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Equity Research
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Hot PD-(L)1xVEGF Space to Continue Delivering Key Data In '25; TIL Upped to Buy

2024 was a banner year for PD-(L)1xVEGF class and we expect the hype to continue in 2025 with two key catalysts on the horizon: HARMONi-2 OS Data (YE25/Early26) and first global Ph3 data (Mid-25). We anticipate positive results from both, and continued excitement to attract more deals in the space. We see sig upside for TIL as its SYN2510 is the 3rd US asset w/ global trial planned in 2025 and stock is currently trading ~cash. Upgrade to Buy w/ $52 PT.

KEY STOCKS FEATURED INCLUDE:

TICKER	RATING	PRICE TARGET
TIL	**BUY**	$52.00
SMMT	**BUY**	$31.00

KEY CHANGES INCLUDE:

TICKER	RATING	PRICE TARGET
TIL	↑ **BUY**	↑ $52.00 ($11.00)

HARMONi-2 OS Data (YE25/Early26) from Akeso and First Global Data (Mid-25) from SMMT are Highly Anticipated; Our Analyses Suggest Likely (+) Results. 2024 was a fruitful year for ivonescimab (ivo, first-in-class PD-1xVEGF) w/ its first approval in China and unprecedented Keytruda-beating PFS in Ph3 HARMONi-2 trial in 1L PD-L1+ NSCLC, which sparked industry buzz and drove SMMT shares up ~150%, BNTX up ~40%, and TIL up ~500% (three companies w/ global trials ongoing/planned and will likely enter the market in the order of SMMT/BNTX/TIL). We estimate PD-(L)1xVEGF class could reach $40B+ (**Ex2**), similar to PD-(L)1 class, and we think the excitement in the space will continue in 2025 and highlight two major catalysts (**Ex1**) **1):** HARMONi-2 (in 1L PD-L1+ NSCLC) OS data likely in YE25/early26. Our regression model (**Slide8-10**) est. mOS of ~25m for ivo and ~17m for pembro arm, leading to an HR of ~0.7 (95%CI: 0.58-0.79). Add'ly, our KOL commented the well-separated PFS curves could translate to (+) OS. **2)** HARMONi topline data in 2L+ EGFRm NSCLC in mid-25; as Akeso has gained China approval in this indication (HARMONi-A), positive global data should ease investor concerns about China data. Our analysis based on comparable China/globally NSCLC trial datasets supports (+) readout.

PD-(L)1xVEGF Excitement Has Attracted Strong Deal Flow (Ex4), and We Anticipate More to Come in 2025. In 2024, we see three deals w/ a total upfront of $1.4B and deal value of $6.4B, namely, TIL's SYN2510 (PD-L1xVEGF-trap), BNTX's acquisition of its China partner for BNT327 (PD-L1xVEGF), and Merck's LM-299 (PD-1xVEGF). Merck deal marks the first large pharma joining the fray, adding confidence in its MOA. We list 14 other assets (12 in China and 3 in US/UK) that we believe could be pursued by other large pharma w/ IO assets **(Ex3),** such as BMS (Opdivo US patent expires in 2028) and Roche (Tecentriq US patent expiries in 2028).

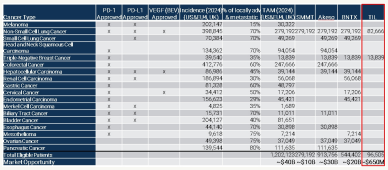
TIL's SYN2510 is an Early Mover in the Race and We See Sig Upside on Both Clinical Data Updates in the Space and BD Interests in This Drug Class; Upgrade TIL to Buy. TIL's initial focus is on NSCLC (Ph2 to start in 2H25) and TNBC w/ China partner running trials in multiple other indications w/ dose escalation data update in 1H25. SYN2510 presents a unique molecular design: **1)** VEGF arm uses "Trap" (VEGFR fusion protein) vs bev (mAb) used in ivo and BNT327; **2)** an intact Fc domain vs silenced in ivo and BNT327; **3)** PD-L1 (same w/ BNT327) vs PD-1 in ivo. The

Exhibit 1 - Major Data Events in PD-(L)1xVEGF Space in 2025

Timeline	Program/Originator	Catalyst
Mid 2025	Ivonescimab/Summit	Top-line data from global Ph3 HARMONi trial in 2L+ EGFRm NSCLC
YE25/1Q26 (E)	Ivonescimab/Akeso	Top-line data from China Ph3 HARMONi-6 trial in 1L sqNSCLC
YE25/1Q26 (E)	Ivonescimab/Akeso	OS data from China Ph3 HARMONi-2 trial in 1L PD-L1+ NSCLC
2025 (E)	BNT327/Biotheus	Top-line data from China Ph2/3 data in 2L+ EGFRm NSCLC
2025 (E)	BNT327/Biotheus	Top-line data from China Ph2/3 data in ES-SCLC
1H25	SYN2510/ImmuneOnco	Dose-escalation data update in China trial

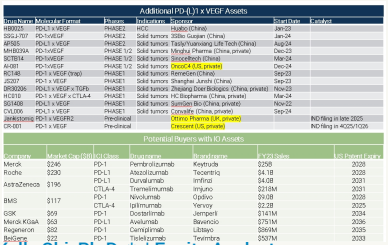
Source: Jefferies research

Exhibit 2 - Market Opportunity for PD-(L)1xVEGF Bispecifics at Tens of $B



Source: Jefferies research

Exhibit 3 - We Found 14 Additional PD-(L)1 x VEGF Assets for Biotech/Pharma Buyers



Source: Jefferies research

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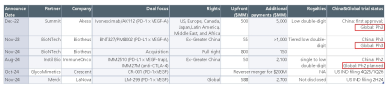
early (subtherapeutic doses) dose-esc data showed similar ORR vs BNT327. So far, we don't see enough evidence for differentiation. However, even the base case scenario (similar clinical profile to SMMT's or BNTX's) should reflect a largely undervalued oppy. As the third asset w/ global trials in plan, we see sig upside for TIL shares as it is currently trading at ~cash value at ~$135M market cap (vs SMMT at ~$13B; vs BNTX at ~$28B) (~1/5 of our risk-adj peak sales of $650M). We upgrade TIL to Buy with a PT of $52.

In this deep dive, we summarize ongoing/planned PD-(L)1xVEGF trials and all the clinical data reported so far (also in SMMT's initiation report link), and dig deep into SYN2510's molecular design. We also highlight ivo's differentiated tolerability profile vs BNT327 (**Slide32**).

Exhibit 4 - Six PD-(L)1 x VEGF BsAb Deals in Last Two Years



Source: Jefferies research

Summary of Changes

				EPS Estimates			P/E		
Company	Rating	Price^	Price Target	2023	2024	2025	2023	2024	2025
Instil Bio TIL	↑ BUY	$20.35	$52.00 ↑ +373%	$(24.00)	$(13.41) ↓ -61%	$(7.34) ↓ -436%	NM	NM	NM
Previous	HOLD		$11.00	$(24.00)	$(8.34)	$(1.37)			
Summit Therapeutics SMMT	BUY	$17.47	$31.00	$(0.99)	$(0.31)	$(0.43)	NM	NM	NM

^Prior trading day's closing price unless otherwise noted.

Exhibit 5 - TIL Income Statement

Instil Bio

Income Statement

(All values in $MM except EPS and average shares)

	2021A FY	2022A FY	2023A FY	2024E FY	2025E FY	2026E FY	2027E FY	2028E FY	2029E FY	2030E FY	2031E FY	2032E FY	2033E FY	2034E FY	2035E FY
Revenue:															
SYN-2510 US Sales (NSCLC)									51.8	119.4	199.6	268.1	322.5	371.9	386.0
SYN-2510 EU Sales (NSCLC)									0.0	24.8	55.1	93.8	121.5	149.3	166.0
SYN-2510 US Sales (TNBC)									0.0	9.1	15.2	33.6	42.6	53.5	75.0
SYN-2510 EU Sales (TNBC)									0.0	0.0	5.6	9.3	20.4	26.0	32.6
Collaboration revenues	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Total revenue, net	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**53.8**	**155.3**	**277.5**	**406.7**	**509.2**	**602.7**	**661.6**
Costs and expenses:															
Cost of goods sold	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.8	23.0	41.3	60.7	76.1	90.1	98.9
Research & development	107.3	141.1	39.6	35.7	44.7	55.8	72.6	76.2	80.0	84.0	88.2	92.7	97.3	102.1	107.3
Selling, general & administrative	48.3	82.2	47.6	45.8	55.0	66.0	79.2	99.0	104.0	109.2	114.6	120.3	126.4	132.7	139.3
Other	0.0	23.2	72.0	7.1	-	-	-	-	-	-	-	-	-	-	-
Total operating expenses	**155.6**	**226.5**	**159.2**	**88.7**	**99.7**	**121.8**	**151.8**	**175.2**	**195.3**	**217.6**	**245.1**	**274.4**	**300.3**	**325.5**	**346.0**
Income (loss) from operations	**(155.6)**	**(226.5)**	**(159.2)**	**(88.7)**	**(99.7)**	**(121.8)**	**(151.8)**	**(175.2)**	**(141.6)**	**(62.3)**	**32.4**	**132.3**	**208.9**	**277.2**	**315.5**
Other income (expense):															
Interest income, net	(1.2)	1.4	4.293	3.7	3.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Other	0.0	(0.1)	(1.154)	(2.2)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Net profit (loss) before income taxes	**(156.8)**	**(225.3)**	**(156.0)**	**(87.2)**	**(96.7)**	**(119.8)**	**(149.8)**	**(173.2)**	**(139.5)**	**(60.2)**	**34.5**	**134.4**	**210.9**	**279.3**	**317.6**
Income tax expense (benefit)	0.0	(2.1)	0.1	0.0	0.0	0.0	0.0	0.0	0.0	(1.9)	1.6	13.2	27.2	47.1	60.0
Income tax (%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	3.0%	5.0%	10.0%	13.0%	17.0%	19.0%
Net income (GAAP)	**(156.8)**	**(223.2)**	**(156.1)**	**(87.2)**	**(96.7)**	**(119.8)**	**(149.8)**	**(173.2)**	**(139.5)**	**(58.4)**	**32.9**	**121.1**	**183.8**	**232.1**	**257.6**
EPS, GAAP															
Basic	(1.48)	(1.72)	(24.00)	(13.41)	(7.34)	(6.02)	(7.45)	(6.59)	(5.25)	(1.78)	0.99	3.62	5.43	6.80	7.47
Diluted	**($1.48)**	**($1.72)**	**($24.00)**	**($13.41)**	**($7.34)**	**($6.02)**	**($7.45)**	**($6.59)**	**($5.25)**	**($1.78)**	**$0.99**	**$3.62**	**$5.43**	**$6.80**	**$7.47**
Basic shares	106.0	129.5	6.5	6.5	13.2	19.9	20.1	26.3	26.6	32.8	33.2	33.5	33.8	34.2	34.5
Diluted shares	106.0	129.5	6.5	6.5	13.2	19.9	20.1	26.3	26.6	32.8	33.2	33.5	33.8	34.2	34.5

Source: Jefferies research; Company data

Exhibit 6 - TIL DCF Sensitivity Analysis

Disc Rate	Equity Value	Price/Sh
12.0%	$657.2	101.10
13.0%	$529.7	81.49
14.0%	$425.4	65.45
15.0%	$339.3	52.20
16.0%	$267.7	41.18

Source: Jefferies research; Company data

Exhibit 7 - SMMT Income Statement

Summit therapeutics (SMMT)

(All values in $M, except per share data)

GAAP Income Statement	2021A	2022A	2023A	2024E	2025E	2026E	2027E	2028E	2029E	2030E	2031E	2032E	2033E	2034E	2035E
Product revenue:	-	-	-	-	-	**10.0**	**202.2**	**1,084.8**	**2,842.0**	**4,797.2**	**7,122.5**	**9,513.9**	**10,456.6**	**10,316.8**	**10,588.5**
Ivonescimab in NSCLC (U.S)	-	-	-	-	-	10.0	197.0	981.2	2,344.7	3,651.0	5,305.5	6,967.4	7,231.3	7,088.3	7,356.8
Ivonescimab in NSCLC (E.U)						-	5.2	103.5	497.3	1,146.1	1,816.9	2,546.5	3,225.3	3,228.5	3,231.7
Regulatory Milestones to Akeso (risk-adjusted)	-	-	-	-	-	(87.5)	(58.3)	(58.3)	(58.3)	(58.3)	(58.3)	(58.3)	(58.3)	(58.3)	(58.3)
Sales Royalties to Akeso (risk-adjusted)	-	-	-	-	-	(1.2)	(24.3)	(130.2)	(341.0)	(575.7)	(854.7)	(1,141.7)	(1,254.8)	(1,238.0)	(1,270.6)
Commercial Milestones to Akeso (risk-adjusted)	-	-	-	-	-	(4.2)	(20.8)	(20.8)	(41.7)	(83.3)	(166.7)	(208.3)	(208.3)	(333.3)	(350.0)
Total revenues	**1.8**	**0.7**	**-**	**-**	**-**	**(82.9)**	**98.8**	**875.4**	**2,401.0**	**4,079.9**	**6,042.8**	**8,105.5**	**8,935.1**	**8,687.1**	**8,909.5**
Cost of sales - products	-	-	-	-	-	2.0	38.4	195.3	426.3	719.6	1,068.4	1,427.1	1,568.5	1,547.5	1,588.3
Research and development	85.4	52.0	59.5	142.7	214.1	299.7	359.7	395.6	435.2	478.7	526.6	552.9	580.6	609.6	640.1
In-process R&D			520.9	15.0											
SG&A	23.6	26.7	30.3	69.6	111.4	167.1	250.6	325.8	374.6	412.1	453.3	498.6	548.5	603.4	663.7
Impairment of intangible assets		8.5	-	-											
Total operation cost and expenses (OPEX)	**109.0**	**87.2**	**610.7**	**227.3**	**325.5**	**468.8**	**648.7**	**916.7**	**1,236.2**	**1,610.4**	**2,048.3**	**2,478.7**	**2,697.6**	**2,760.5**	**2,892.1**
Other operating income (expense)	**21.0**	**14.4**	**1.0**	**0.1**											
Operating income (EBIT)	**(86.2)**	**(72.1)**	**(609.7)**	**(227.2)**	**(325.5)**	**(551.7)**	**(549.9)**	**(41.3)**	**1,164.8**	**2,469.4**	**3,994.5**	**5,626.9**	**6,237.5**	**5,926.6**	**6,017.5**
Other income (expense), net	-2.4	(6.7)	(5.3)	1.4											
Pretax income (loss)	**(88.6)**	**(78.8)**	**(614.9)**	**(225.8)**	**(325.5)**	**(551.7)**	**(549.9)**	**(41.3)**	**1,164.8**	**2,469.4**	**3,994.5**	**5,626.9**	**6,237.5**	**5,926.6**	**6,017.5**
Effective tax rate						*0%*	*0%*	*2%*	*5%*	*7%*	*10%*	*13%*	*15%*	*21%*	*21%*
Income tax (benefit) expense	-	-	-	-	-	-	-	0.8	(58.2)	(172.9)	(399.4)	(731.5)	(935.6)	(1,244.6)	(1,263.7)
Net income to common shareholders	**(88.6)**	**(78.8)**	**(614.9)**	**(225.8)**	**(325.5)**	**(551.7)**	**(549.9)**	**(40.4)**	**1,106.6**	**2,296.6**	**3,595.0**	**4,895.4**	**5,301.9**	**4,682.0**	**4,753.8**
EPS (GAAP)															
Basic ($)	$ (0.96)	$ (0.41)	$ (0.99)	$ (0.31)	$ (0.43)	$ (0.70)	$ (0.68)	$ (0.05)	$ 1.31	$ 2.67	$ 4.10	$ 5.48	$ 5.82	$ 5.04	$ 5.01
Diluted ($)	**$ (0.96)**	**$ (0.41)**	**$ (0.99)**	**$ (0.31)**	**$ (0.43)**	**$ (0.70)**	**$ (0.68)**	**$ (0.05)**	**$ 1.31**	**$ 2.67**	**$ 4.10**	**$ 5.48**	**$ 5.82**	**$ 5.04**	**$ 5.01**
Weighted average shares outstanding (Basic)	92.2	193.3	619.6	717.6	758.6	783.8	809.4	825.6	842.2	859.0	876.2	893.7	911.6	929.8	948.4
Weighted average shares outstanding (Diluted)	92.2	193.3	619.6	717.6	758.6	783.8	809.4	825.6	842.2	859.0	876.2	893.7	911.6	929.8	948.4

Source: Jefferies research; Company data

DCF Sensitivity Analysis

Exhibit 8 - SMMT DCF Sensitivity Analysis

Discount Rate	Terminal Value Multiple		
	(1%)	0%	1%
10.0%	$38.29	$40.65	$43.53
11.0%	$33.51	$35.31	$37.47
12.0%	$29.55	$30.95	$32.60
13.0%	$26.22	$27.32	$28.60
14.0%	$23.39	$24.26	$25.27
15.0%	$20.97	$21.67	$22.47

Source: Jefferies research; Company data

PD-(L)1xVEGF Bispecifics 2025 Outlook

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Table of Contents

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Major Events in PD-(L)1xVEGF Space in 2025

2025 Catalysts		
Timeline	Program/Originator	Catalyst
Mid 2025	Ivonescimab/Summit	Top-line data from global Ph3 HARMONi trial in 2L+ EGFRm NSCLC
YE25/1Q26 (E)	Ivonescimab/Akeso	Top-line data from China Ph3 HARMONi-6 trial in 1L sqNSCLC
YE25/1Q26 (E)	Ivonescimab/Akeso	OS data from China Ph3 HARMONi-2 trial in 1L PD-L1+ NSCLC
2025 (E)	BNT327/Biotheus	Top-line data from China Ph2/3 data in 2L+ EGFRm NSCLC
2025 (E)	BNT327/Biotheus	Top-line data from China Ph2/3 data in ES-SCLC
1H25	SYN2510/ImmuneOnco	Dose-escalation data update in China trial

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Source: Company reports; Jefferies research

OS Data From China Ph3 HARMONi-2 Trial in 1L PD-L1+ NSCLC

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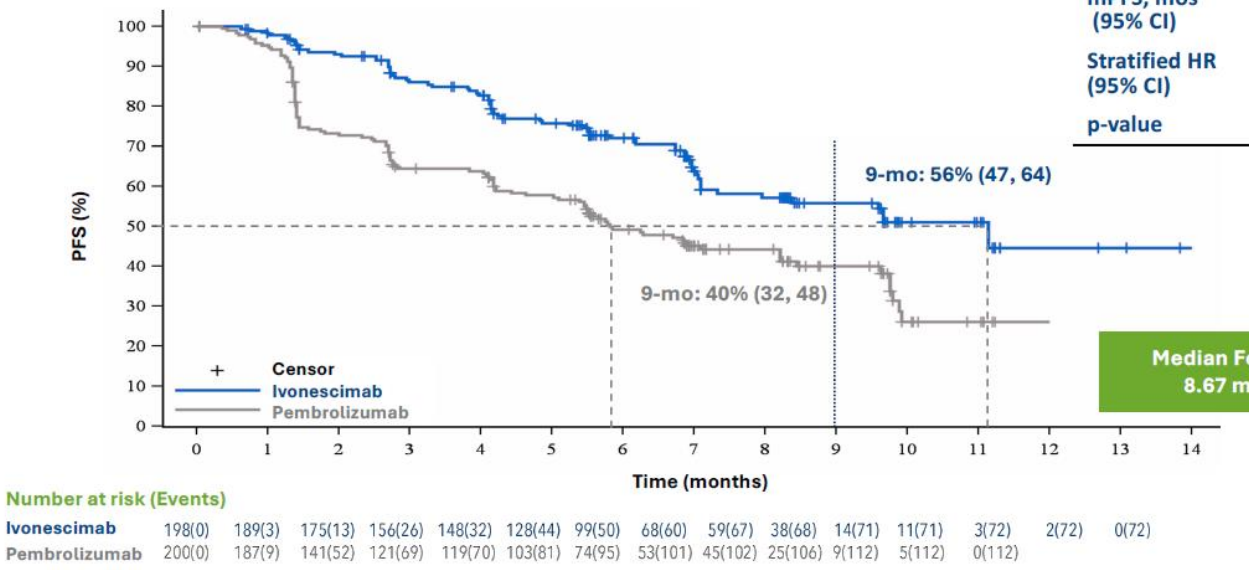
HARMONi-2: Ivonescimab Achieved Unprecedented Superior PFS vs Pembrolizumab in 1L PD-L1+ NSCLC (HR=0.51) at WCLC 2024, Setting Off an Industry-Wide Buzz

HARMONi-2 Primary Endpoint PFS per IRRC



	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	

Median Follow-up: 8.67 months

Ivonescimab is the first compound to demonstrate a statistically significant improvement in PFS vs pembrolizumab with HR = 0.51 (mPFS of 11.14 vs 5.82 m, a 5.3 months improvement)

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Source: Company presentation

HARMONi-2: KOL Likes the Well-Separated PFS Curve, Which Bodes Well for OS Superiority; KOL also Highlighted the Benefit in PD-L1 Low Group, Where Keytruda is Not Preferred in Real World

We hosted dinners with Dr. Jared Weiss, a Professor at UNC School of Medicine, post WCLC'24

- KOL described ivonescimab's data as "gorgeous" at HR of 0.51 against Keytruda.
- He especially liked the shape of ivo's PFS curve, which remained well-separated at ~1 year, and thinks this is critical for predicting potential OS performance.
- He saw historical good correlation between PFS and OS for immunotherapy, but not with anti-VEGF, but ivo's PFS curve gives him confidence in the OS superiority.
- KOL also highlighted the spare of "cliff" (sharp decline) at the beginning of ivo's PFS curve, and the lack of convergence in past six months, suggesting durable control of the disease by ivo.
- In addition, KOL liked ivo's consistent PFS improvement across patient subgroups, especially in the TPS 1-49% group where he said physicians do not prefer pembro in real-world practices, despite it being approved in all PD-L1+ patients.
- Lastly, KOL discussed the impact of demographic difference on data interpretation, and he believes the historical data differences between Asians vs non-Asians, if any, were mainly driven by genomic alterations such as EGFR rather than histology (sq vs non-sq).

