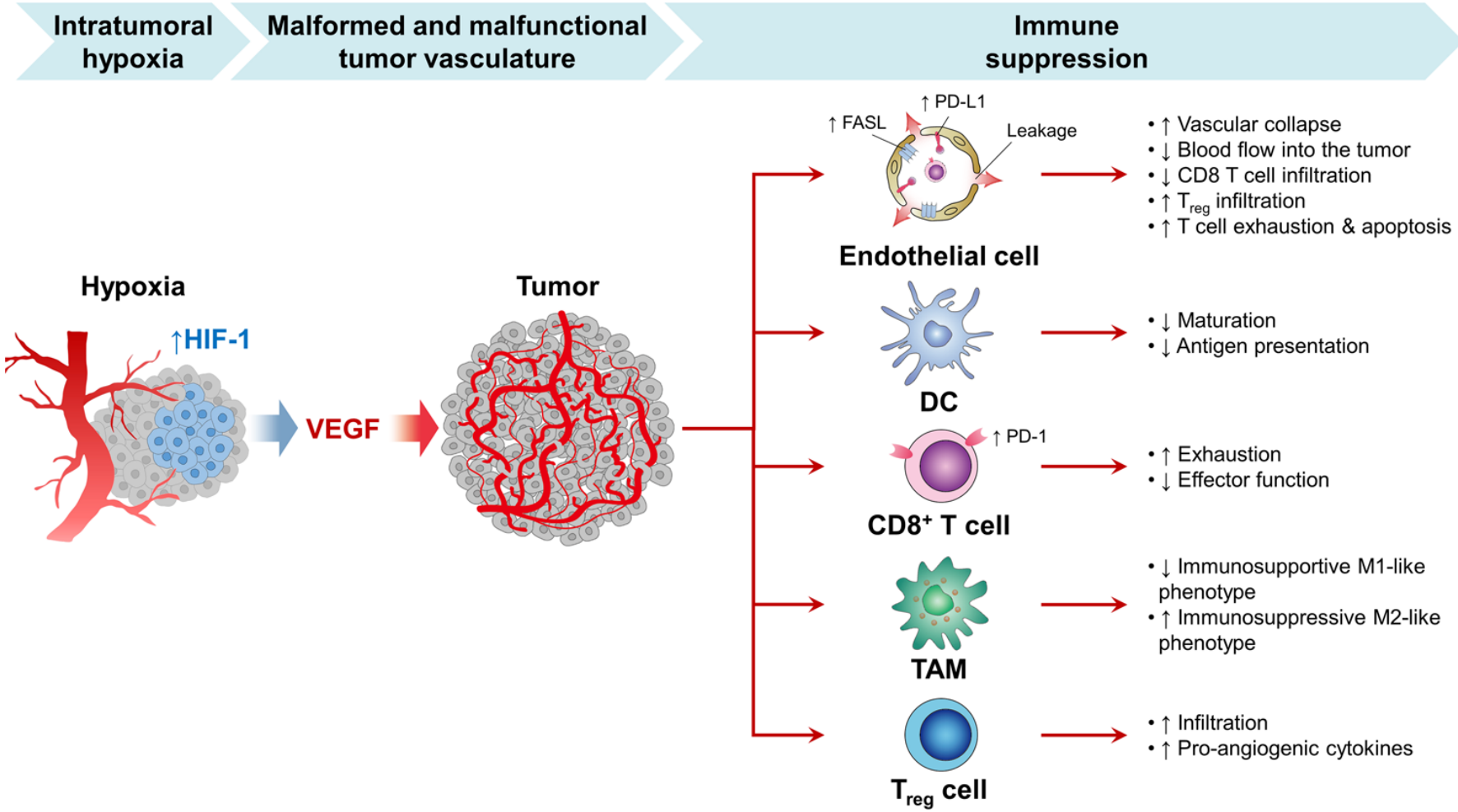
Hu-Lieskovan et al., Future Oncol 2021

Numerous strategies are under study to overcome IO resistance

Strategy	Selected targets or mechanisms under study
Immune inhibitory agents	CTLA-4, TIGIT, LAG-3, TIM-3
Immune stimulatory signals	OX-40, CD40, ICOS
T cell priming	TIL therapy, CAR-T therapy, personalized vaccines
Cytokines	IL-2, IL-15
VGEF axis	Multiple VEGF monoclonal Abs & small molecules
Oncogene pathways	STAT3, RAF, MEK, AXL, PI3K, c-MET
Other TME targets	Adenosine, arginase, HDAC, RORγ, CDK4/6
Microbiome-based therapy	E. gallinarum, Lactococcus lactis

Passaro et al., J Clin Oncol 2022

VEGF may contribute to immunosuppressive TME and resistance to immune checkpoint inhibitors



Lee et al., Exp Mol Med 2020

Preclinical data has led to study of many immunotherapy + VEGF agent combinations

VEGF agent	Treatment strategy	NCT identifier
Ramucirumab	Atezolizumab + ramucirumab	NCT03689855 (phase II)
	Pembrolizumab + ramucirumab *(v SOC)*	NCT03971474 (phase II) NCT05633602 (phase III)
	Pembrolizumab + ramucirumab + docetaxel	NCT04340882 (phase II)
Lenvatinib	Pembrolizumab + lenvatinib *(v docetaxel)*	NCT03976375 (phase III)
Nintedanib	Nivolumab +/- ipilimumab + nintedanib	NCT03377023 (phase I/II) NCT04046614 (phase I/II)
Sitravatinib	Nivolumab + sitravatinib *(v docetaxel)*	NCT03906071 (phase III)
Axitinib	Avelumab + axitinib	NCT03472560 (phase II)
Ivonescimab (AK112)	Anti-PD-1/VEGF bi-specific antibody	NCT04736823 (phase II)

Passaro et al., J Clin Oncol 2022

Pembrolizumab + ramucirumab may have role in immunotherapy resistance setting for NSCLC

S1800A Schema—Randomized Phase II trial

NCT03971474

Stratified by 1) PD-L1 expression, 2) histology, 3) intent to receive ramucirumab in standard of care arm

Primary endpoint: OS

Secondary endpoints: RR, DCR, DoR, PFS, Toxicities

ARM A
Investigator's Choice Standard of Care
docetaxel + ramucirumab; docetaxel; gemcitabine; pemetrexed (nonSCC only)