We will discuss in more depth in the following slides.

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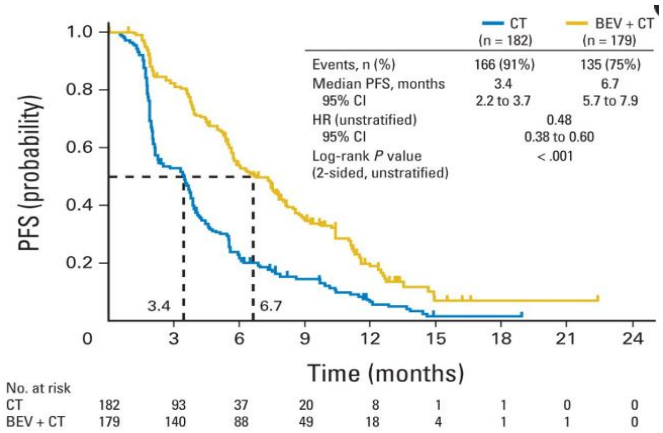
Source: Jefferies research

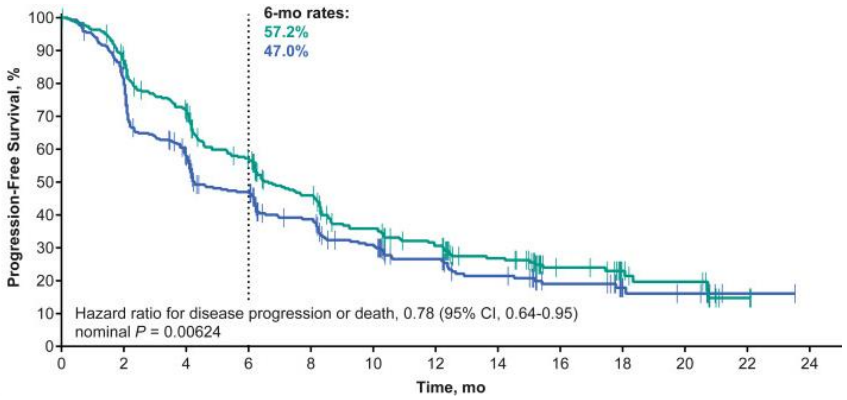
One Question is Whether PFS Can be Translated into OS with PD-(L)1/VEGF BsAbs, Given Many Bev Trials and Combo Trials of Anti-PD-(L)1 and Anti-Angiogenic Therapies Did not Show Translatability

Phase 3 Trials that PFS Benefit Did not Translate into OS Benefit

AURELIA in PROC[1]



LEAP-007 in 1L NSCLC[2]



- In SMMT's Ph3 HARMONi-2 study in 1L NSCLC, the overall survival data was immature when it was presented at WCLC'24. It is not surprising that KOLs commented that OS data would be important to evaluate ivonescimab's competitiveness vs pembro, so the key question is whether ivo's HR=0.51 mPFS (11.1 vs 5.8m) could be translated into OS.

- However, the association between OS and PFS is often under debate, especially given the negative OS results seen in several Bev trials and more prominently in ovarian cancer, including GOG-0218, ICON7, OCEANS, and AURELIA trial (as shown in the example above), as well as combo trials of anti-PD-(L)1 and anti-angiogenic therapies such as MRK's LEADP-007, which studies pembro + lenvatinib (anti-angiogenic multikinase inhibitor) vs pembro in 1L NSCLC.

Kelly Shi, Ph.D., Equity Analyst, (212) 336-6937, kshi@jefferies.com
Source: 1. Pujade-Lauraine et al. JCO 2014; 2. Yang et a., J Thorac Oncol., 2024

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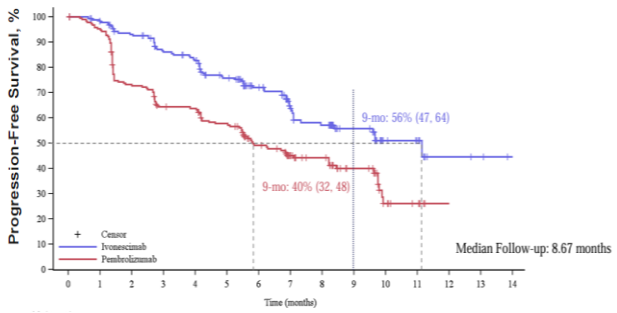
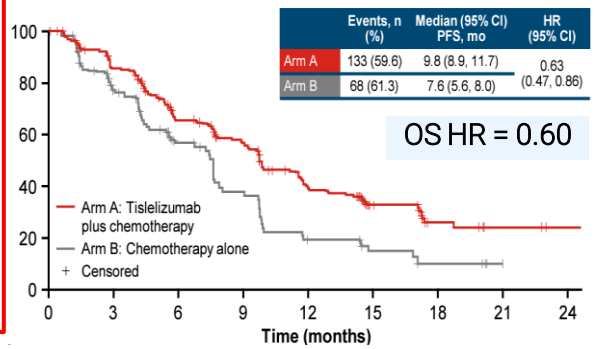
Notably, our KOL Commented that Ivo's PFS Curve Is More Like IO Curves and Likely will Translate to OS Benefit: Spare of "Cliff" at the Beginning of PFS Curve, and the Lack of Convergence Past Six Months

HARMONi-2 PFS Curve Compared to Other IO Trials in 1L NSCLC

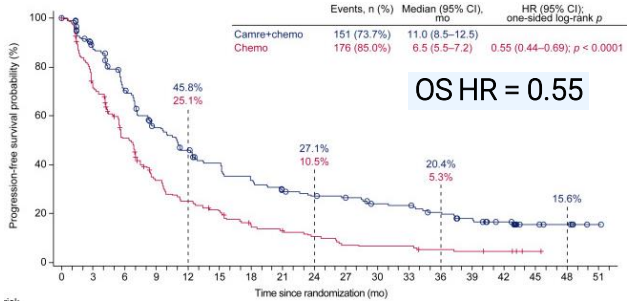
SMMT/Akeso's Ph3 HARMONi-2



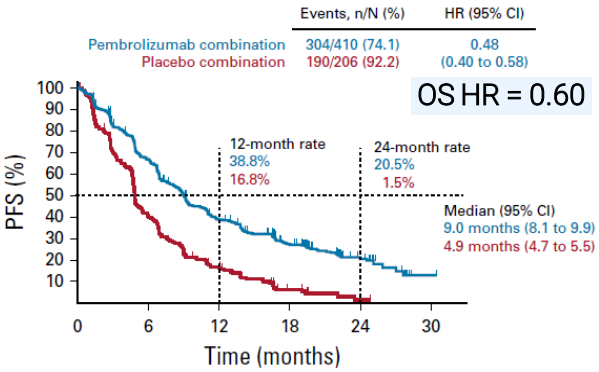
BGNE's Ph3 RATIONALE-314



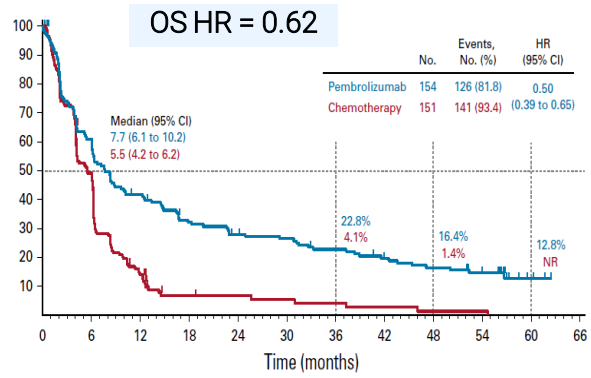
Hengrui's Ph3 CameL



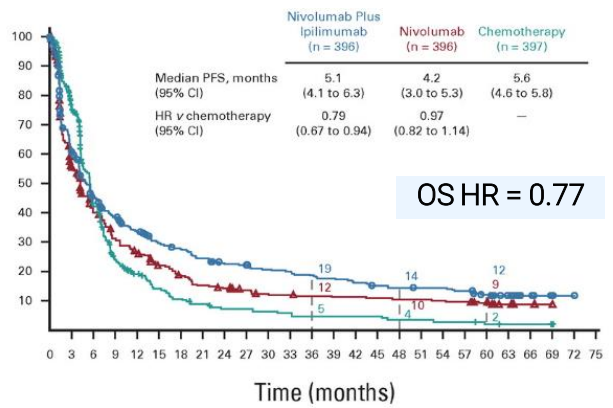
MRK's Ph3 KEYNOTE-189



MRK's Ph3 KEYNOTE-024



BMY's Ph3 CheckMate-227



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Source Industry literatures, Jefferies research

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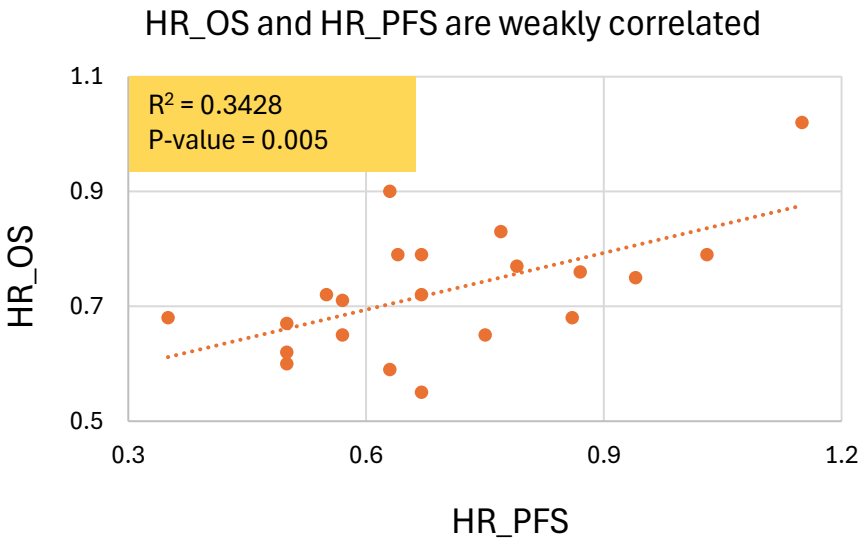
We Tried to Use the Same Dataset to Extrapolate OS Hazard Ratio, but It Appears HR of OS and HR of PFS are Weakly Correlated – The HR of OS Can't be Reliably Predicted Based on the HR of PFS

OS and PFS Correlation in Immuno-Oncology Trials in 1L NSCLC

Trial	TPS	Regimen	PFS (m)	OS (m)	PFS HR	OS HR
KEYNOTE-042	≥ 50%	PD1 vs Chemo	6.5	20.0	0.86	0.68
	≥ 20%		6.2	18.0	0.94	0.75
	≥ 1%		5.6	16.4	1.03	0.79
KEYNOTE-024	≥ 50%	PD1 vs Chemo	7.7	26.3	0.5	0.62
KEYNOTE-189 (non-squamous)	All (ITT)	PD1+Chemo vs Chemo	9.0	22.0	0.5	0.6
	≥ 50%		11.3	27.7	0.35	0.68
	1-49%		9.4	21.8	0.57	0.65
	<1%		6.2	17.2	0.67	0.55
KEYNOTE-407 (squamous)	All (ITT)	PD1+Chemo vs Chemo	8.0	17.1	0.57	0.71
	≥ 1%		8.2	18.9	0.5	0.67
	< 1%		6.3	15.0	0.67	0.79
RATIONALE-304	All (ITT)	PD1+Chemo vs Chemo	9.8	21.4	0.63	0.9
CameL	All (ITT)	PD1+Chemo vs Chemo	11.0	27.1	0.55	0.72
CheckMate-277	≥ 1%	PD1+Chemo vs Chemo	5.1	17.1	0.79	0.77
	< 1%		5.1	17.4	0.75	0.65
CheckMate-026	≥ 1%	PD1 vs Chemo	4.2	14.4	1.15	1.02
IMPower130	All (ITT)	PDL1+Chemo vs Chemo	7	18.6	0.64	0.79
MYSTIC	All (ITT)	PDL1 vs Chemo	4.7	16.3	0.87	0.76
Impower110	≥ 50%	PDL1 vs Chemo	8.1	20.2	0.63	0.59
	≥ 5%		7.2	18.2	0.67	0.72
	≥ 1%		5.7	17.5	0.77	0.83



Kelly Shi, Ph.D., Equity Analyst, (212) 336-6937, kshi@jefferies.com
Source: Industry literatures, Jefferies research

Jefferies

In 1L NSCLC, our Analysis Suggests that OS and PFS Are Strongly Correlated ($R^2 \approx 0.70$, P-value < 0.0001), and We Estimate HARMONi-2 mOS at ~25 Months (95% CI: 23.2M – 27.6M)

OS and PFS Correlation in Immuno-Oncology Trials in 1L NSCLC

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KEYNOTE-042	≥ 50%	PD1 vs Chemo	6.5	20.0	0.86	0.68
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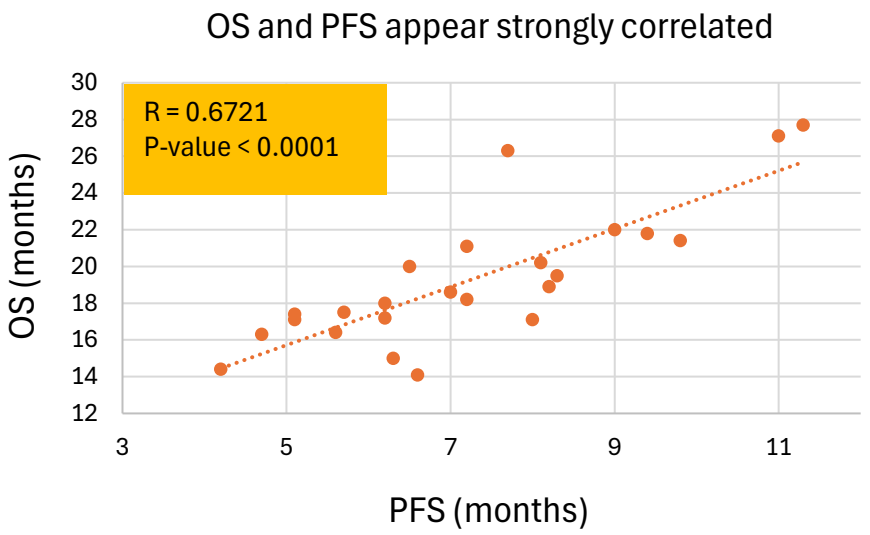
	≥ 1%		5.7	17.5	0.77	0.83
Impower150	All	PDL1+VEGF vs VEGF	8.3	19.5	0.62	0.8
LEAP007	All	PD1+VEGF vs PD1	6.6	14.1	0.78	1.1
ORIENT	All	PD1+VEGF vs PD1	7.2	21.1	NA	NA



- HARMONi-2 trial mPFS = 11.14 months*,
Predicted OS = 25.4m, with 95% confidence interval (23.2, 27.6)

- If we delete the "outlier" (KEYNOTE-024 Trial),
Predicted OS = 25.0m, with 95% confidence interval (23.2, 26.8)

*Note that the accuracy of predictions in linear regression decreases as the input values deviate further from the center of the data.

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Source: Industry literatures, Jefferies research

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Thus, We Use Predicted mOS of Both Arms' mPFS to Estimate HR of OS and Calculate HR = 0.68 (95% CI: 0.58, 0.79)

$$HR = \frac{Median\ OS\ (Pembrolizumab)}{Median\ OS\ (Ivonescimab)} = \frac{17.2\ m}{25.4\ m} = 0.68^{*}$$

95% confidence interval for HR [0.58, 0.79]

95% confidence interval for mOS (Ivonescimab) [23.2m – 27.6m]

95% confidence interval for mOS (Pembrolizumab) [16m –18.4m]

Our prediction of 17.2m is consistent with the mOS of prior Pembrolizumab monotherapy trial (16.4m in TPS≥1% in KN042)

*We use predicted median OS values of pembrolizumab and ivonescimab to estimate HR due to the absence of KM curves. To apply this simplified equation for HR calculation, the following assumptions were made:

- Survival times are assumed to follow an exponential distribution with a constant hazard rate.
- The hazard ratio between the two arms is assumed to remain constant over time.
- Censoring is assumed to have minimal impact on the median OS values.
- Survival curves are assumed to have similar shapes without significant deviations.