Randomization

R (1:1)
N= 130

ARM B
Pembrolizumab
200 mg Q3W for up to 35 cycles
+
Ramucirumab
10 mg/kg Q3W

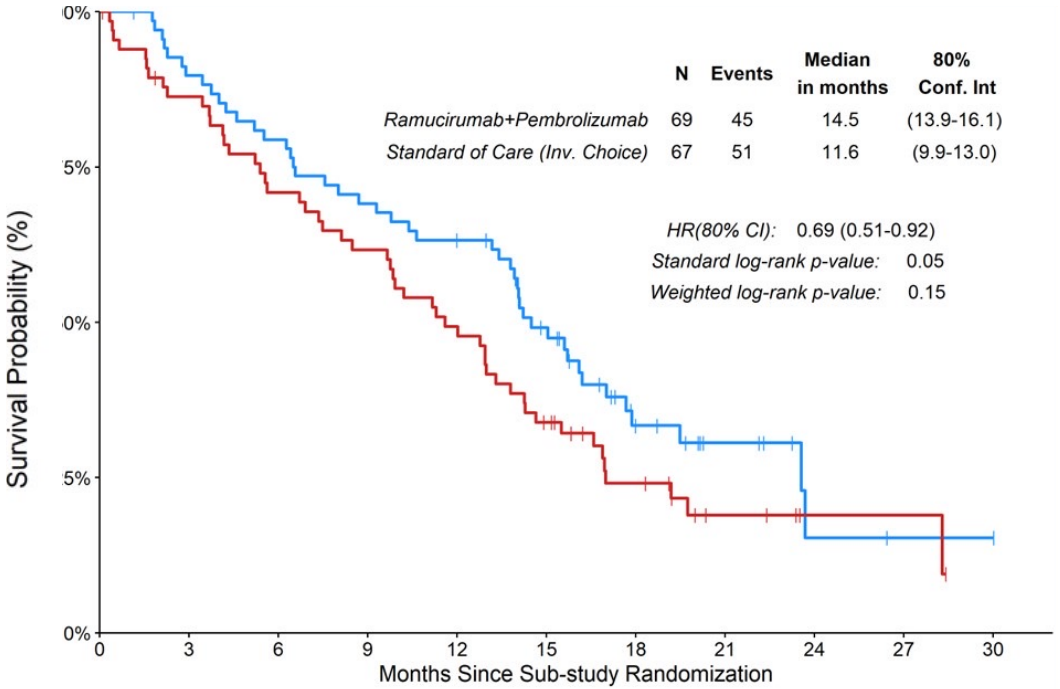
Key eligibility: 1) Previously received both PD-1 or PD-L1 inhibitor therapy and platinum-based doublet chemotherapy either sequentially or combined, with PD on at least 84 days after initiation of ICI and platinum-based doublet therapy; 2) ECOG 0-1; 3) all patients met eligibility to receive ramucirumab

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY: Karen L. Reckamp, MD, MS

LUNG-MAP

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER



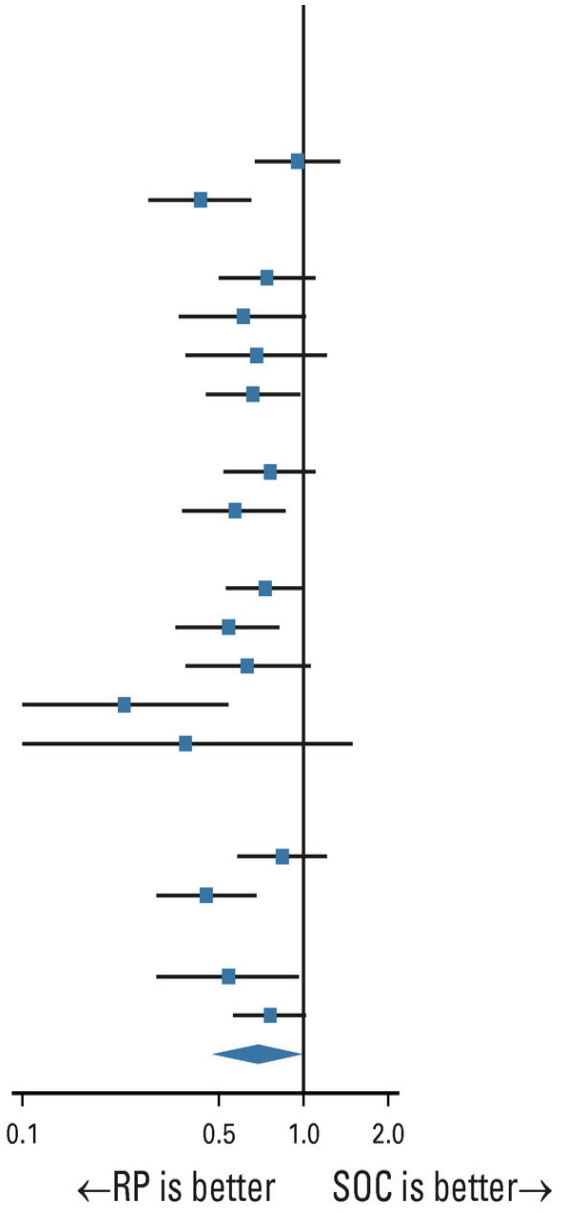
- **Median OS for pembro + ram 14.5 months versus SOC 11.6 months (HR=0.69)**
- **45 of 67 pts in SOC received docetaxel + ram**
- **No significant differences in PFS**

Reckamp et al., J Clin Oncol 2022

Although analysis is limited by small sample size, benefit noted among sub-groups2

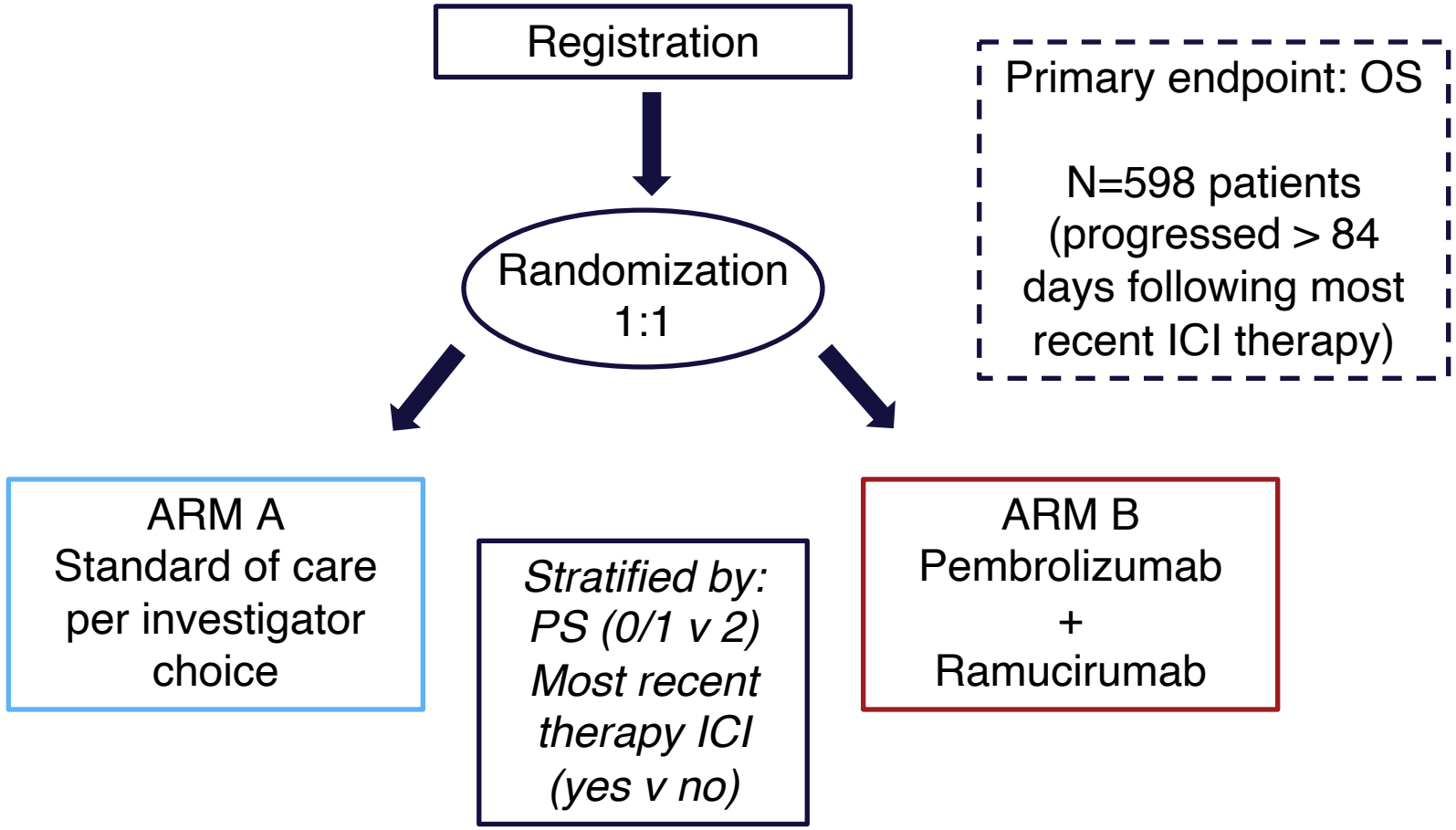
- Benefit among squamous/mixed histology
- HRs by PD-L1 status were similar
- Co-mutations did not affect OS improvement