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Source: Industry literatures, Jefferies research

Top-line Data From Global Ph3 HARMONi Trial in 2L+ EGFRm NSCLC

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HARMONi-2 PFS HR of 0.51 Looks Competitive Compared to Recent 1L NSCLC Approvals (0.46-0.7); Estimated OS HR of 0.68 is also In-line with Recent 1L NSCLC Approvals (0.6-0.8)

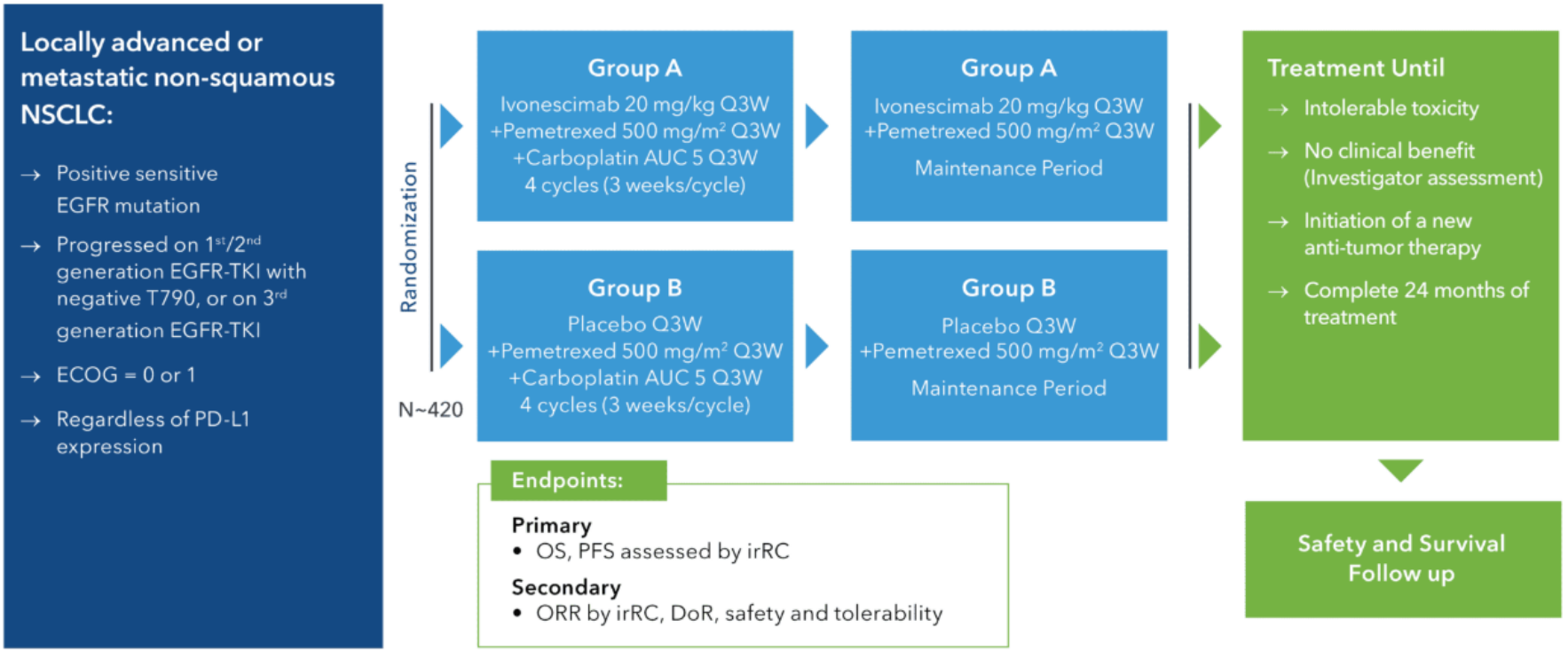
Company	Drug Regimen	Approval Year	Trial	LOT	PFS HR	OS HR
Merck	Pembrolizumab vs Chemo	2015	KEYNOTE-010	2L	0.79-0.88	0.61/0.71
	Pembrolizumab vs Chemo	2016	KEYNOTE-024	1L	0.5	**0.62**
	Pembrolizumab+Chemo vs Chemo	2018	KeyNOTE-189	1L	0.5	**0.6**
BMS	Nivolumab vs Chemo	2015	CheckMate-057	2L	0.92	0.73
	Nivolumab+Ipilimumab vs Chemo	2020	CheckMate-227	1L	0.81	**0.79**
Roche	Atezolizumab vs Chemo	2016	OAK and POPLAR	2L	0.95/0.94	0.74/0.69
	Atezolizumab+Chemo vs Chemo	2019	IMPower-130	1L	0.64	**0.79**
Regeneron	Cemiplimab+Chemo vs Chemo	2022	EMPOWER-Lung3	1L	0.56	**0.71**
AZN	Osimertinib vs EGFR-TKI	2018	FLAURA	1L	0.46	**0.8**
JNJ	Amivantamab+Lazertinib vs Osi	2024	MARIPOSA	1L	0.7	**0.8**
JNJ	Amivantamab+Chemo vs Chemo	2024	MARIPOSA-2	2L	0.48	0.73

Kelly Shi, Ph.D., Equity Analyst, (212) 336-6937, kshi@jefferies.com

Source: Industry literatures, Jefferies research

HARMONi: a Randomized PhIII Study Comparing Ivonescimab+Chemo with Pembrolizumab+Chemo in 2L+ EGFRm nsqNSCLC

HARMONi Trial Design

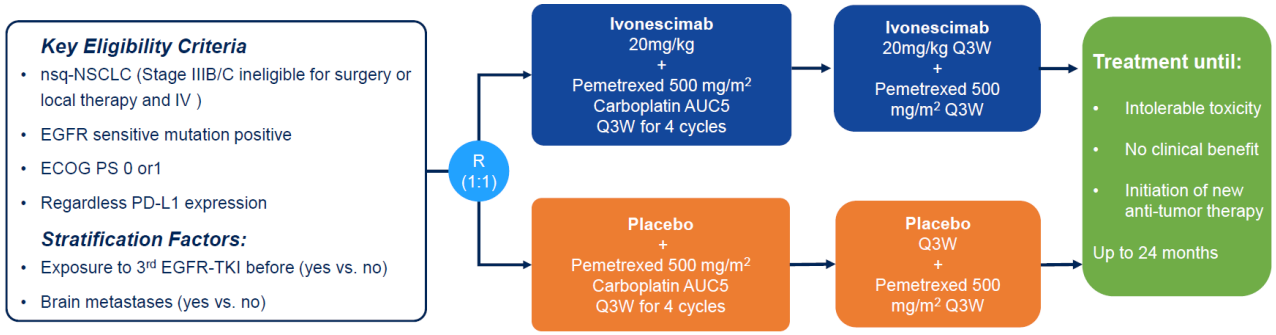


- The trial is sponsored by Summit and is being conducted globally, initiated in May 2023.
- Enrollment was completed in Oct 2024 and top-line data is expected in mid-2025.
- HARMONi has essentially the same trial design as Akeso's HARMONi-A China trial

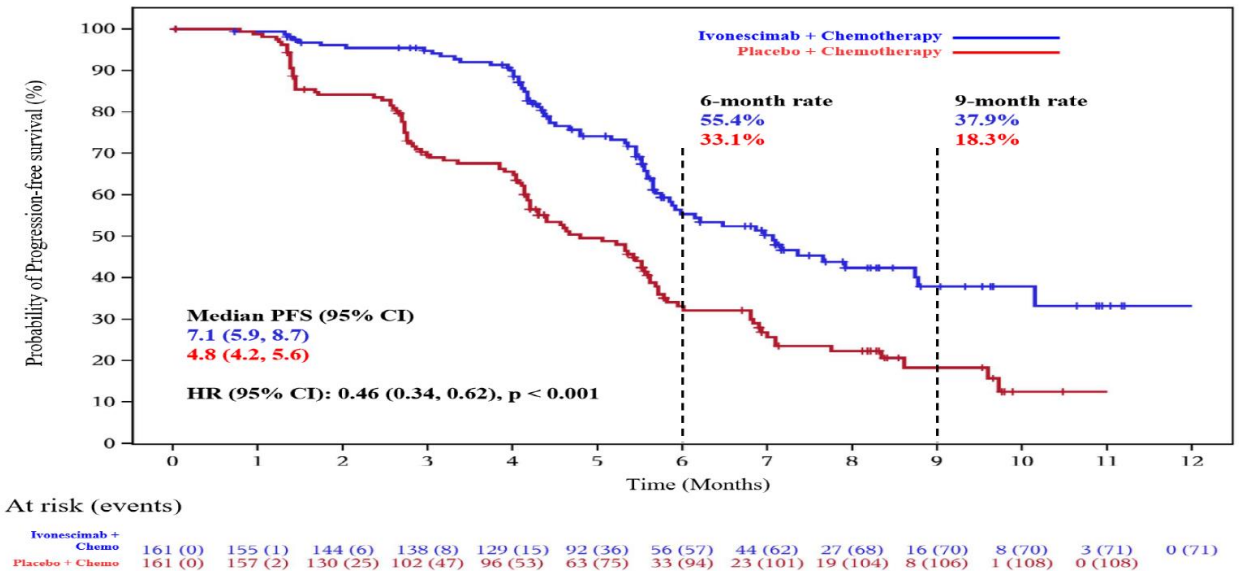
Kelly Shi, Ph.D., Equity Analyst, (212) 336-6937, kshi@jefferies.com
Source: Company presentation

HARMONi-A: Ivonescimab+Chemo Achieved Superior PFS vs Pembrolizumab+Chemo in 2L+ EGFRm nsqNSCLC (HR=0.46)

HARMONi-A Trial Design (China)



Study Met Primary Endpoint of PFS per IRRC



- The trial was sponsored by Akeso in China, initiated in Jan 2022; China NDA accepted in Aug 2023 for priority review w/ approval granted in May 2024
- ASCO'24 data cutoff of Mar 2023 and median follow-up of 7.9 months
  - mPFS: 7.1 vs 4.8 m, HR 0.46, p<0.001
  - ORR: 50.6% vs 35.4%
  - DCR: 93.1% vs 83.2%
  - mDOR: 6.6 vs 4.2 m
  - mOS: 17.1 vs 14.5 m, HR 0.80 (mFU is 17.6m)

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Source: Company presentation, ASCO 2024

Jefferies

Another Heated Debate Is Whether China Trials Are Translatable Globally; We Believe They Are Based on Historical Trials and HARMONi Data will help Ease the Concerns

Historical NSCLC Trials Comparison Between Global and China

- HARMONi-2 Ph3 trial was conducted on a 100% Chinese population, leading to debate over its translatability to the global population
- We collected data from 5 different trials of pembro, nivo, or bev in NSCLC and compared their PFS/OS HR results between China and global Ph3 trials
- Our analysis suggests China data does not seem to differ from global data in oncology Ph3 trials, but there are two outliers:
  - KEYNOTE-407, a single-site China trial (per CT.gov)
  - Bev China trial, conducted 10 years after the global trial
- **HARMONi-2 was conducted at ~ 60 sites in China (according to SMMT) and global trial HARMONi-7 will start in early 2025 (only ~2 years after HARMONi-2). Thus, we think HARMONi-2 data will likely translate to the global population.**

PFS HR			OS HR		
Global	China	Δ	Global	China	Δ
0.57	0.35	0.22	0.71	0.44	0.27
0.86	0.84	0.02	0.68	0.63	0.05
0.94	0.95	-0.01	0.75	0.66	0.09
1.03	1	0.03	0.79	0.67	0.12
0.62	0.66	-0.04	0.59	0.64	-0.05
0.92	0.88	0.04	0.73	0.84	-0.11
0.46	0.56	-0.1	0.8	0.85	-0.05
0.66	0.4	0.26	0.79	0.68	0.11
	P-value	0.272		P-value	0.252

KEYNOTE-407 ITT population (Squamous) US vs China

	Global ITT		China ITT		Δ (Global vs China)	
	P + C (n=278)	Chemo (n=281)	P + C (n=65)	Chemo (n=60)	P + C	Chemo
mOS (months)	17.1	11.6	30.1	12.7	-13.0	-1.1
HR (95% CI)	0.71 (0.69-0.88)		0.44 (0.28-0.70)		0.27	
mPFS (months)	8.0	5.1	8.3	4.2	-0.3	0.9
HR (95% CI)	0.57 (0.47-0.69)		0.35 (0.24-0.52)		0.22	
ORR	62.6%	38.4%	80.0%	43.3%	-17%	-5%

Bevacizumab US vs China

	Global		China		Δ (Global vs China)	
	B (n=444)	Pbo (n=434)	B (n=138)	Pbo (n=138)	Beva	Pbo
mOS (months)	12.3	10.3	24.3	17.7	-12.0	-7.4
HR (95% CI)	0.79 (0.67-0.92)		0.68 (0.50-0.93)		0.11	
mPFS (months)	6.2	4.5	9.2	6.5	-3.0	-2.0
HR (95% CI)	0.66 (0.57-0.77)		0.40 (0.29-0.54)		0.26	
ORR	35.0%	15.0%	54.0%	26.0%	-19%	-11%

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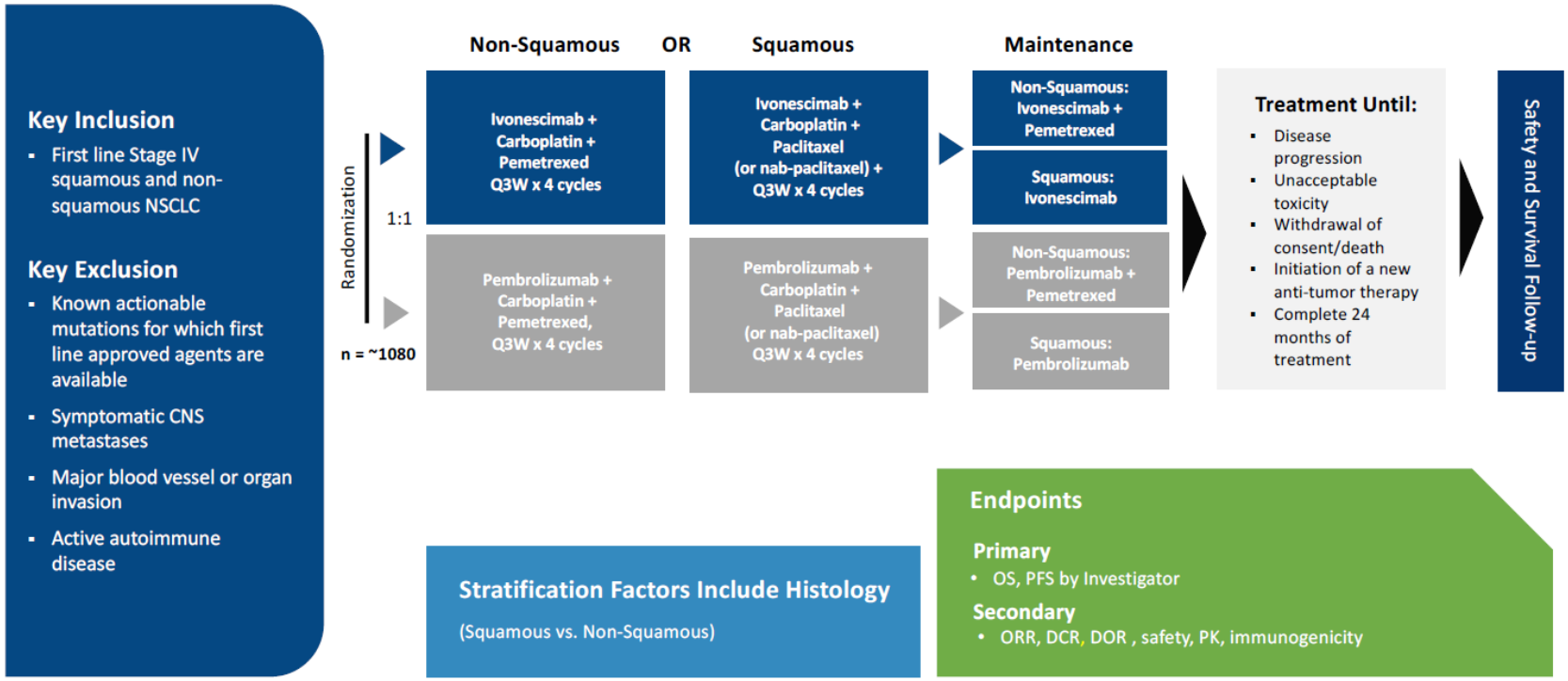
Source: Jefferies research

Top-line Data From China Ph3 HARMONi-6 Trial in 1L sqNSCLC

Jefferies

HARMONi-3: A Randomized PhIII Study Comparing Ivonescimab+Chemo with Pembrolizumab+Chemo in 1L sqNSCLC, Recently Expanded to Include nsqNSCLC

HARMONi-3 Trial Design



- The trial was sponsored by Summit and is being conducted globally
- Summit recently announced trial modification to add nsqNSCLC, which would triple the market opportunity as sqNSCLC is only ~30% of NSCLC (target enrollment increased from 400 to 1080)
- By indication size, HARMONi-3 now covers the broadest patient base in 1L NSCLC (both sq and nsq) and we know pembro+chemo was approved in 1L sq (KEYNOTE-407) and nsq (KEYNOTE-189)

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Source: Company presentation

HARMONi-6: A Randomized PhIII China Study Comparing Ivonescimab+Chemo with Tislelizumab+Chemo in 1L sqNSCLC

- The trial (also called AK112-306) is sponsored by Akeso and is being conducted in China with estimated completion of enrollment at YE24; Topline data is expected around YE25 or early 2026
- The trial differs from HARMONi-3: 1) uses Tislelizumab instead of Pembrolizumab in control arm (both are PD-1 mAbs), 2) primary endpoint is PFS vs OS and PFS, 3) only enrolled squamous NSCLC patients
- The trial has been relatively under the radar compared to HARMONi-2 in 1L PD-L1+ NSCLC and HARMONi-A in 2L+ EGFRm NSCLC. However, it is a directly relevant trial and could provide great readthrough to SMMT's HARMONi-3 trial

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Deal Summary and We See More to Come

Jefferies

BioNTech Buys Out China Partner; Merck Hops Onto the PD-(L)1xVEGF Train

Summary of PD-(L)1 x VEGF BsAb Deals

Announce Date	Partner	Company	Deal focus	Rights	Upfront ($MM)	Additional payments ($MM)	Royalties	China&Global trial status
Dec-22	Summit	Akeso	Ivonescimab/AK112 (PD-1 x VEGF-A)	US, Europe, Canada, Japan,Latin America, Middle East, and Africa	500	5,000	Low double-digit	China: first approval; Global: Ph3
Nov-23	BioNTech	Biotheus	BNT327/PM8002 (PD-L1 x VEGF-A)	Ex-Greater China	55	>1,000	Tiered low double-digit	China: Ph3 Global: Ph3
Nov-24	BioNTech	Biotheus	Acquisition	Full right	800	150		
Aug-24	Instil Bio	ImmuneOnco	IMM2510 (PD-L1 x VEGF-trap), IMM27M (anti-CTLA-4)	Ex-Greater China	50	2,100	single to low double-digit	China: Ph2 Global: Ph2 planned
Oct-24	GlycoMimetics	Crescent	CR-001 (PD-1xVEGF)		Reverser merger for $200M		NA	US IND filing 4Q25/1Q26
Nov-24	Merck	LaNova	LM-299 (PD-1 x VEGF)	Global	588	2,700	Not disclosed	US IND filing 2H24

China is leading the innovation in PD-(L)1xVEGF BsAb:

- SMMT's in-licensing deal of Akeso's ivonescimab/AK112 in Dec 2022 marks the first PD-(L)1x VEGF BsAb deal which was signed between a US and a Chinese company.
- Since then, five more deals have been announced, four of which are also in-licensing deals signed between US and Chinese companies.
- In Aug '24, TIL started new inning by licensing the ex-China rights of two assets: SYN/IMM-2510 (PD-L1xVEGF BsAb) and SYN/IMM-27M (Next-Gen anti-CTLA-4) from China-based ImmuneOnco through a ~$2B deal.
- Crescent is a private US company with a lead asset CR-001, a tetravalent PD-1xVEGF BsAb, in preclinical development. Company went public through a reverse merger with GlycoMimetics and expects to file an IND in 4Q25/1Q26.
- First large pharma inked a PD-(L)1xVEGF asset, LM-299, again from a Chinese company, LaNova Medicines. LM-299 is currently in a Ph1 China study and US IND filing was expected in 2H24.