	RP Events/n	SOC Events/n	HR (80% CI)	*P*
Histology				
Nonsquamous	27/40	27/39	0.95 (0.67 to 1.35)	.43
Squamous/mixed	18/29	24/28	0.43 (0.28 to 0.65)	.005
PD-L1				
0	21/29	21/26	0.74 (0.50 to 1.10)	.16
1-49	11/21	15/22	0.61 (0.36 to 1.02)	.11
≥ 50	8/12	12/16	0.68 (0.38 to 1.21)	.20
≥ 1	19/33	27/38	0.66 (0.45 to 0.97)	.08
TMB				
< 10	23/32	28/38	0.76 (0.52 to 1.10)	.17
≥ 10	18/33	20/25	0.57 (0.37 to 0.86)	.04
Biomarker				
TP53	31/48	35/48	0.73 (0.53 to 1.00)	.10
CDKN2A	18/27	21/24	0.54 (0.35 to 0.82)	.03
KRAS	12/21	13/16	0.63 (0.38 to 1.06)	.13
STK11	4/7	10/10	0.23 (0.10 to 0.54)	.01
KEAP1	1/3	7/10	0.38 (0.10 to 1.49)	.18
Prior Treatment				
IO + Chemotherapy combination	20/32	32/42	0.84 (0.58 to 1.21)	.27
Chemotherapy→IO	25/36	18/23	0.45 (0.30 to 0.68)	.006
PS				
0	15/23	8/9	0.54 (0.30 to 0.96)	.08
1	30/46	43/58	0.76 (0.56 to 1.02)	.12
Overall	45/69	51/67	0.69 (0.51 to 0.92)	.05



Reckamp et al., J Clin Oncol 2022

Pragmatica-Lung is upcoming streamlined, real-world clinical trial to study pembrolizumab + ramucirumab in phase III setting



Primary endpoint: OS

N=598 patients (progressed > 84 days following most recent ICI therapy)

- Condensed, simplified format to encourage rapid enrollment and access to diverse patient population
- No tissue specimens, protocol-required lab tests or disease assessments, no reporting of concomitant medications, and limited adverse event reporting