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Source: Jefferies research; Clinicaltrials.gov; company presentation

11 More Assets in China and 3 In US/UK in the Race; We See More Deals Coming Likely from Biotech/Pharma with IO Assets

Additional PD-(L)1 x VEGF Assets						
Drug Name	Molecular Format	Phases	Indications	Sponsor	Start Date	Catalyst
HB0025	PD-L1 x VEGF	PHASE2	HCC	Huabo (China)	Jan-23	
SSGJ-707	PD-1xVEGF	PHASE2	Solid tumors	3SBio Guojian (China)	Jan-24	
AP505	PD-L1 x VEGF	PHASE2	Solid tumors	Tasly/Yuanxiang Life Tech (China)	Aug-24	
MHB039A	PD-1xVEGF	PHASE 1/2	Solid tumors	Minghui Pharma (China, private)	Dec-23	
SCTB14	PD-1xVEGF	PHASE 1/2	Solid tumors	Sinocelltech (China)	Mar-24	
AI-081	PD-1xVEGF	PHASE 1/2	Solid tumors	OncoC4 (US, private)	Dec-24	
RC148	PD-1 x VEGF (trap)	PHASE1	Solid tumors	RemeGen (China)	Sep-23	
JS207	PD-1 x VEGF	PHASE1	Solid tumors	Shanghai Junshi (China)	Sep-23	
DR30206	PD-L1 x VEGF x TGFb	PHASE1	Solid tumors	Zhejiang Doer Biologics (China, private)	Nov-23	
HC010	PD-1 x VEGF x CTLA-4	PHASE1	Solid tumors	HC Biopharma (China, private)	Mar-24	
SG1408	PD-L1 x VEGF	PHASE1	Solid tumors	SumGen Bio (China, private)	Nov-22	
CVL006	PD-L1 x VEGF	PHASE1	Solid tumors	Convalife (China, private)	Sep-24	
Jankistomig	PD-1 x VEGFR2	Pre-clinical		Ottimo Pharma (UK, private)		IND filing in late 2025
CR-001	PD-1 x VEGF	Pre-clinical		Crescent (US, private)		IND filing in 4Q25/1Q26

Potential Buyers with IO Assets						
Company	Market Cap ($B)	ICI Class	Drug name	Brand name	FY23 Sales	US Patent Expiry
Merck	$246	PD-1	Pembrolizumab	Keytruda	$25B	2028
Roche	$230	PD-L1	Atezolizumab	Tecentriq	$4.1B	2028
AstraZeneca	$196	PD-L1	Durvalumab	Imfinzi	$4.0B	2031
		CTLA-4	Tremelimumab	Imjuno	$218M	2031
BMS	$117	PD-1	Nivolumab	Opdivo	$9.0B	2028
		CTLA-4	Ipilimumab	Yervoy	$2.2B	2025
GSK	$69	PD-1	Dostarlimab	Jemperli	$141M	2034
Merck KGaA	$63	PD-L1	Avelumab	Bavencio	$751M	2036
Regeneron	$82	PD-1	Cemiplimab	Libtayo	$869M	2035
BeiGene	$22	PD-1	Tislelizumab	Tevimbra	$537M	2033

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Source: Jefferies research; Clinicaltrials.gov; company presentation

PD-(L)1 x VEGF BsAb Market Opportunity

Jefferies

Market Opportunity for PD-(L)1xVEGF Bispecifics

Cancer Type	PD-1 Approved	PD-L1 Approved	VEGF (BEV) Approved	Incidence (2024) (US&EU4, UK)	% of locally adv & metastatic	TAM (2024) (US&EU4, UK)	SMMT	Akeso	BNTX	TIL
Melanoma	x	x		202,147	15%	30,322				
Non-Small Cell Lung Cancer	x	x	x	398,845	70%	279,192	279,192	279,192	279,192	82,666
Small Cell Lung Cancer		x		70,384	70%	49,269		49,269	49,269	
Head and Neck Squamous Cell Carcinoma	x			134,362	70%	94,054		94,054		
Triple-Negative Breast Cancer	x			39,540	35%	13,839		13,839	13,839	13,839
Colorectal Cancer	x			412,776	60%	247,666		247,666		
Hepatocellular Carcinoma	x	x	x	86,986	45%	39,144		39,144	39,144	
Renal Cell Carcinoma	x	x		186,894	30%	56,068			56,068	
Gastric Cancer	x			81,328	60%	48,797				
Cervical Cancer	x		x	34,412	50%	17,206			17,206	
Endometrial Carcinoma	x			156,623	29%	45,421			45,421	
Merkel Cell Carcinoma	x	x		4,825	35%	1,689				
Biliary Tract Cancer	x	x		15,731	70%	11,011		11,011		
Bladder Cancer	x	x		204,127	40%	81,651				
Esophagus Cancer	x			44,140	70%	30,898		30,898		
Mesothelioma	x			9,618	75%	7,214			7,214	
Ovarian Cancer				49,398	75%	37,049		37,049	37,049	
Pancreatic Cancer				139,544	80%	111,635		111,635		
Total Eligible Patients						1,202,123	279,192	913,756	544,402	96,505
Market Opportunity						~$40B	~$10B	~$30B	~$20B	~$650M

We estimated potential market opportunity for PD-(L)1xVEGF bispecifics based on incidence in US and EU4 plus UK, and % of locally advanced and metastatic patients*:

- Our SMMT model only includes future revenue of ivonescimab in NSCLC, which we estimate ~$10B risk-adj (55-65% POS) peak sales; TIL model included 2L PD-L1+ NSCLC pts and 1L TNBC and we estimate ~$650M risk-adj (10% POS) peak sales
- If we include all the indications that China partner Akeso is pursuing, then the market opportunity will be ~3x at ~$30B
- Based on the indications that BNTX is pursuing, the market opportunity is ~2x at ~$20B
- If we include all the indications that PD-(L)1 have gained approval, the market opportunity will be ~4x at >$40B

** For simplified estimation for Akeso and BNTX, we did not delve into lines of therapy, probability of success, or market penetration for each indication*

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Source: Jefferies research;. NCI SEER, ECIS, company presentation

Market Movement on Key Data Drops in 2024; We Believe the Trend will Continue on Positive Data in 2025

May 30, 2024
HARMONi-2 announced positive top line

Sep 9, 2024
HARMONi-2 data at WCLC

Dec 31, 2024

- HARMONi-2 data drop led to stock jump:
  - SMMT up ~150% (+$13B)
  - BNTX up ~40% (+$9B)
  - TIL up ~500% (+$450M)
- And as of Dec 31st, 2024, compared to pre-HARMONi-2 data, stocks are valued at
  - SMMT up ~50% (+$4B)
  - BNTX up ~30% (+$6B)
  - TIL up ~40% (+$40M)

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Source: Jefferies research

PD-(L)1 x VEGF Trial Summary

Jefferies

Development Progress of The Three US PD-(L)1 x VEGF BsAb Assets in Clinic and Their Catalysts

- Akeso gains the first approval of ivonescimab plus chemo in 2L+ post-TKI EGFRm NSCLC based on HARMONi-A trial (PFS HR 0.46, OS HR 0.8) in China in May 2024
- For global trials, SMMT and TIL initially focus on NSCLC, and BNTX elected NSCLC, SCLC and TNBC
- **For NSCLC, BNTX is ~1.5+ years behind Summit, TIL is ~3+ years behind**
- Triple-targeting combos with CD47, CTLA-4, TIGIT, TROP2, HER2, B7-H3, etc are on the way
- **We expect several Ph3 data updates from mid-2025 to 2026**

Phases	Ongoing/Planned Trials	Sponsor	Start Date	Catalyst (Est.)
Summit/Akeso				
PHASE3	HARMONi-3: Ivonescimab vs Pembrolizumab (chemo combo) in 1L NSCLC (sq+nsq)	Summit (Global)	Oct-23	
PHASE3	HARMONi: Ivonescimab in 2L post-TKI EGFRm NSCLC	Summit (Global)	May-23	Data mid-2025
PHASE3	HARMONi-7: Ivonescimab in 1L PD-L1 TPS ≥50% NSCLC	Summit (Global)	Planned initiation early 2025	
PHASE3	HARMONi-2: Ivonescimab in 1L PD-L1 TPS ≥1% NSCLC	Akeso (China)	Nov-22	OS data YE25/early 2026 (E)
PHASE3	HARMONi-A: Ivonescimab in 2L post TKI EGFRm NSCLC	Akeso (China)	Jan-22	
PHASE3	HARMONi-6: Ivonescimab vs Tislelizumab (chemo combo) in 1L sqNSCLC	Akeso (China)	Aug-23	YE25/early 2026 (E)
PHASE3	HARMONi-GI-01: Ivonescimab vs Durvalumab (chemo combo) in 1L BTC	Akeso (China)	Oct-24	
PHASE3	AK117-302: Ivonescimab+ AK117 (CD47) vs Pembrolizumab in R/M HNSCC	Akeso (China)	Oct-24	
PHASE3	1L HNSCC, 1L PDAC	Akeso (China)	Planned	
PHASE2	Ivonescimab in resectable NSCLC	Akeso (China)	Feb-22	
PHASE2	Ivonescimab + chemo in 1L or 2L NSCLC	Akeso (China)	Feb-21	
PHASE1/2	Ivonescimab + cadonilimab (PD1/CTLA4 BsAb) + chemo in 1L NSCLC	Akeso (China)	Jul-23	
PHASE2	Ivonescimab in unresectable HCC	Akeso (China)	2022-08	
PHASE2	Ivonescimab + cadonilimab (PD1/CTLA4 BsAb) in 2L HCC	Akeso (China)	Jan-24	
PHASE2	Ivonescimab + cadonilimab (PD1/CTLA4 BsAb) in recurrent ovarian cancer	Akeso (China)	Sep-24	
PHASE2	Ivonescimab + chemo +/- AK117 (CD47) in TNBC	Akeso (China)	Mar-22	
PHASE1/2	Ivonescimab + AK119 (CD73) in CRC	Akeso (China)	May-23	
PHASE1/2	Ivonescimab + AK119 (CD73) in solid tumors	Akeso (China)	Apr-23	
PHASE1/2	Ivonescimab + AK127 (TIGIT) in solid tumors	Akeso (China)	2023-07	
PHASE1/2	Ivonescimab in solid tumors	Akeso (China)	Jan-22	
PHASE1/2	Ivonescimab +/- AK117 (CD47) or +/- chemo in solid tumors	Akeso (China)	Jan-22	
PHASE2	Ivonescimab in cutaneous squamous cell carcinoma	MD Anderson	Dec-24	
PHASE1/2	Ivonescimab in 2L glioblastoma	MD Anderson	Apr-25	
BioNTech/Biotheus				
PHASE3	BNT327 vs Atezolizumab (chemo combo) in 1L ES-SCLC	BioNTech (Global)	Dec-24	
PHASE2/3	BNT327 vs Pembrolizumab (chemo combo) in 1L NSCLC	BioNTech (Global)	Dec-24	
PHASE3	1L TNBC	BioNTech (Global)	Planned initiation in 2025	
PHASE2	BNT327 + chemo in TNBC	BioNTech (Global)	Aug-24	
PHASE2	BNT327 + chemo in SCLC	BioNTech (Global)	Aug-24	
PHASE1/2	BNT327 + DB-1305 (TROP2-ADC) in solid tumors	BioNTech (Global)	Jul-22	
PHASE1/2	BNT327 + DB-1311 (B7-H3-ADC) in solid tumors	BioNTech (Global)	Planned initiation in 2025	
PHASE1/2	BNT327 + DB-1303 (HER2-ADC) in solid tumors	BioNTech (Global)	Planned initiation in 2025	
PHASE3	PM8002 + chemo vs chemo in 1L TNBC	Biotheus (China)	Jun-24	Data mid-2027 (E)
PHASE3	PM8002 + chemo vs chemo in 2L SCLC	Biotheus (China)	Nov-24	Data 2H26 (E)
PHASE2/3	PM8002 vs Atezolizumab (chemo combo) in 1L ES-SCLC	Biotheus (China)	Jun-23	Data 2025 (E)
PHASE2/3	PM8002 + chemo vs chemo in 2L+ EGFRm NSCLC	Biotheus (China)	Jun-23	Data 2025 (E)
PHASE2	PM8002 + chemo in SCLC	Biotheus (China)	May-22	Data 2025
PHASE2	PM8002 + chemo in 1L HCC	Biotheus (China)	Apr-22	
PHASE2	PM8002 + chemo in neuendocrine neoplasm	Biotheus (China)	May-23	
PHASE2	PM8002 + chemo in unresectable mesothelioma	Biotheus (China)	Aug-22	
PHASE1/2	PM8002 in solid tumors	Biotheus (China)	Mar-21	
PHASE1/2	PM8002 + PM1009 (TIGIT x PVRIG BsAb) in 1L HCC	Biotheus (China)	2024-10	
PHASE1/2	PM8002 + chemo in 1L TNBC	Biotheus (China)	Jul-22	
Instil/ImmuneOnco				
PHASE2	IMM2510 in 2L+ NSCLC	Instil (Global)	Planned initiation 2H25	
PHASE2	IMM2510 + chemo in 1L NSCLC or TNBC	ImmuneOnco (China)	Dec-24	
PHASE1	IMM2510 in solid tumors (STS, NSCLC, HCC, TNBC)	ImmuneOnco (China)	Aug-21	Data 1H25
PHASE1/2	IMM2510 + IMM27M (CTLA-4) in 2L HCC and TNBC	ImmuneOnco (China)	Jul-24	

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Source: Jefferies research; Clinicaltrials.gov; company presentation

PD-(L)1 x VEGF BsAb Data Summary

Jefferies

We Summarized All Clinical Data So Far from Three Assets

Company	Summit (partner Akeso)	BioNTech (partner Biotheus)	Instil Bio (partner ImmuneOnco)
Drug name	Ivonescimab/AK112	BNT327/PM8002	SYN-2510/IMM2510
MOA	PD-1 x VEGF-A	PD-L1 x VEGF-A	PD-L1 x VEGF (Trap_R1D2)
RP2D	20mg/kg Q3W	20mg/kg Q2W and 30mg/kg Q3W	20mg/kg Q2W
Efficacy (Monotherapy)			
Dose-esc in solid tumors	n=47, ORR 26%, DCR 64% (not all RP2D)★	n=254, ORR 16%, DCR 74%, mDOR 7.4m, mPFS 5.6m (Majority at or above RP2D)	n=25, ORR 12% (3PRs, 2 sqNSCLC, 1 thymus carcinoma) and 7SDs (not all RP2D)
Resectable NSCLC	n=11, ORR 82%, DCR 91%, pCR 30%, MPR 60%		
1L PD-L1+ NSCLC w/o EGFR/ALK	n=35, ORR 60%, DCR 97% *Ph3 HARMONi-2, ivo vs pembro:* mPFS 11.1 vs 5.8m, HR 0.51, P<0.0001 ORR 50% vs 39%, DCR 90% vs 71%, mDOR NR	n=17, ORR 47% (1uPR), DCR 100%, mPFS 13.6m, mOS 13.9m	
2L+ NSCLC w/o EGFR/ALK		n=8, ORR 13%, DCR 63%, mDOR 3.7m, mPFS 6.7m, mOS 9.4m	
1L nccRCC		n=22, ORR 36% (1uPR), DCR 91%, mPFS 15.1m	
2L+ ccRCC		n=28, ORR 25%, DCR 79%, mPFS 10.9m	
2L+ RCC			
2L+ Cervical cancer		n=45, ORR 42%, DCR 93%, mPFS 8.3m	
1-2L PROC		n=34, ORR 21%, DCR 68%, mDOR 9.6m, mPFS 5.5m, mOS 11.6m	
Efficacy (Chemo combo)			
Resectable NSCLC	n=49, ORR 82%, DCR 91%, pCR 44%, MPR 72%		
1L NSCLC w/o EGFR/ALK	squamous n=63, ORR 71%, DCR 91%, mDOR 12.7m non-squamous n=72, ORR 54%, DCR 96%, mDOR 15.4m		
2L+ NSCLC	n=20, ORR 40%, DCR 80%, mPFS 6.6m		
2L+ EGFRm nsqNSCLC (post TKI)	n=19, ORR 68%, DCR 95%, mPFS 8.2m *Ph3 HARMONi-A, ivo + chemo vs chemo:* mPFS 7.1 vs 4.8m, HR 0.46, P<0.001 mOS 17.1 vs 14.5m, HR 0.80 (52% maturity) ORR 51% vs 35%, DCR 93% vs 83%, mDOR 6.6m vs 4.2m	n=64, ORR 58%, DCR 95%	
2L SCLC		ITT n=36, ORR 61%, DCR 86%, mDOR 10.0m, mPFS 5.5m IO-naïve, n=22, ORR 73%, DCR 82%, mDOR 10.0m, mPFS 5.9m IO-treated, n=14, ORR 43%, DCR 93%, mDOR 2.6m, mPFS 3.9m	
1L TNBC	n=35, ORR 80%, DCR 100%, mDOR 7.5m, mPFS 9.4m	n=42, ORR 74%, DCR 95%, mDOR 11.7m, mPFS 13.5m, mOS NR	
1L Biliary tract cancer	n=22, ORR 64%, DCR 100%, mPFS 8.5m, mOS 16.8m		
Efficacy (other combos)			
1L PD-L1+ HNSCC	mono or combo w/ ligufalimab (CD47) mono: n=10, ORR 30%, DCR 80%, mPFS 5.0m combo: n=20, ORR 60%, DCR 90%, mPFS 7.1m		
1L CRC	ivo + FOLFOXIRI +/- ligufalimab (CD47) - ligufalimab, n=22, ORR 82%, DCR 100% + ligufalimab, n=17, ORR 88%, DCR 100%		

- Almost all the data we have seen so far are from China except one trial marked with ★ in the table
- Indications with red border will be discussed in detail in following slides

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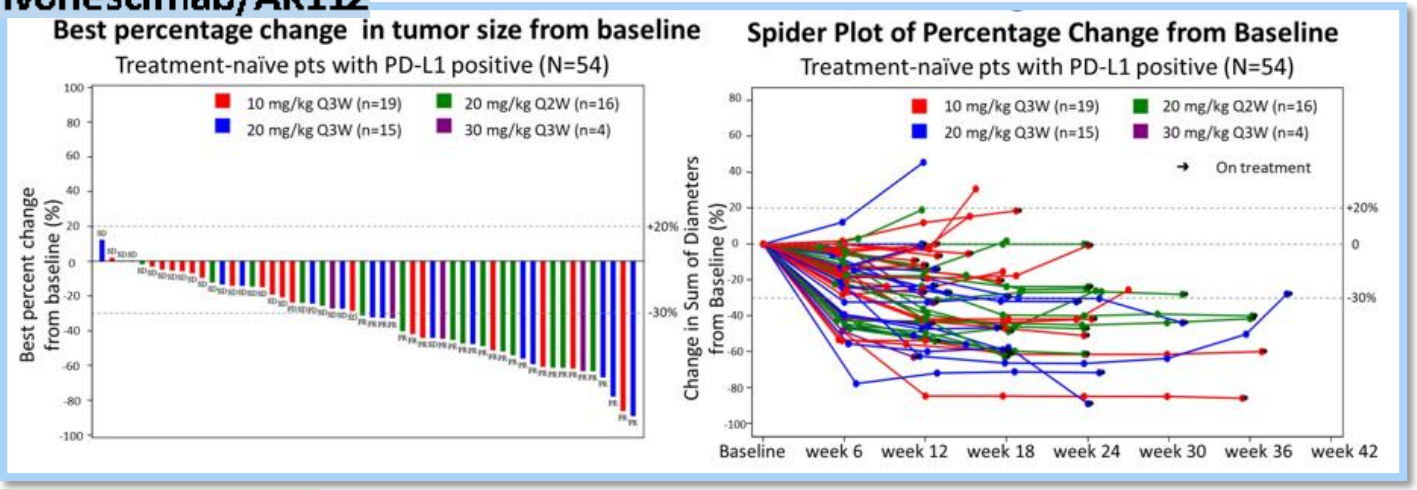
Source: Company data; Jefferies research

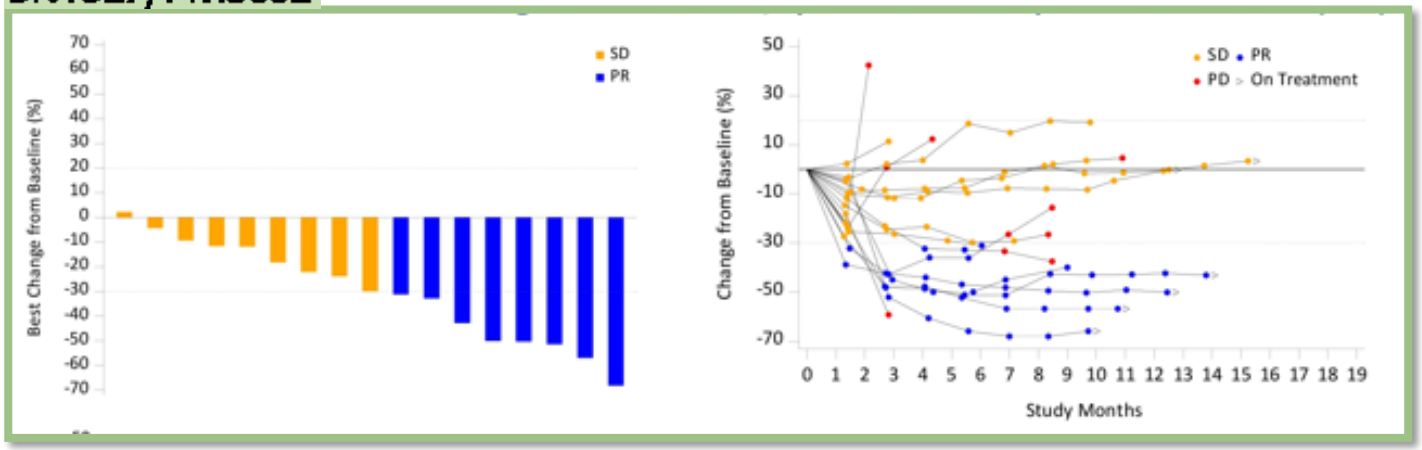
Ivonescimab ORR Looks Slightly Better than BNT327 as Monotherapy in 1L PD-L1+ NSCLC

Drug name	Company	MOA	Dose	n	ORR	DCR	mPFS	mOS	Source
Ivonescimab/AK112	Summit/Akeso	PD-1 x VEGF-A	>10mg/kg Q3W	**35**	**60%**	**97%**			ASCO 2022
BNT327/PM8002	BioNTech/Biotheus	PD-L1 x VEGF-A	20mg/kg Q2W	**17**	**47% (1uPR)**	**100%**	**13.6 m**	**13.9 m**	ASCO 2024

Ivonescimab/AK112



BNT327/PM8002



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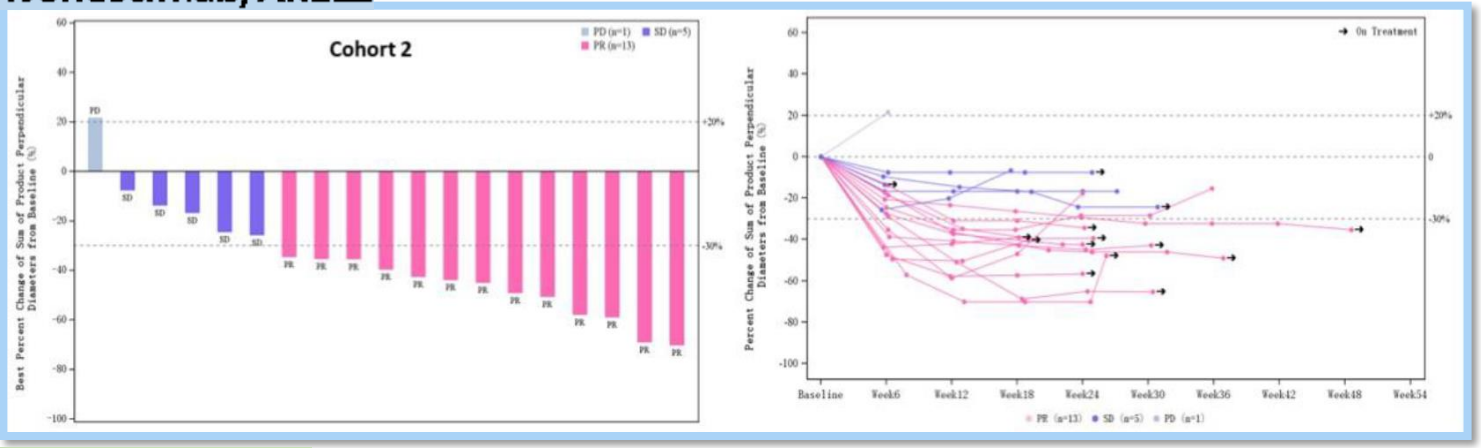
Source: Jefferies research; Conference presentations

Jefferies

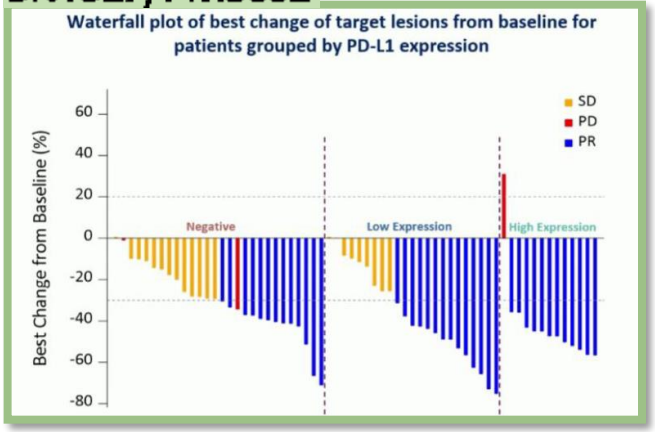
Ivonescimab ORR Also Looks Slightly Better than BNT327 when Combined with Chemo in 2L+ EGFRm nsqNSCLC (post TKI)

Drug name	Company	Combo	Dose	n	ORR	DCR	mPFS	mOS	Source
Ivonescimab/AK112	Summit/Akeso	plus chemo	20mg/kg Q3W	**19**	**68%**	**95%**	**8.2 m**		ASCO 2022
BNT327/PM8002	BioNTech/Biotheus	plus chemo	30mg/kg Q3W	**64**	**58%**	**95%**			ESMO 2024

Ivonescimab/AK112



BNT327/PM8002



Response Assessment	Overall n=64	PD-L1 negative n=28	PD-L1 low expression n=23	PD-L1 high expression n=13
ORR by investigator, n (%) [95% CI]	39 (60.9) [47.9,72.9]	13 (46.4) [27.5,66.1]	14 (60.9) [38.5,80.3]	12 (92.3) [64.0,99.8]
Confirmed ORR by investigator, n (%) [95% CI]	37 (57.8) [44.8,70.0]	11 (39.3) [21.5,59.4]	14 (60.9) [38.5,80.3]	12 (92.3) [64.0,99.8]
Best overall response, n (%)				
PR	37 (57.8)	11 (39.3)	14 (60.9)	12 (92.3)
SD	24 (37.5)	15 (53.6)	9 (39.1)	0 (0)
PD	3 (4.7)	2 (7.1)	0 (0)	1 (7.7)
DCR, n (%) [95% CI]	61 (95.3) [86.9,99.0]	26 (92.9) [76.5,99.1]	23 (100) [85.2,100.0]	12 (92.3) [64.0,99.8]
Median TTR, months [95% CI]	2.9 [1.5,4.1]	5.8 [2.7, NE]	2.9 [1.4, NE]	1.6 [1.5,2.9]

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Source: Jefferies research; Conference presentations

Ivonescimab and BNT327 Chemo Combo ORR Data in 1L TNBC is Largely Similar with Some Differences in Subgroups (Higher in PD-L1 Low, but Lower in PD-L1 High)

Drug name	Company	Combo	Dose	n	ORR	DCR	mDOR	mPFS	mOS	Source
Ivonescimab/AK112	Summit/Akeso	plus chemo	20mg/kg Q3W	**35**	**80%**	**100%**	**7.5 m**	**9.4 m**		SABCS 2024
				29	**72%**	**100%**		**9.3 m**		ESMO 2024
BNT327/PM8002	BioNTech/Biotheus	plus chemo	20mg/kg Q2W	**42**	**74%**	**95%**	**11.7 m**	**13.5 m**		SABCS 2024
				42	**74%**	**95%**	**11.7 m**	**13.5 m**		ESMO 2024

Ivonescimab/AK112

	All patients N = 35[a]	PD-L1 CPS ≥10 n = 6	PD-L1 CPS <10 n = 29	PD-L1 CPS <1 n = 17
ORR, % (95% CI)	80.0 (63.1-91.1)	83.3 (35.9-99.6)	79.3 (60.3-92.0)	88.2 (63.6-98.5)
BOR, n (%)				
CR	2 (5.7)	1 (16.7)	1 (3.4)	0
PR	26 (74.3)	4 (66.7)	22 (75.9)	15 (88.2)
SD	7 (20.0)	1 (16.7)	6 (20.7)	2 (11.8)
DCR, % (95% CI)	100.0 (90.0-100.0)	100.0 (54.1-100.0)	100.0 (88.1-100.0)	100 (80.5-100.0)
DOR				
Median, months (95% CI)	7.49 (5.32-NE)	NR (3.58-NE)	7.49 (3.91-NE)	7.49 (3.45-NE)
6-month DOR rate, % (95% CI)	72.2 (45.4-87.4)	80.0 (20.4-96.9)	70.0 (38.2-87.6)	64.2 (30.2-84.8)
PFS				
Median, months (95% CI)	9.36 (6.24-NE)	NR (5.36-NE)	9.30 (5.55-NE)	9.30 (5.26-NE)
6-month PFS rate, % (95% CI)	73.8 (52.7-86.6)	83.3 (27.3-97.5)	71.2 (46.6-86.0)	70.0 (38.2-87.6)
9-month PFS rate, % (95% CI)	61.3 (39.7-77.1)	66.7 (19.5-90.4)	59.8 (35.0-77.7)	61.3 (30.0-81.9)

BNT327/PM8002

Variable	ITT	PD-L1 CPS<1	PD-L1 1≤CPS<10	PD-L1 CPS≥10	NOT DONE
Population (n)	42	13	16	9	4
CR	1 (2.4)	0	1 (6.3)	0	0
PR	32 (76.2)	10 (76.9)	10 (62.5)	9 (100)	3 (75.0)
SD	7 (16.7)	3 (23.1)	4 (25.0)	0	0
PD	2 (4.8)	0	1 (6.3)	0	1 (25.0)
ORR %	78.6	76.9	68.8	100	75.0
(95% CI)	(63.2, 89.7)	(46.2, 95.0)	(41.3, 89.0)	(66.4, 100)	(19.4, 99.4)
cORR %	73.8	76.9	56.3	100	75.0
(95% CI)	(58.0, 86.1)	(46.2, 95.0)	(29.9, 80.3)	(66.4, 100)	(19.4, 99.4)
DCR %	95.2	100	93.8	100	75.0
(95% CI)	(83.8, 99.4)	(75.3, 100)	(69.8, 99.8)	(66.4, 100)	(19.4, 99.4)
mPFS	13.5	18.1	14.0	10.8	14.0
(Mo), (95%CI)	(9.4, 19.3)	(5.7, --)	(7.2, --)	(5.5, 13.5)	(1.8, --)
12-mo OS rate%	80.8	76.9	80.8	77.8	100
(95%CI)	(65.3, 89.9)	(44.2 ,91.9)	(51.4, 93.4)	(36.5, 93.9)	(100, 100)
15-mo OS rate%	78.1	76.9	72.7	77.8	100
(95%CI)	(62.1, 88.0)	(44.2, 91.9)	(42.0, 88.9)	(36.5, 93.9)	(100, 100)
18-mo OS rate%	69.7	76.9	64.6	55.6	100
(95%CI)	(52.7, 81.6)	(44.2, 91.9)	(34.1, 83.8)	(20.4, 80.5)	(100, 100)

We Also Compared Key Safety Data –Ivonescimab Appears Consistently Better than BNT327

Company	Summit (partner Akeso)					BioNTech (partner Biotheus)		
Drug name	Ivonescimab/AK112					BNT327/PM8002		
MOA	PD-1 x VEGF-A					PD-L1 x VEGF-A		
ADCC	Silenced					Silenced		
Indication	1l NSCLC	2L+ EGFRm NSCLC	NSCLC	NSCLC	1L TNBC	1L TNBC	2L+ EGFRm NSCLC	NSCLC
Trial	HARMONi-2	HARMONi-A	Ph2	Ph1	Ph2	Ph2	Ph2	Ph1/2
Comparison arms	ivo vs pembro	ivo+chemo vs chemo	ivo+chemo	mono	ivo+chemo	PM8002+chemo	PM8002+chemo	mono
Treatment Dose	20mg/kg Q3W	20mg/kg Q3W	20mg/kg Q3W	10-30mg/kg Q2/3W	20mg/kg Q3W	20mg/kg Q2W	30mg/kg Q3W	20mg/kg Q2W
TRAE % (Any Grade/Grade≥3)	**90/29 vs 82/16**	**98/54 vs 95/43**	**86/24**	**89/14**	**100/50**	**100/60**	**98/61**	**85/20**
Leading to discontinuation %	1.5 vs 3.0	5.6 vs 2.5	3.6	0	0	9.5	14.2	8.2
Leading to death %	0.5 vs 1.0	0 vs 0	1.2	0	0		1.6	0
irAEs % (Any Grade/Grade≥3)	**30/7 vs 28/8**	**24/6 vs 6/3**		**NA**	**NA**	**31/10**	**41/6**	**39/NA**
VEGF-Related AEs % (Any Grade/Grade≥	**48/10 vs 21/1**	**NA/3 vs NA/3**		**NA**			**NA/11**	
Proteinuria	32/3 vs 10/0	17/1 vs 8/0		20/1	<20	64/NA	39/NA	54/5
Hypertension	16/5 vs 3/1	8/2 vs 3/2		16/1	<20	24/NA	22/NA	25/10
Haemorrhage	15/1 vs 11/1	7/0 vs 5/0	29/NA					
Arterial thromboembolism	1/1 vs 1/0	1/0 vs 1/1						
Venous thromboembolism	0/0 vs 1/0							

We compared safety data of Ivonescimab and BNT327 (SYN2510 has only limited data in early dose-escalation), with a focus on NSCLC and TNBC as they have the most comparable data sets:

- As a monotherapy for NSCLC, ivo showed lower VEGF-related TRAEs (all grade/Gr3+: 20%/1% vs 54%/5% proteinuria, 16%/1% vs 25%/10% hypertension) and lower dose discontinuation (0% vs 8.2%)
- When combined with chemo, ivo appears to have lower irAEs (all grade: 24% vs 41% in 2L+ EGFRm NSCLC), and lower VEGF-related TRAEs (Gr3+: 3% vs 11% in 2L+ EGFRm NSCLC), as well as lower dose discontinuation (5.6 % vs 14.2% in 2L+ EGFRm NSCLC, and 0% vs 9.5% in 1L TNBC)

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Source: Jefferies research; company presentation

To Summarize, Available Data to Date Suggest Ivonescimab is Slightly Better in Efficacy with Potentially Differentiated Safety Compared to BNT327

- Ivonescimab ORR data looks slightly better than BNT327 as monotherapy in 1L PD-L1+ NSCLC
- Ivonescimab ORR data also looks slightly better than BNT327 when combined with chemo in 2L+ EGFRm nsqNSCLC (post TKI)
- ORR data of Ivonescimab and BNT327 when combined with chemo is largely similar in 1L TNBC with some differences in subgroups (higher ORR in PD-L1 low, but lower in PD-L1 high)
- **Ivonescimab appears to have better tolerability than BNT327, both as monotherapy and in combination with chemotherapy, with lower rates of irAEs and VEGF-related AEs, as well as lower rates of TRAE-led dose discontinuations, which is an important differentiator when combined with other novel agents such as ADCs**
- We note BioNTech is testing BNT327 in two RP2Ds (20mg/kg Q2W and 30mg/kg Q3W) in various indications, and the data so far suggest Ivonescimab (20mg/kg Q3W) having a more favorable therapeutic window

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Could TIL's SYN-2510 Molecular Design Differentiate?

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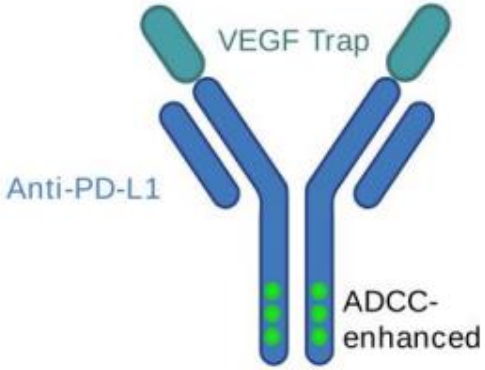
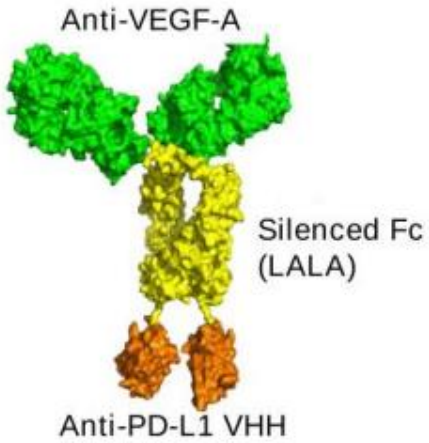
Could SYN-2510 Molecular Design Differentiate from BNT327 and Ivonescimab?

Key Competitor Landscape

	SYN-2510	BNT327 (Biotheus / BioNTech)	Ivonescimab (Akeso / Summit)
VEGF binding	VEGF-A, VEGF-B, PLGF	VEGF-A	VEGF-A
PD-1 or PD-L1	PD-L1	PD-L1	PD-1
ADCC	Enhanced ADCC	None	None
Key clinical data	Multiple responses in patients w/ prior PD-1 in Phase 1a trial	1L NSCLC: 47% ORR 1L TNBC: 79% ORR 2L SCLC: 61% ORR	Superiority over Keytruda® in 1L NSCLC Approved in 2L EGFRm NSCLC





InstilBio

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Kelly Shi, Ph.D., Equity Analyst, (212) 336-6937, kshi@jefferies.com
Source: Instil Bio corporate presentation Sept 2024

How Could SYN-2510 Molecular Design Differentiate?

We present three hypotheses based on SYN-2510's molecular structure:

Hypothesis 1 – Broader VEGF blockade by VEGF-trap could enhance anti-tumor efficacy

Hypothesis 2 – Intact Fc could induce ADCC and generate better efficacy

Hypothesis 3 – PD-L1 is better than PD-1 when combining with VEGF as bispecifics

We discuss each hypothesis…

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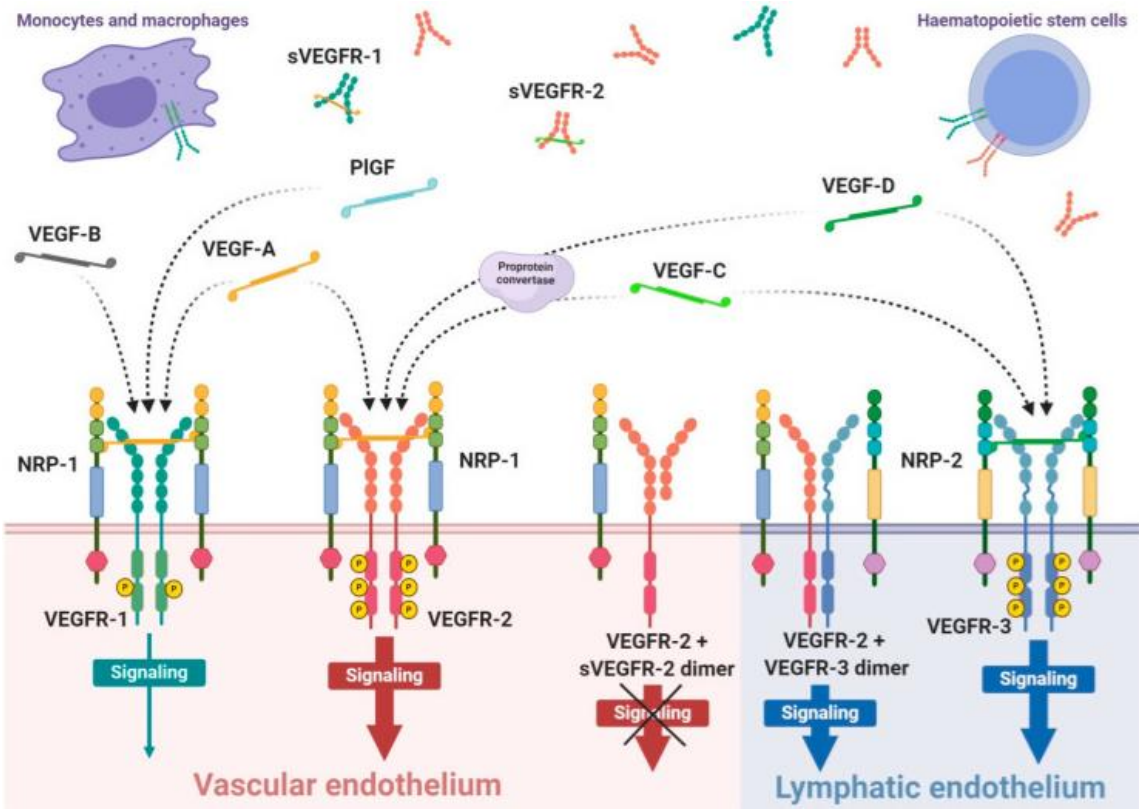
VEGF-A Has Been the Key Target in the VEGF Family for Anti-Angiogenic Therapy

- The VEGF family includes VEGF-A, -B, -C, -D and PlGF.
- VEGF receptors include VEGFR-1, R-2, R-3
- VEGF ligands and receptors are active as dimers
- **VEGF-A is the most well-studied member and key target for anti-angiogenic therapies, and it signals primarily through VEGF-R2**
- Soluble receptors (sVEGFR-1, sVEGFR-2) can act as decoy (high affinity but incapable of signaling, also called trap)