The Cancer Letter 2022; NCT05633602

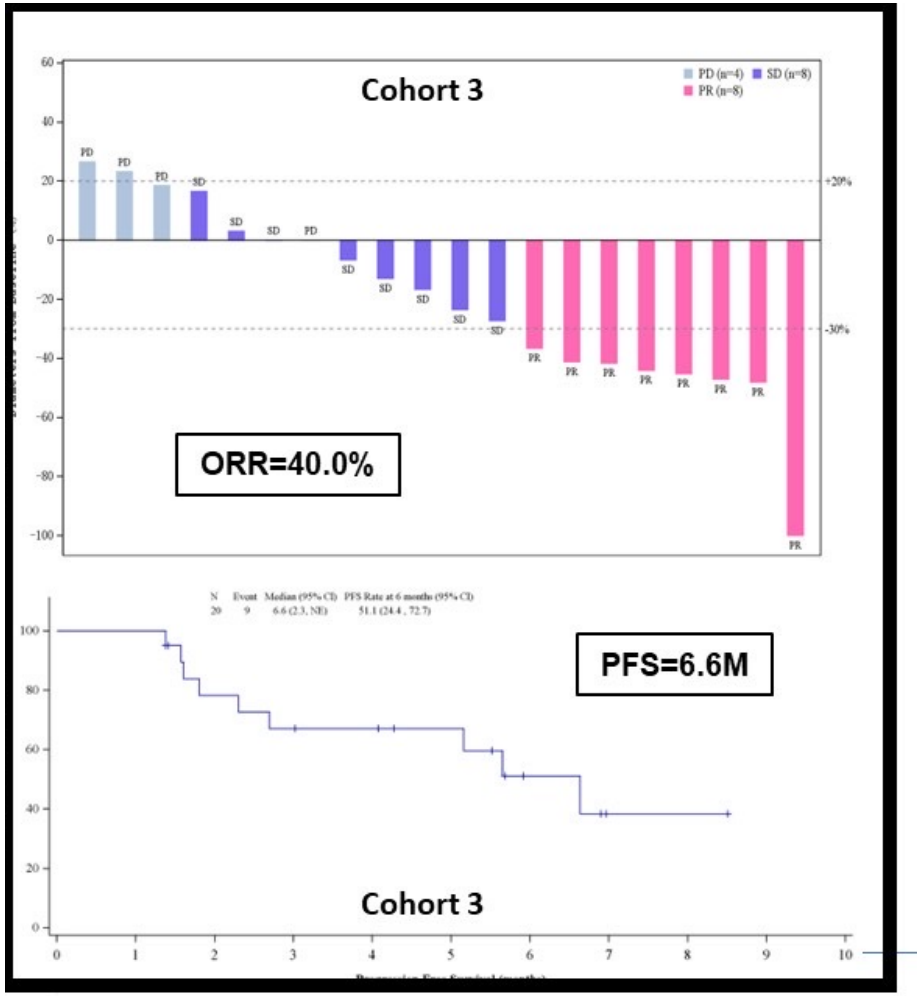
Ivonescimab (AK112) is PD-1/VEGF bispecific antibody demonstrating preliminary activity in advanced, IO-resistant NSCLC

Phase II trial of AK112 + chemotherapy in patients with advanced NSCLC

Cohort 1: 1L NSCLC without EGFR/ALK alterations	AK112 + Pem 500 mg/m^2 (non-squamous) or paclitaxel 175 mg/m^2 (squamous) + carboplatin AUC 5mg*min/ml
Cohort 2: EGFR+ NSCLC with POD after prior EGFR-TKI	AK112 + Pem 500 mg/m^2 + carboplatin AUC 5 mg*min/ml
Cohort 3: NSCLC With POD after platinum-based chemo + anti-PD-1	AK112 + docetaxel 75 mg/m^2

Primary endpoints

- Safety and tolerability
- Objective response rate (ORR) assessed by RECIST v1.1