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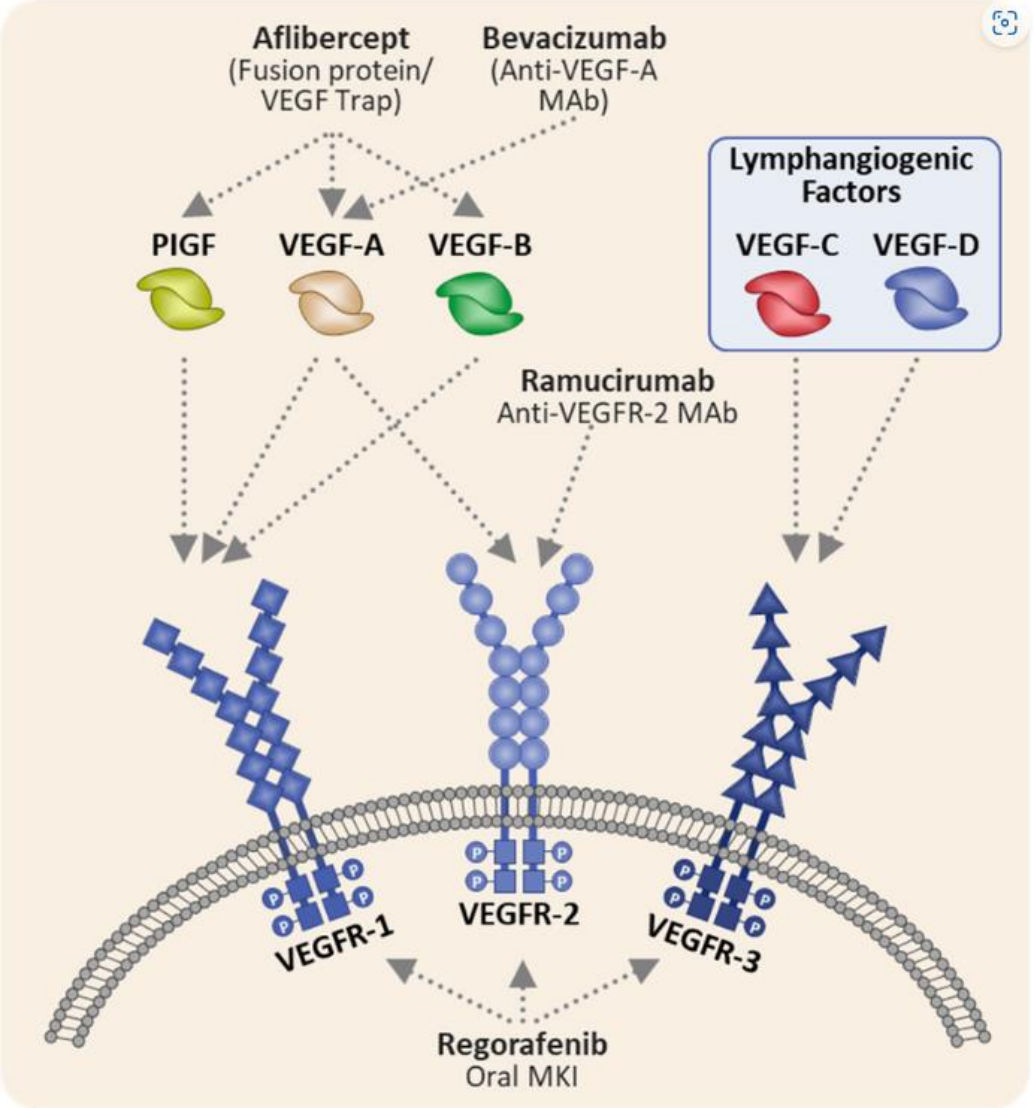
Source: Katarzyna M. et al. Cancers. 2021

We See Different MOAs of Anti-Angiogenic Therapies Approved in Cancer (Take Metastatic Colorectal Cancer as an Example)

- **Avastin (bevacizumab, anti-VEGF-A mAb)** is the first drug approved that targets angiogenesis (first approval in Feb 2004 for metastatic CRC)

- Drugs with other MOA were also approved in CRC including:

- **Zaltrap (ziv-aflibercept, VEGF-trap blocks VEGF-A, VEGF-B, PlGF)**
- Cyramza (ramucirumab, anti-VEGFR-2 mAb)
- Stivarga (regorafenib, oral multi-kinase inhibitor)



Source: Muro K. et al. Cancers. 2020

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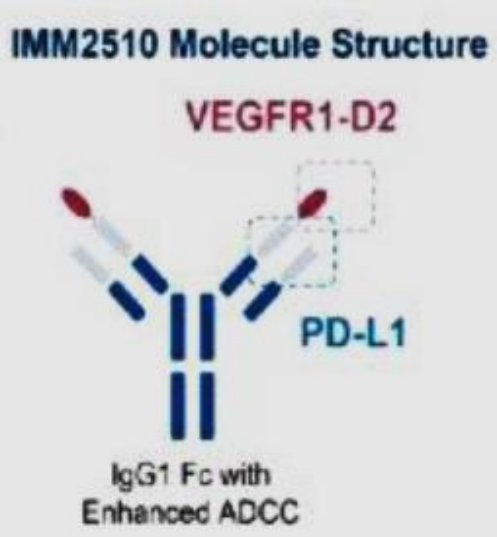
Ivonescimab and BNT327 Employed VEGF mAb, while IMM2510 Uses a VEGF-Trap Construct (Similar to Zaltrap)

- IMM2510 molecule used VEGF-Trap instead of VEGF mAb (bevacizumab)
- IMM2510 contains two VEGFR1-D2s (VEGF-Trap), each linked via a GS-linker, to the N-terminal of each heavy chain of an anti-PD-L1 antibody. VEGFR1-D2 is one type of VEGF-Trap that contains the second Ig domain of VEGFR1 (one receptor of VEGF)
- We note VEGFR1-D2 is different from Zaltrap (VEGFR1D2-R2D3), but they both belong to VEGF-trap category
- Limited preclinical data found with VEGFR1-D2 Trap, thus we use Zaltrap as an analog for efficacy comparison with bevacizumab



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Source: Company presentation; ASCO 2023

Zaltrap (VEGF-Trap) Binds to VEGF-A ~100x Than Bevacizumab and Zaltrap Also Binds to VEGF-B and PlGF

- Bevacizumab only blocks VEGF-A

- Zaltrap (here called VEGF Trap) blocks VEGF-A, VEGF-B, and PlGF

- Comparing to the binding affinity (K_D), Zaltrap binds to VEGF-A_{165} ~100x tighter than bevacizumab (VEGF-A_{165} is the predominant VEGF-A isoform) [1]

Table 1 Kinetic binding parameters for VEGF Trap, ranibizumab and bevacizumab binding to human VEGF family ligands determined by SPR-Biacore

VEGF inhibitor	Ligand	Kinetic binding parameters		
		$k_a/10^5$ (M^{-1} s^{-1})	$k_d/10^{-5}$ (s^{-1})	K_D (pM)
VEGF Trap[a]	VEGF-A_{121}	375.0 (5.0)	1.35 (.02)	0.360
VEGF Trap[a]	VEGF-A_{165}	410.0 (10.0)	2.01 (.01)	0.490
Ranibizumab[b]	VEGF-A_{165}	1.6 (0.003)	0.73 (.005)	46
Bevacizumab[a]	VEGF-A_{165}	5.3 (0.01)	3.10 (.02)	58
hVEGFR1-Fc[a]	VEGF-A_{165}	300.0 (20.0)	28.0 (1.0)	9.33
hVEGFR2-Fc[a]	VEGF-A_{165}	152.0 (5.0)	135 (6.0)	88.8
VEGF Trap[a]	PlGF-2	17.5 (0.06)	6.81 (.03)	38.9
Ranibizumab[b]	PlGF-2	NB	NB	NB
Bevacizumab[a]	PlGF-2	NB	NB	NB
VEGF Trap[a]	VEGF-$B_{(10-108)}$	352.0 (3.0)	6.74 (.09)	1.92

Numbers in parentheses represent the standard error of the kinetic fit

NB No binding under assay conditions used

[a] VEGF inhibitor captured on a Protein A-coupled sensor chip

[b] VEGF inhibitor captured on an anti-human Fab polyclonal antibody-captured sensor chip

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Source: [1] Papadopoulos N. et al. Angiogenesis 2012.

However, Bevacizumab Works Better Than Zaltrap in Cancer

We summarize all the approved anti-angiogenic therapies in cancer:

- Avastin (only blocks VEGF-A) has been approved in 7 cancer types, yet Zaltrap (blocks VEGF-A, -B, PlGF with higher affinity) was only approved in CRC in 2012, and failed in pivotal trials in NSCLC (VITAL: PFS HR 0.82, OS HR 1.01), CRPC (VENICE: PFS HR 0.84, OS HR 0.94), and pancreatic cancer (AFFIRM: PFS HR 0.93, OS HR 1.065), and was not advanced to pivotal trials in PROC, RCC and TNBC.

Drug name	Company	Mechanism	Approved cancer type (mono or combo)	Approved with PD-(L)1 combo
Bevacizumab (Avastin)	Genentech/Roche	Monoclonal antibody targeting VEGF-A	CRC, NSCLC, RCC, glioblastoma, ovarian cancer, cervical cancer, HCC	Atezolizumab in NSCLC and HCC, pembrolizumab in cervical cancer
Ziv-aflibercept (Zaltrap)	Sanofi	VEGF-trap fusion protein (VEGF-A, VEGF-B, PlGF)	CRC	
Ramucirumab (Cyramza)	Eli Lilly	Monoclonal antibody targeting VEGFR-2	Gastric cancer, NSCLC, CRC, HCC	
Sunitinib (Sutent)	Pfizer	Multikinase inhibitor (VEGFR1-3, PDGFR, FLT3)	GIST, RCC, NETs in pancreas	
Sorafenib (Nexavar)	Bayer/Onyx	Multikinase inhibitor (VEGFR1-3, PDGFR, RAF, KIT)	RCC, HCC, thyroid cancer	
Pazopanib (Votrient)	GSK	Multikinase inhibitor (VEGFR1-3, PDGFR, KIT, FGFR)	RCC, soft tissue sarcoma	
Axitinib (Inlyta)	Pfizer	Multikinase inhibitor (VEGFR1-3)	RCC	Pembrolizumab in RCC, avelumab in RCC
Regorafenib (Stivarga)	Bayer	Multikinase inhibitor (VEGFR1-3, TIE2, PDGFR, FGFR, KIT, RET, RAF)	CRC, GIST, HCC	
Cabozantinib (Cabometyx)	Exelixis/Ipsen	Multikinase inhibitor (VEGFR2, MET, RET, KIT, FLT3, AXL)	RCC, HCC, thyroid cancer	Nivolumab in RCC
Lenvatinib (Lenvima)	Eisai	Multikinase inhibitor (VEGFR1-3, PDGFR, FGFR, KIT, RET)	Thyroid cancer, RCC, HCC, endometrial carcinoma,	Pembrolizumab in endometrial carcinoma and RCC
Fruquintinib (Fruzaqla)	Takeda	Multikinase inhibitor (VEGFR1-3, RET, FGFR1, KIT)	CRC	

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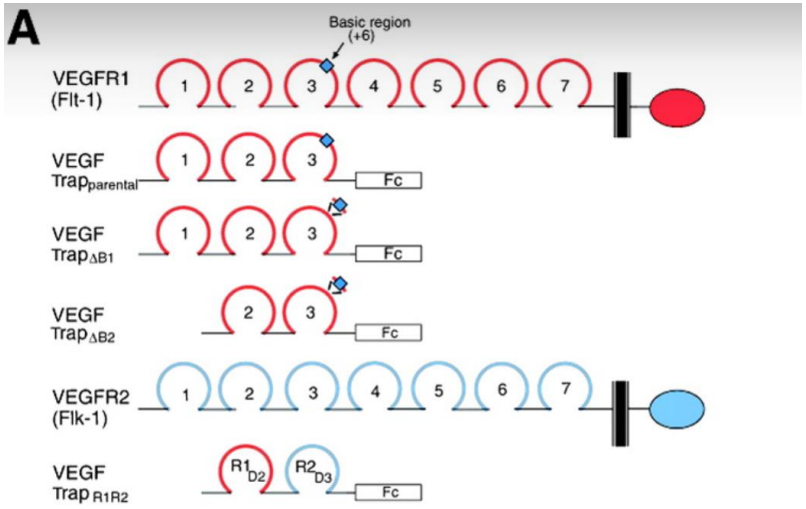
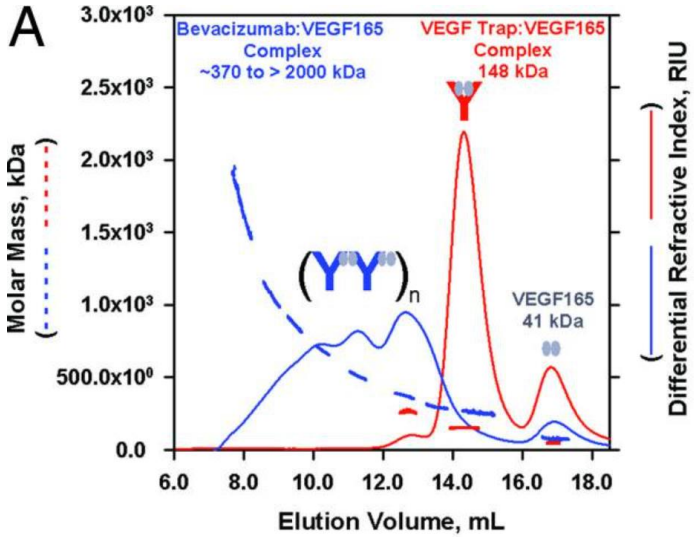
Source: Company data, Jefferies research

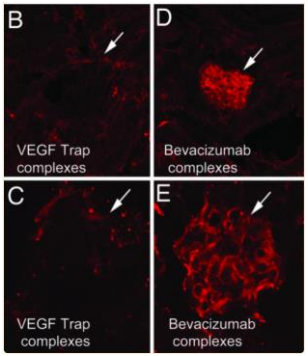
Another Difference is Bev Can Form Multimeric Immune Complexes with VEGF-A Dimer to Increase Overall Binding Strength While VEGF-Trap Only Forms a 1 to 1 Complex

Different constructs of VEGF-Trap with VEGFR1 (red) and VEGFR2 (blue) Ig domains[1]



Bev forms higher order complexes with VEGF-A dimer, while VEGF-Trap forms an inert 1 to 1 complex[2]





This could be another reason why bevacizumab performs better than Zaltrap in cancer

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Source: 1. Holash et al. PNAS 2002; 2. Rudge et al. PNAS 2007

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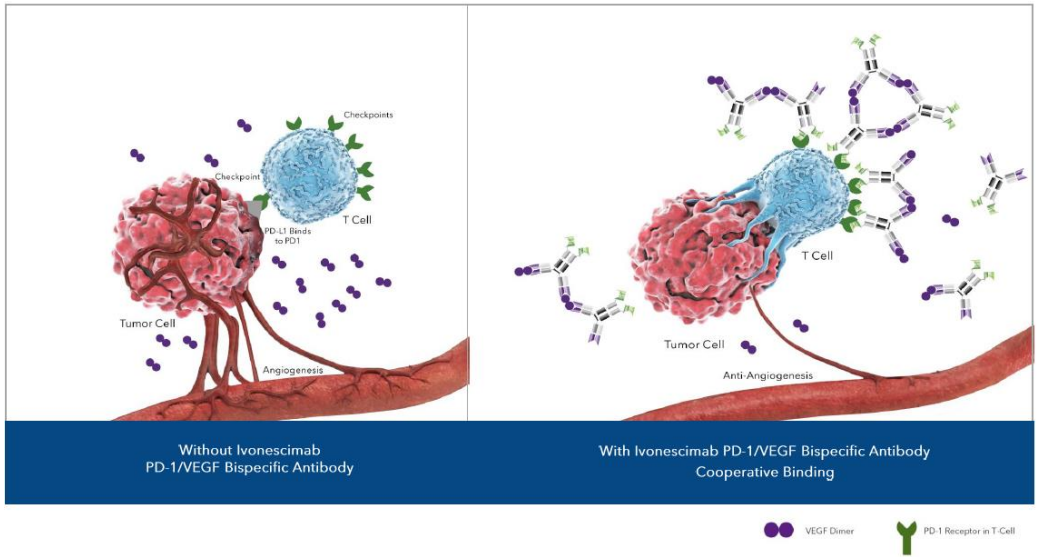
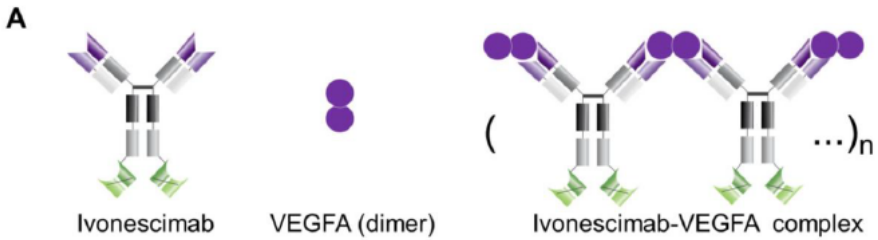
Preclinical Data Show That Ivonescimab Binds to VEGF-A Dimer and Form Higher Order Complexes

We assume BNT327 could form higher order complexes too as it also uses VEGF mAb, but no published supporting data are available





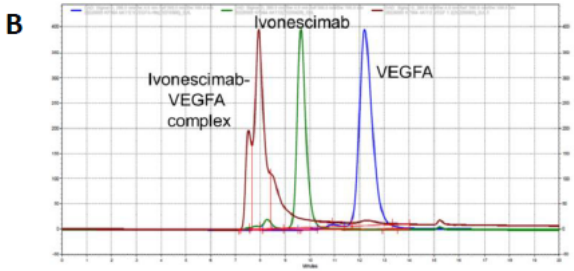


Fig 3. Ivonescimab forms soluble complexes with VEGF. (A) Diagram representing ivonescimab, VEGF and proposed ivonescimab-VEGF complex structure. (B) Ivonescimab-VEGFA complex formation determined by SEC-HPLC. Ivonescimab were premixed with 2x VEGFA and then analyzed on SEC-HPLC (Red color). Ivonescimab alone (Green color) and VEGFA alone (Blue color) were also analyzed on SEC-HPLC as references. The results were merged.

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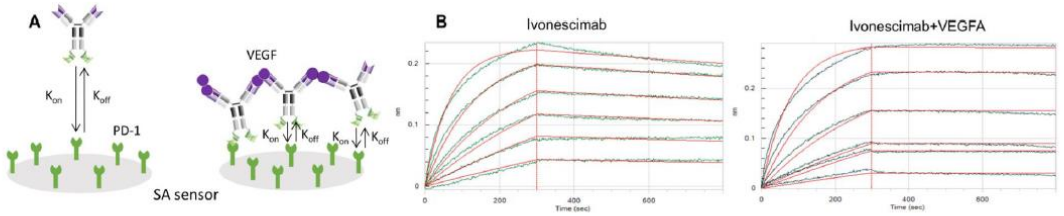
Source: AACR-NCI-EORTC 2023

Ivonescimab Presents Synergistic Binding to VEGF and PD-1, Potentially Driving Enhanced Anti-Tumor Effect

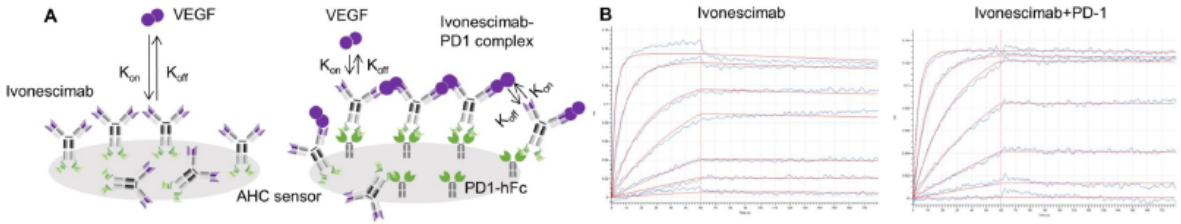
Ivonescimab Preclinical Data in vitro



Fixed antigen	Antibody	VEGFA-his (nM)	K_D (M)	k_{on} (1/ms)	k_{dis} (1/s)
PD1-his, 200 nM	Ivonescimab	0	7.15E-10	2.94E+05	2.10E-04
	Ivonescimab + VEGF	50-1.56	3.83E-11	2.51E+05	9.62E-05

Fig 4. VEGF promotes cooperative binding of ivonescimab to human PD-1. (A) Diagram representing the binding profile of ivonescimab to PD-1 in the presence/absence of VEGF. (B) Ivonescimab (50 nM) alone (left) or pre-incubated with human VEGF-His at same conc (right) and then diluted from 50 nM to 1.56 nM. The binding kinetics of ivonescimab alone or ivonescimab-VEGF to immobilized PD-1-His-biotin were determined by Octet BLI. The binding kinetic results show >18x increase in K_D, mainly driven by the slower dissociation rate (k_{dis}).

- VEGF binding enhances Ivonescimab's affinity to PD-1 (>18x)



Fixed antigen	Analyte	K_D (M)	k_{on} (1/ms)	k_{dis} (1/s)
Ivonescimab	VEGFA-his[b]	1.96E-09	2.04E+05	4.01E-04
Ivonescimab+ PD1-hFc[a]		4.11E-10	1.60E+05	6.58E-05

Fig 5. PD-1 enhances binding avidity of ivonescimab to human VEGF. (A) Diagram representing the binding profile of ivonescimab to VEGF with or without PD-1. (B) Ivonescimab (7 nM) alone (left) or mixture of ivonescimab (7 nM) with PD-1-human Fc (PD-1-hFc, 7 nM) (right) were immobilized on the AHC sensor. The binding kinetics of serial dilution of human VEGF-his protein (1000 to 1.37 nM) to immobilized ivonescimab or ivonescimab-PD-1-hFc were determined by Octet BLI. The binding kinetic results show a >4x increase of affinity to VEGF in the presence of PD-1. a, ivonescimab was pre-incubated with PD1-hFc at same concentration (7 nM); b, VEGFA-his with three-fold serial dilution from 1000 nM to 1.37 nM.

- PD-1 binding enhances Ivonescimab's affinity to VEGF (>4x)

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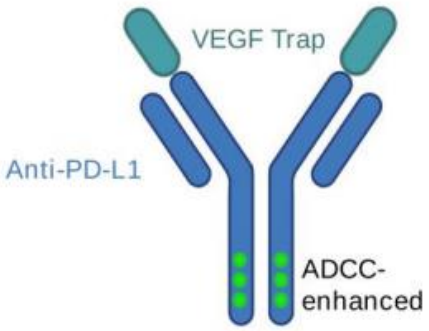
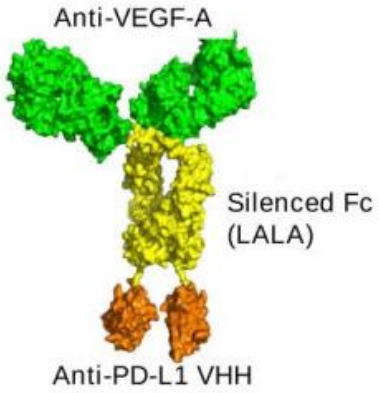
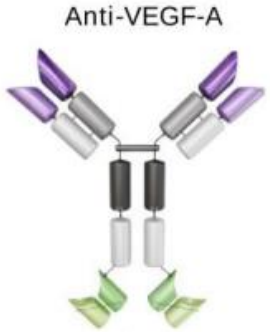
Source: AACR-NCI-EORTC 2023

SYN-2510 Doesn't Seem to Differ Much in Half-Life, but Differ Subtly in Binding Potency (EC50)

	SYN-2510	BNT327 (Biotheus / BioNTech)	Ivonescimab (Akeso / Summit)
VEGF binding	VEGF-A, VEGF-B, PLGF	VEGF-A	VEGF-A
PD-1 or PD-L1	PD-L1	PD-L1	PD-1







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Drug name	Company	MOA	Half-Life	VEGF-A	VEGF-B	PlGF-2	PD-1/PD-L1
Anti-VEGF agents							
Avastin (bevacizumab)	Roche	VEGF mAb	~20 days	Kd=58pM [1]	Not binding	Not binding	
Zaltrap (ziv-aflibercept)	RGEN/Sanofi	VEGF-trap (VEGFR1D2 and VEGFR2D3)	~6 days	Kd=0.49pM (118x bev) [1]	Kd=1.92pM [1]	Kd=38.9pM [1]	
HB-002.1	Instil Bio/ImmuneOnco	VEG-trap (VEGFR1D2)	~5 days	Kd=180pM (5x bev) [2]	modest	low	
PD-(L)1 x VEGF agents							
Ivonescimab/AK112	Summit/Akeso	Bispecific PD-1xVEGF	6-7 days	EC50=0.036nM (1x bev) [3]	Not binding	Not binding	EC50=1.22nM (0.37x nivo) [3]
BNT327/PM8002	BioNTech/Biotheus	Bispecific PD-L1xVEGF	4-9 days	EC50=0.95nM (1x bev) [4]	Not binding	Not binding	EC50=2.97nM [4]
SYN-2510/IMM2510	Instil Bio/ImmuneOnco	Bispecific PD-L1xVEGF (VEGFR1D2 trap)	~6 days	EC50=0.24nM (2x bev) [5]	Not reported	Not reported	EC50=0.85nM (0.25x atezo) [5]

Source: [1] Papadopoulos N, et al. Angiogenesis 2012. [2] Lily L, et al. BMC Cancer 2015. [3] AACR-NCI-EORTC2023. [4] US20230340158A1. [5] US20200172623A1

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Could TIL's SYN-2510 Molecular Design Differentiate?

We present three hypotheses based on SYN-2510's molecular structure:

Hypothesis 1 – Broader VEGF blockade by VEGF-Trap could enhance anti-tumor efficacy

Hypothesis 2 – Intact Fc could induce ADCC and generate better efficacy

Hypothesis 3 – PD-L1 is better than PD-1 when combining with VEGF as bispecifics

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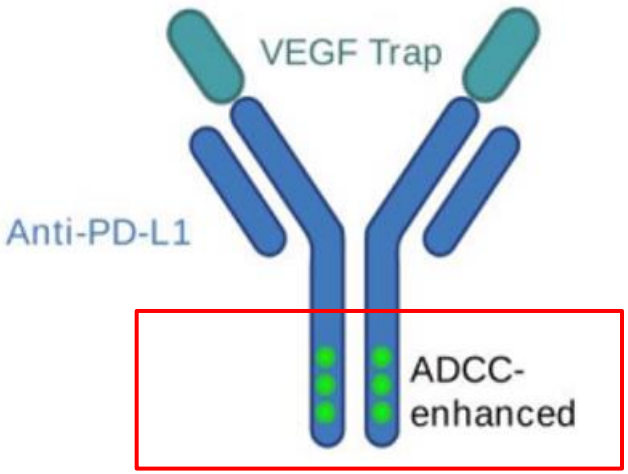
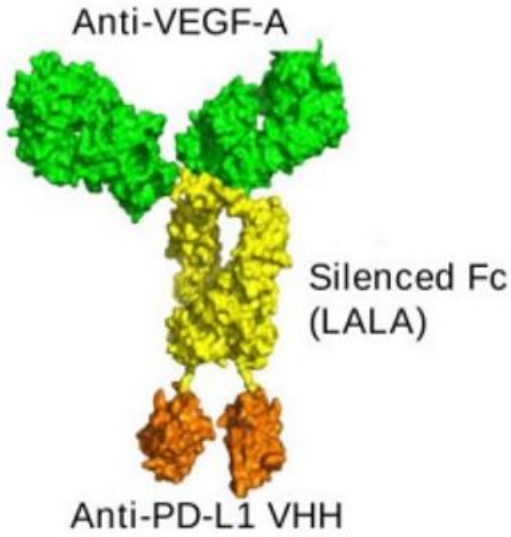
SMMT's and BNTX's PD-1/VEGF BsAb Molecules Have Silenced Fc, Whereas TIL Has Intact Fc Domain

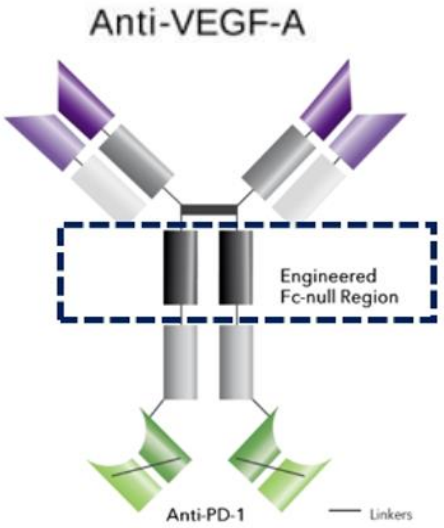
SYN-2510/IMM2510 (TIL)



BNT327 (BNTX)



Ivonescimab (SMMT)



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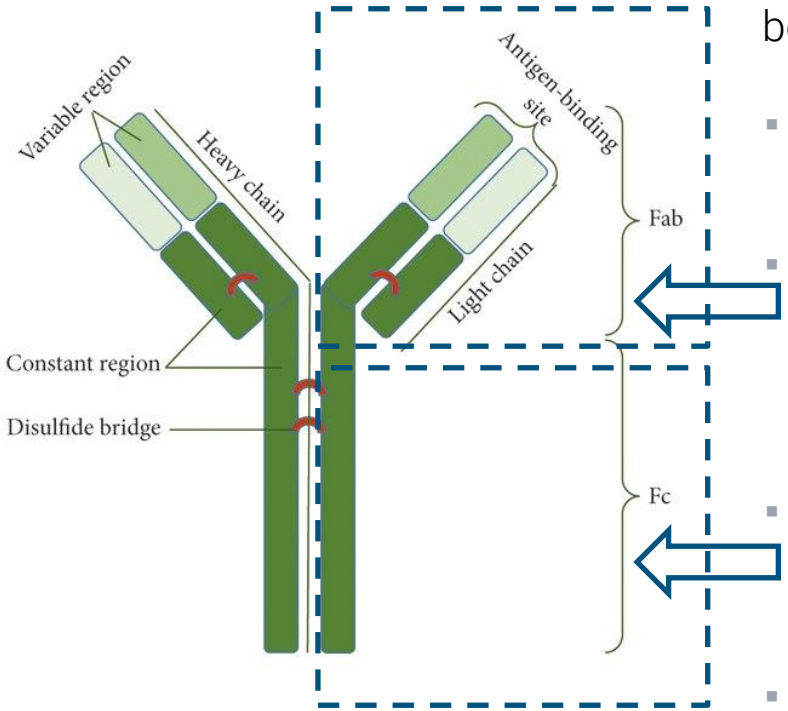
Source: Company presentation; Conference presentations

The Fc Region of an Antibody is Essential to Mediate Effector Function During an Immune Response.



Each antibody consists of 4 polypeptides (2 heavy chains and 2 light chains) linked together by disulfide bonds to form a "Y" shaped molecule.

- The 2 heavy chains and 2 light chains are identical, giving an antibody molecule 2 antigen binding sites
- The **Fab (fragment antigen-binding)** is composed of one constant and one variable domain of each of the heavy and the light chain.
  - The variable domain of the Fab is composed of 110-130 amino acids, giving the antibody its specificity for binding antigen
- The **fragment crystallizable (Fc)** region is the tail region of an antibody that interacts with cell surface Fc receptors to enhance effector function.
- Antibodies have five major classes, IgM, IgG, IgA, IgD, and IgE, and IgG is the main type of antibody found in blood and extracellular fluid, and the main class used in monoclonal and bispecific antibodies.

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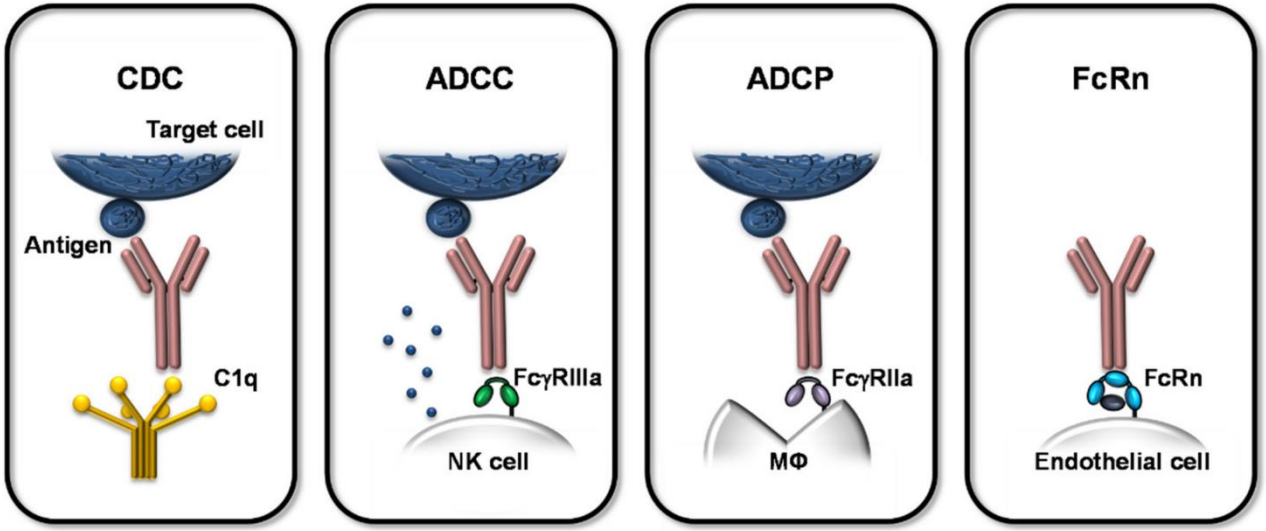
Source: Golpour M et al., Adv Pharmacol Pharm Sci, 2021

When Designing Antibody Molecules, One Approach Can be Taken Differently - Whether to Silence the Fc Domain



- The constant region Fc can allow antibody engagement with Fcγ receptors (FcγRs), proteins that are found on the surface of immune cells, including macrophages, neutrophils, B cells, mast cells etc.
- Such interactions can lead to Fc-mediated effector functions such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP) which are critical for desired antitumor activity.
- On the other hand, the Fcγ engagement could also potentially lead to unwanted immune responses against healthy tissue, resulting in undesired side effects.
- Therefore, different Fc engineering approaches have been taken when designing antibody molecules, and one strategy that is often debated is whether to silence the Fc domain to remove the Fcγ binding.

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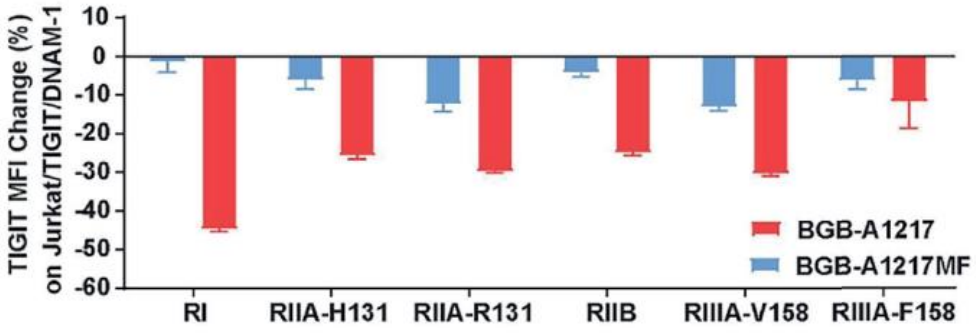
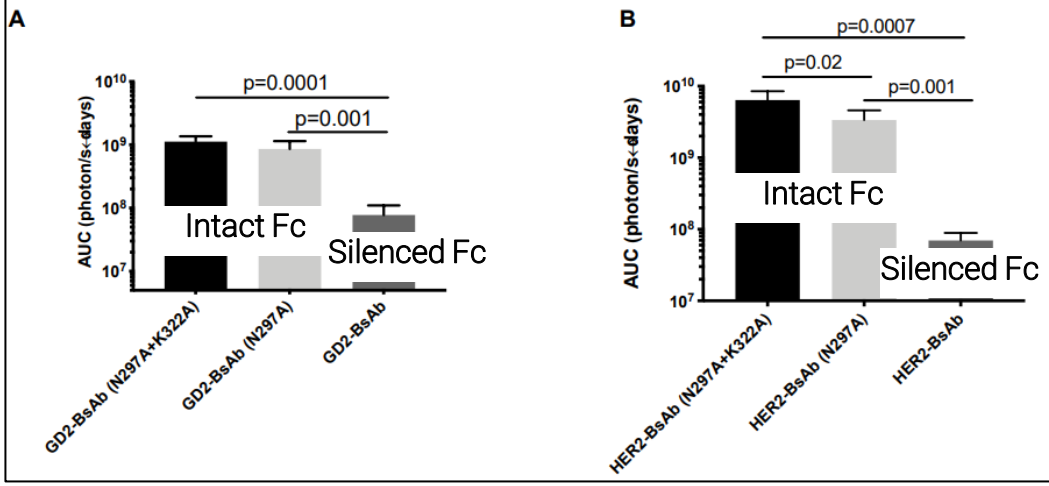
Source:: Gogesch P et al., Int. J. Mol. Sci. 2021,

However, Both Strategies (Silent or Intact Fc) are Under Debate; Preclinical Evidences to Date Seem to Support Both Arguments



- One preclinical study investigated whether the Fc effector function is critical for anti-TIGIT mAbs. In a cell experiment, only Fc intact version (BGB-A1217) dramatically removed TIGIT from the surface of donor cells in the presence of acceptor cells expressing different FcγRs, whereas the Fc-silent version could not, as demonstrated by the lower mean fluorescence intensity (MFI) fold change.[1]



- In another preclinical clinical study, the authors studied the kinetics of T-cell infiltration from blood into solid tumors and found BsAbs built with intact Fc domain (suppose to have better anti-tumor activity based on MOA) failed to drive T cells to tumor, thereby failing to achieve an antitumor effect in mice.[2]
- AUC analysis showed significant differences in T-cell accumulation with Fc silencing

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Source: [1]Chen X et al., Frontiers in Immunology, 2022; [2]Wang L et al., Cancer Immunol Res, 2019

One Notable Example is Anti-TIGIT mAbs, and Clinical Data is Yet Convincing to Validate the Potential Differentiations with the Silent/Intact Fc Design

	Domvanalimab	Tiragolumab	Tiragolumab	Ociperlimab	Vibostolimab
Company	**Arcus/Gilead**	**Roche**	**Roche**	**BeiGene**	**Merck**
Molecule design	**Fc silenced**	**Fc intact**	**Fc intact**	**Fc intact**	**Fc intact**
Study	**Ph2 Arc-7**	**Ph2 CITYSCAPE**	**Ph3 SKYSCRAPER-1**	**Ph1 AdvanTIG-105**	**Ph1 FIH study**
Patient characteristics	1L PD-L1-high NSCLC	1L PD-L1-high NSCLC	1L PD-L1-high NSCLC	1L PD-L1-high NSCLC	1L NSCLC
Study arms	Z vs DZ vd EDZ	T+ atezo vs atezo	T+ atezo vs atezo	Oci + Tisle	Vibo + pembro
Reference	ASCO 2023	Lancet 2022	Aug 2023 PR	WCLC 2022	Ann Oncol. 2022
ORR	30% vs 40% vs 44%	69% vs 24%		71%	26%
DOR	13.2 vs NR vs 23.7			NE	NR
Median PFS	5.4 vs 9.3 vs 9.9	16.6 vs 4.1		5.6	5.0
HR	DZ vs Z: 0.67 EDZ vs Z: 0.72	0.29			
Median OS			22.9 / 16.7 (HR = 0.81)		11.0
Any TRAE	100% / 98% / 98% (TEAE)	82% / 71%		78%	62%
Grade ≥3 TRAE	58% / 47% / 52% (TEAE)			10%	17%
Immune-related TEAE	48% / 50% / 66%	76% / 47%			15%

Roche's tiragolumab, Merck's vibostolimab, BGNE's ociperlimab, and ITOS/GSK's belrestotug are all designed with active Fc effector function. RCUS/GILD's domvanalimab is designed with disabled Fc receptor.