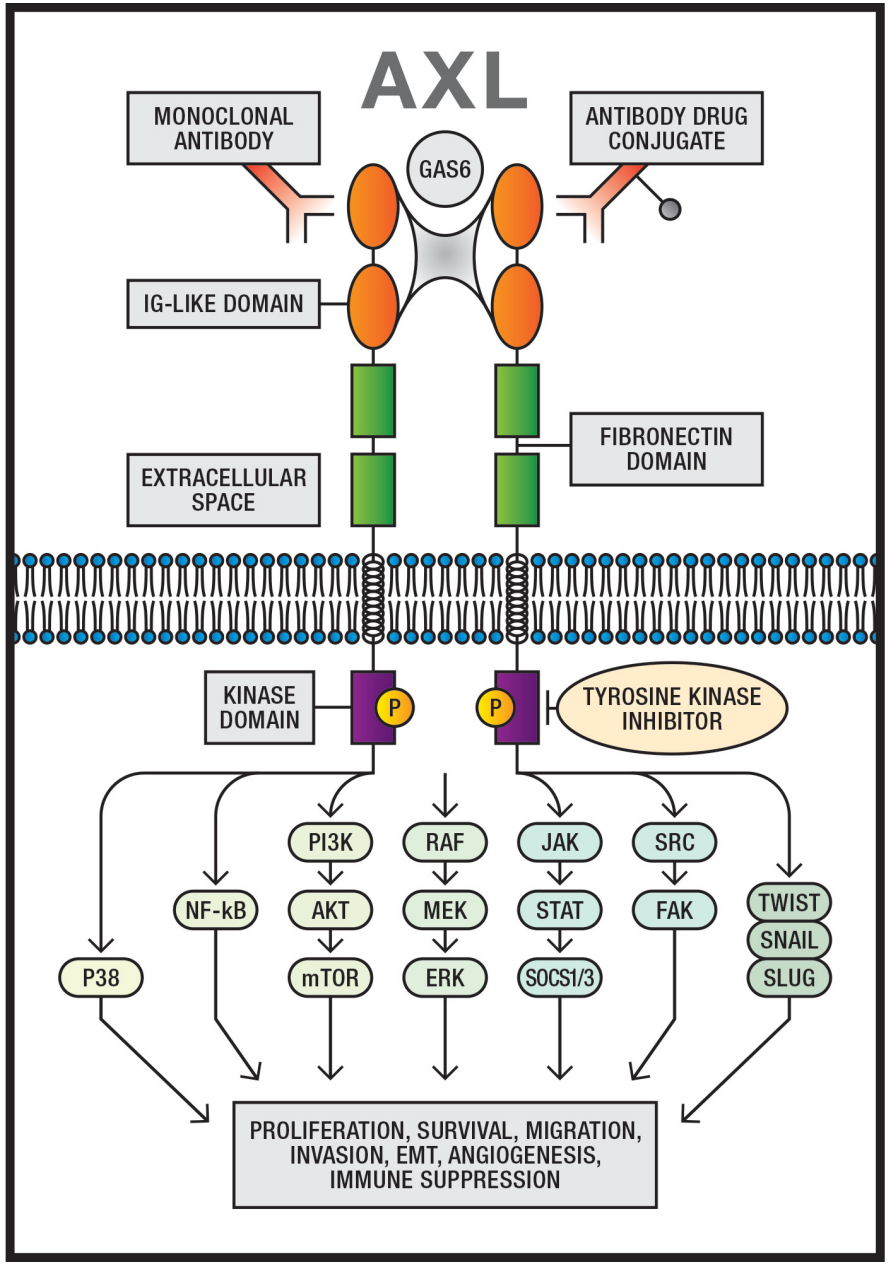


Zhao et al., ASCO Annual Meeting 2022

Activation of TAM receptors such as AXL may contribute to an immunosuppressive TME

- TAM receptors (Tyro3, AXL, MerTK) upregulate pro-tumorigenic functions and have prominent role in immunomodulation including efferocytosis and suppression of innate immune inflammatory response

- Murine lung cancer models show that AXL inhibition + ICI promotes infiltration of CTLs and NK cells into TME, increasing anti-tumor activity



Bhalla et al., Curr Oncol Rep (in press); Guo et al., Oncotarget 2017

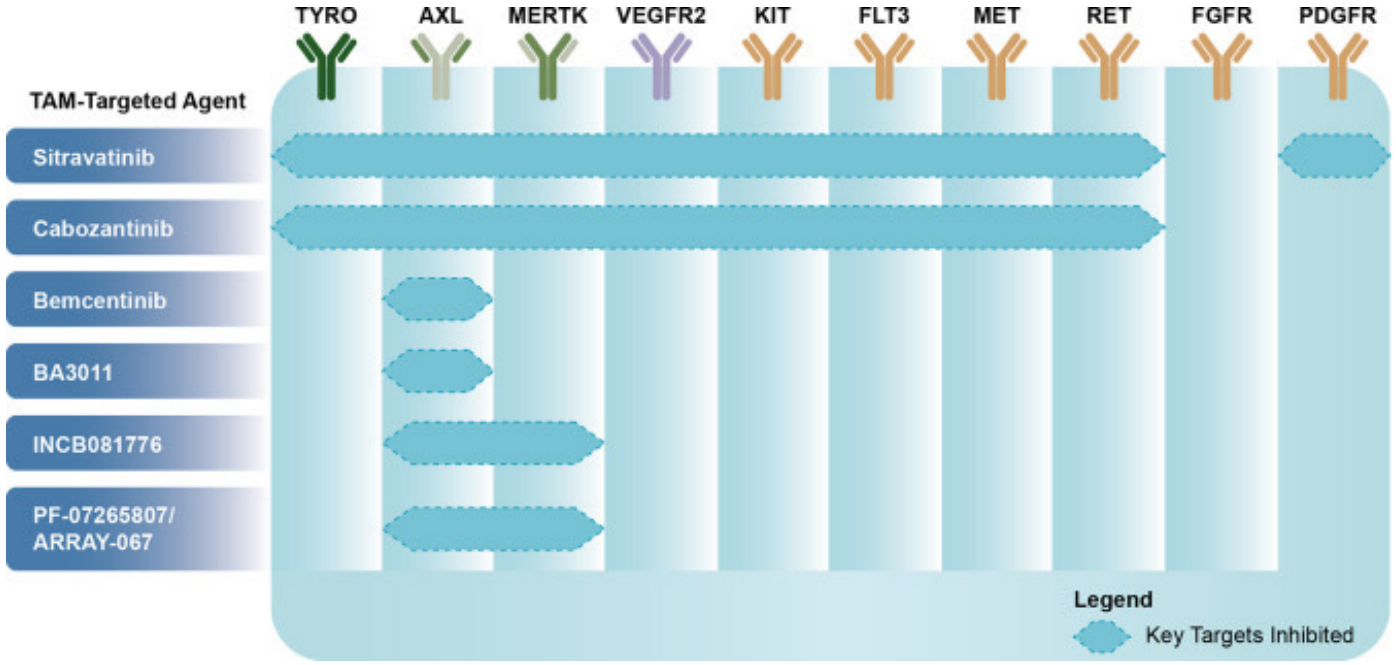
Clinical trials of TAM targeted agents + ICIs in advanced NSCLC are ongoing

Sitravatinib + nivolumab

- Ph 2 trial in NSQ NSCLC pts after prior ICI: ORR 16%, PFS 6m, OS 15m
- Grade 3/4 TRAEs 60% with discontinuation rate due to any AE ~30%
- Awaiting Phase 3 SAPPHIRE data

Cabozantinib + atezolizumab

- Ph 3 trial in NSCLC pts after prior ICI: did not meet primary endpoint of OS



Bemcentinib + pembrolizumab

- Ph 2 trial in NSQ pts after prior chemo±ICI: ORR 11.1%, PFS 6.2m, OS 13m
- AXL expression as biomarker? AXL TPS > 5: mOS 14.8m (ORR 21.9%) versus AXL TPS < 5: mOS 9.9m
- AXL inhibition may restore response to PD-1 blockade in STK11 mt NSCLC, prompting 1st line phase 1/2 trial

Solange et al. J Immunother Cancer 2022; Leal et al., Ann Oncol 2021; Krebs et al., J Thorac Oncol 2021; Li et al., Cell Rep 2022

Take home points

- Resistance to immunotherapy is an unfortunate occurrence for most patients with advanced NSCLC
- Definitions for primary and secondary immunotherapy resistance vary among trials; future studies should incorporate standardized, consensus-based definitions
- Mechanisms of resistance to immunotherapy are complex and multifactorial, with an immunosuppressive TME being one of the key mechanisms of resistance
- Promising ICI combination approaches may overcome an immunosuppressive TME and augment antitumor responses, such as strategies targeting the VEGF axis and TAM receptors
- Further collaborative efforts to understand distinct mechanisms of immunotherapy resistance and identify potential biomarkers are needed to guide future clinical trials