- Roche's tiragolumab has intact Fc and showed positive Ph2 data (16.6m mPFS vs 4.1m atezolizumab alone, HR = 0.29) in 1L PD-1 highlight NSCLC, but missed PFS and OS co-primary endpoints in Ph3 SKYSCRAPER-01.
- RCUS/GILD's domavanlimab showed 9.3m mPFS in combination with anti-PD1 zimberelimab vs 5.4m mPFS with zim alone (HR = 0.67), but the control arm seems to underperform compared to historical pembro monotherapy, making it hard to interpretate the magnitude of clinical benefit. In early 2024, Gilead stopped Ph3 study evaluating TIGIT-PD-1 combination in 1L PD-L1 high NSCLC.

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Source: Jefferies research

Could TIL's SYN-2510 Molecular Design Differentiate?

We present three hypotheses based on SYN-2510's molecular structure:

Hypothesis 1 – Broader VEGF blockade by VEGF-Trap could enhance anti-tumor efficacy

Hypothesis 2 – Intact Fc could induce ADCC and generate better efficacy

Hypothesis 3 – PD-L1 is better than PD-1 when combining with VEGF as bispecifics

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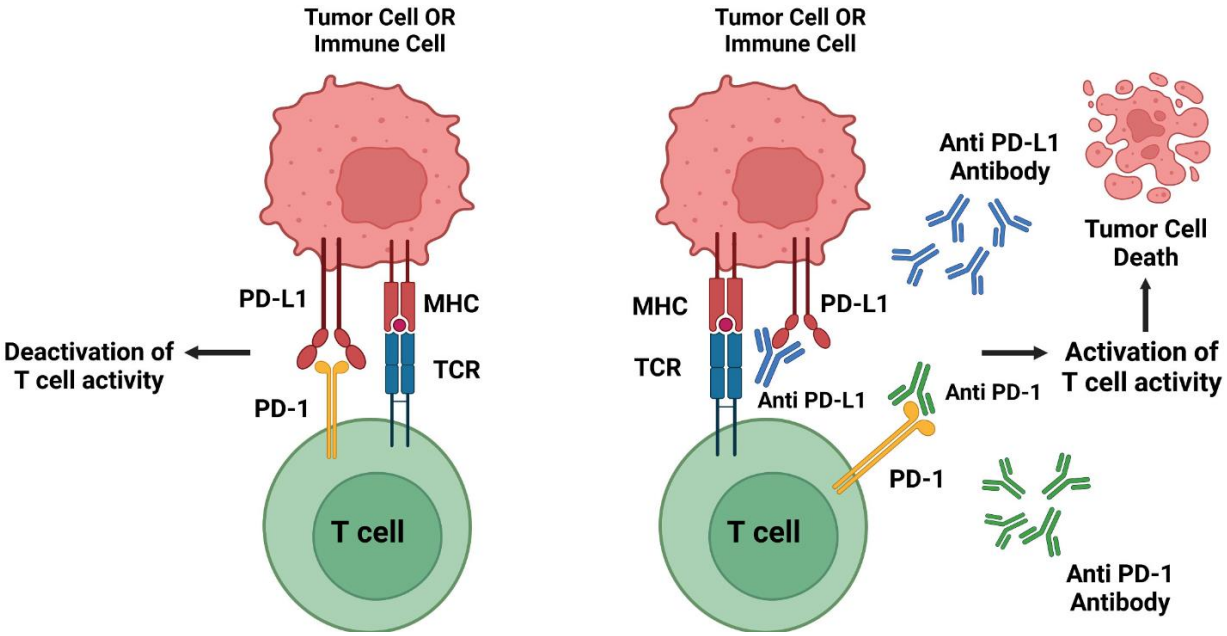
PD-L1 is Expressed by Many Cell Types While PD-1 is Primarily on T Cells

- PD-1 (programed cell death protein-1) and its ligand PD-L1 plays a crucial role in suppressing immune responses in cancer.
- PD-1 is primarily expressed in T cells, while PD-L1 is expressed in several cell types including immune cell, tumor cell, and some epithelial cells.
- PD-L1 has been viewed as more enriched than PD-1 in the tumor microenvironment (TME).



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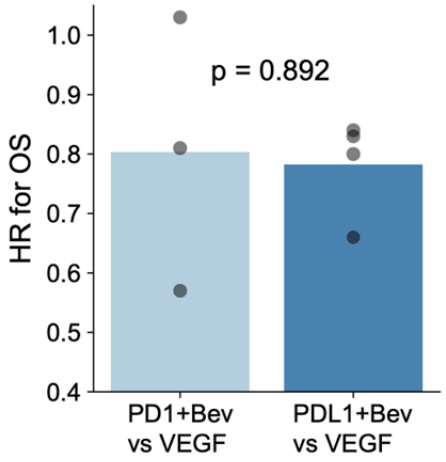
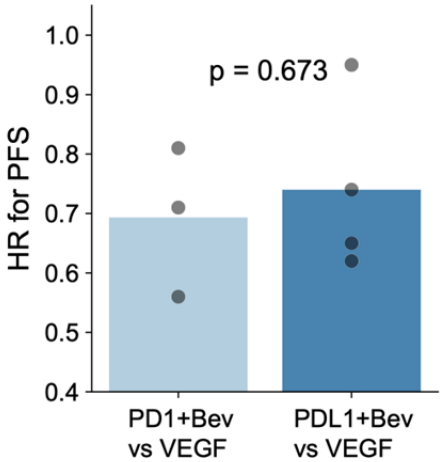
Source: Parvez et al. Front. Immunol. 2023

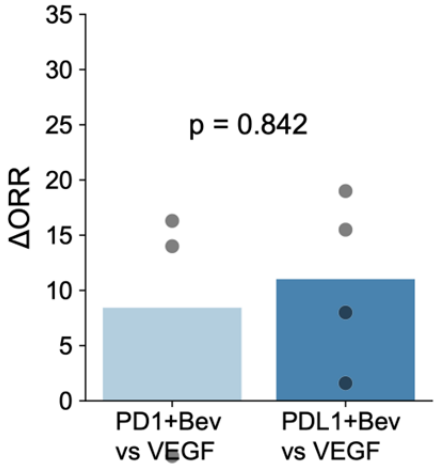
SYN-2510 and BNT327 Target PD-L1 (vs PD-1 for Ivo); Prior Bev Combo Trials Do Not Seem to Suggest Much Difference in Efficiency

We identified 7 Ph 3 studies comparing ICI + bevacizumab combo therapy vs bevacizumab

Cancer	Trial	Regimens	N	OS	PFS	ORR	ΔOS	OS_HR	ΔPFS	PFS_HR	ΔORR	Status
RCC	IMmotion151	Atezolizumab + Bevacizumab	454	34.0	11.2	43	1.3	0.84 (0.62 – 1.15)	3.5	0.74 (0.57 – 0.96)	8%	
		Sunitinib	461	32.7	7.7	35						
NSCLC	IMPower150	Atezolizumab + Bevacizumab + Chemo	400	19.5	8.3	63.5%	4.8	0.80 (0.67 - 0.95)	1.5	0.62 (0.52 - 0.74)	15.5%	Approved
		Bevacizumab + Chemo	400	14.7	6.8	48.0%						
CRC pMMR	MODUL cohort2	FOLFOX + Bevacizumab + Atezolizumab	297	22.5	7.1	16.5%	0.3	0.83 (0.65 - 1.05)	-0.3	0.95 (0.77 - 1.18)	1.6%	
		FOLFOX + Bevacizumab	148	22.2	7.4	14.9%						
CRC pMMR	CheckMate 9X8	Nivolumab + Bevacizumab + FOLFOX6	127	30.5	11.9	60.0%	-1.2	1.03 (0.64 - 1.66)	0	0.81 (0.61 - 1.07)	14.0%	
		Bevacizumab + FOLFOX6	68	31.7	11.9	46.0%						
CRC pMMR	AtezoTRIBE	Nivolumab + Bevacizumab + FOLFOX6	145	33	13.1	59.0%	5.8	0.81 (0.63 - 1.04)	1.6	0.71 (0.58 - 0.87)	-5.0%	
		Bevacizumab + FOLFOX6	73	27.2	11.5	64.0%						
HCC	ORIENT-32	Sintilimab + Bevacizumab biosimilar	380	NR	4.6	21.0%	NR	0.57 (0.43 - 0.75)	1.8	0.56 (0.46 - 0.70)	16.3%	
		Sorafenib	191	10.4	2.8	4.7%						
HCC	IMbrave150	Atezolizumab + Bevacizumab	336	19.2	6.9	30.0%	5.8	0.66 (0.52-0.85)	2.6	0.65 (0.53 - 0.81)	19.0%	Approved
		Sorafenib	165	13.4	4.3	11.0%						







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Source: Industry literatures, Jefferies research

Companies are Pursuing Largely Similar Indications with Some Prioritization Based on PD-1/PD-L1 Approval History

CPIs	PD-1				PD-L1			CTLA-4		PD-1xVEGF		PD-L1xVEGF			
Drug name	Pembrolizumab (Keytruda)	Nivolumab (Opdivo)	Cemiplimab (Libtayo)	Tislelizumab (Tevimbra)	Atezolizumab (Tecentriq)	Avelumab (Bavencio)	Durvalumab (Imfinzi)	Ipilimumab (Yervoy)	Tremelimumab (Imjuno)	Ivonescimab/AK112		BNT327/PM8002		SYN-2510/IMM2510	
Company	Merck	BMS	Regeneron	BeiGene	Roche	EMD Serono	AstraZeneca	BMS	AstraZeneca	Summit	Akeso	BioNTech	Biotheus	Instil Bio	ImmuneOnco
Melanoma	x	x			x			x							
NSCLC	x	x	x		x		x	x	x	Ph3	Approved/Ph3	Ph2/3	Ph2/3	Ph2 planned	Ph2
HNSCC	x	x									Ph3				
TNBC	x				x (withdrawn)						Ph2	Ph3 planned	Ph3		Ph2
CRC	x	x									Ph2				
HCC	x	x			x		x	x (withdrawn)	x		Ph2		Ph2		Ph1b
RCC	x	x				x		x					Ph1/2		Ph1b
GC	x	x													
CC	x												Ph1/2		
SCLC	x (withdrawn)	x (withdrawn)			x		x				Ph1	Ph3	Ph3		
MCC	x					x									
BTC	x						x				Ph3				
BC	x	x	x		x (withdrawn)	x	x (withdrawn)								
EC	x												Ph1/2		
EAC	x	x		x							Ph2				
TMB-H	x														
MSI-H/dMMR	x														
MESO		x						x					Ph2		
ASPS					x										Ph1/2
cSCC			x												
OC											Ph2		Ph1/2		
NEN													Ph2		
PC											Ph3 planned				
HL	x	x													
NHL	x														

NSCLC: Non-Small Cell Lung Cancer; HNSCC: Head and Neck Squamous Cell Carcinoma; TNBC: Triple-Negative Breast Cancer; CRC: Colorectal Cancer; HCC: Hepatocellular Carcinoma; RCC: Renal Cell Carcinoma; SCLC: Small Cell Lung Cancer; GC, Gastric Cancer; CC, Cervical Cancer; SCLC, Small Cell Lung Cancer; MCC, Merkel Cell Carcinoma; BTC, Biliary Tract Cancer; BC, Bladder Cancer; GC, Gastric Cancer, EC, Endometrial Carcinoma; EAC, Esophagus Cancer; TMB-H, Tumor Mutational Burden-High Cancer; MSI-H or dMMR, Microsatellite Instability-High or Mismatch Repair Deficient Cancer; MESO, Mesothelioma; ASPS, Alveolar Soft Part Sarcoma; cSCC, Cutaneous Squamous-Cell Carcinoma; OC, Ovarian Cancer; NEN, Neuroendocrine Neoplasm; PC, Pancreatic Cancer; HL, Hodgkin's Lymphoma; NHL, Non-Hodgkin Lymphoma

- Collectively, all three assets are pursuing NSCLC, TNBC, and HCC (global or China trials); We note PD-(L)1 + Avastin is approved in 1L nsqNSCLC and 1L HCC
- Akeso is the only one pursuing HNSCC as only PD-1s have been approved
- BNTX moves fast into Ph3 SCLC as PD-L1s have shown success but PD-1s have failed
- ImmuneOnco is the only one pursuing sarcoma (ASPS) as it has been approved with Atezolizumab (PD-L1)

x Indications were approved in combination with Avastin

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Source: Jefferies research; Clinicaltrials.gov; company presentation

Our Take: Too Early to Say SYN2510 Could Differentiate Based on Molecular Design

We present three hypotheses for differentiation based on SYN-2510's molecular structure:

Hypothesis 1 – Broader VEGF blockade by VEGF-Trap could enhance anti-tumor efficacy

- Unclear. Historically bevacizumab performs much better than Zaltrap. Also, VEGF-Trap can't form higher order complexes which has shown to improve binding avidity

Hypothesis 2 – Intact Fc could induce ADCC and generate better efficacy

- Unclear. We don't see enough clinical evidence to support this argument based on TIGIT experience

Hypothesis 3 – PD-L1 is better than PD-1 when combining with VEGF as bispecifics

- Case by case. In general, we don't see efficacy difference between PD-L1 and PD-1 in combination therapies with bevacizumab. However, PD-L1 and PD-1 appear to work differently in specific indications.

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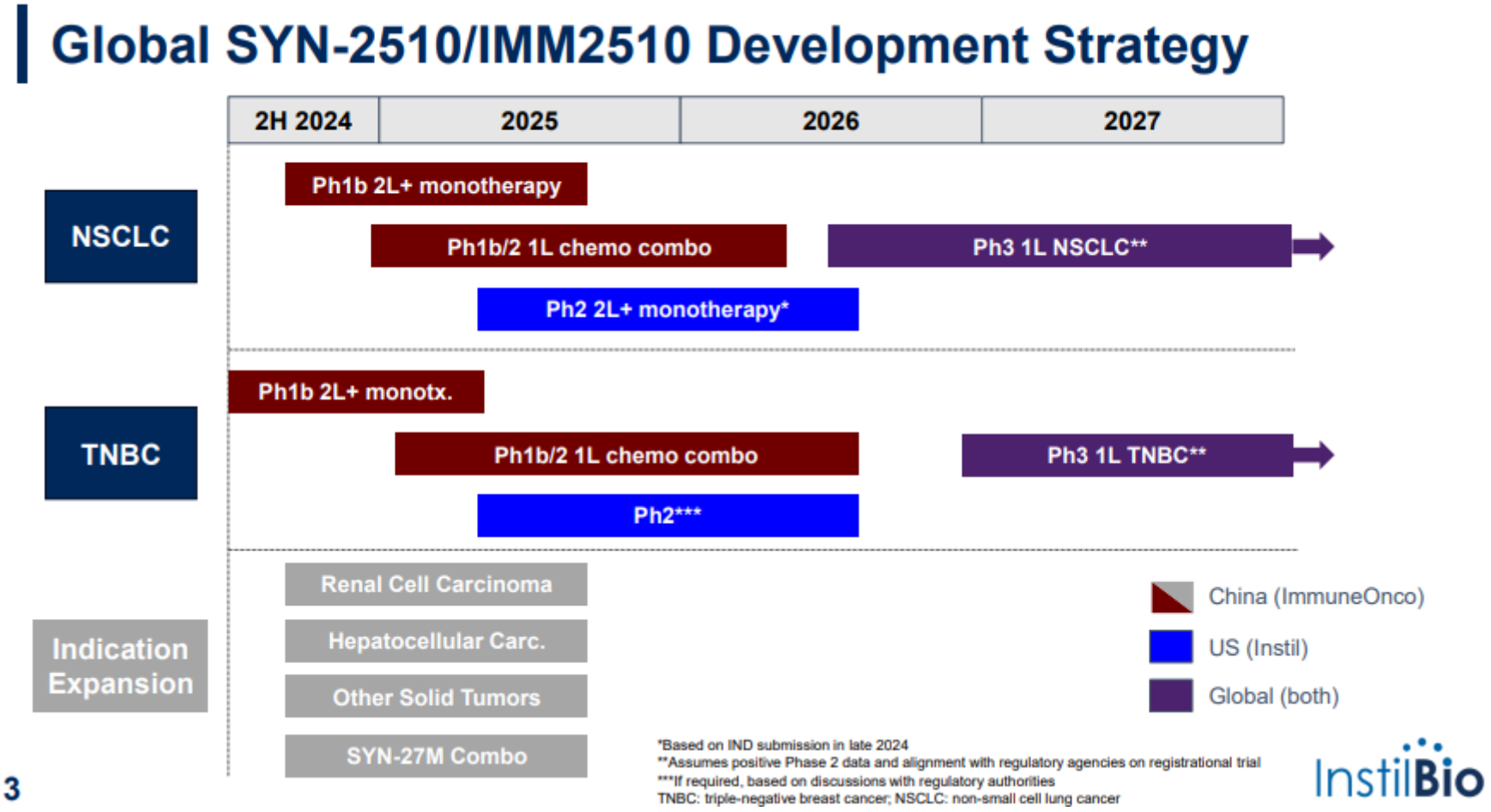
TIL's Development Plan for SYN-2510 with Initial Focus on NSCLC and TNBC



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Source: Instil Bio corporate presentation Sept 2024

In Summary, SYN-2510 Is an Early Mover for PD-(L)1xVEGF Race with Upside from Both Clinical Data and BD Activities in the Space

- SYN2510's only available data in dose-escalation showed very close ORR to BNT327 at subtherapeutic doses (For BNT327, majority pts were dosed at or above RP2D); safety data is too early for comparison

Company	Summit (partner Akeso)	BioNTech (partner Biotheus)	Instil Bio (partner ImmuneOnco)
Drug name	Ivonescimab/AK112	BNT327/PM8002	SYN-2510/IMM2510
MOA	PD-1 x VEGF-A	PD-L1 x VEGF-A	PD-L1 x VEGF (Trap_R1D2)
RP2D	20mg/kg Q3W	20mg/kg Q2W and 30mg/kg Q3W	20mg/kg Q2W
Dose range	0.3 - 30mg/kg Q2W	1 - 45mg/kg Q2/3W	0.007 - 10.0mg/kg Q2W
Efficacy in dose-escalation in solid tumors	n=47, ORR 26%, DCR 64% (not all RP2D)	n=254, ORR 16%, DCR 74%, mDOR 7.4m, mPFS 5.6m (Majority at or above RP2D)	n=25, ORR 12% (3PRs, 2 sqNSCLC, 1 thymus carcinoma) and 7SDs (not all RP2D)

- TIL's development plan for SYN-2510 with initial focus on NSCLC and TNBC. ImmnuneOnco has identified RP2D of 20mg/kg Q2W and is running multiple China trials with monotherapy data update in solid tumors expected in 1H25. Ph 1b/2 China trial in 1L NSCLC and TNBC will start in late 2024 and 1H25, respectively. US study sponsored by TIL will start in 2H25.
- On valuation, TIL is trading at ~$135M market cap, close to cash value (~$123M as of 3Q24). SMMT and BNTX with global trial plans are trading at ~$13B and ~$28B, respectively.
- We upgrade TIL to Buy with a PT of $52; our model includes 2L PD-L1+ NSCLC and 1L TNBC and we estimate ~$650M risk-adj (10% POS) peak sales.

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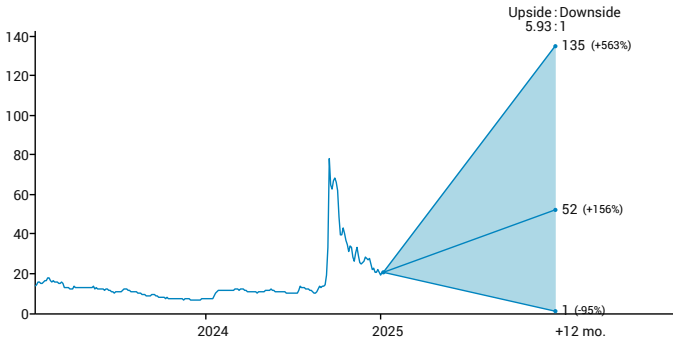
The Long View: Instil Bio

Investment Thesis / Where We Differ

- Instil Bio abandoned its tumor infiltrating lymphocyte (TIL) programs altogether in 2023. In Aug 2024, company in-licensed two assets from ImmuneOnco to develop SYN/IMM2510 (PD-L1xVEGF BsAb) and SYN/IMM27M (next-gen anti-CTLA-4 antibody) in solid tumors outside of China. Instil Bio's long-term lease on its cell therapy manufacturing facility could strengthen its financials to support next catalyst.

Risk/Reward - 12 Month View



Base Case,
$52, +156%

- Assume WACC of 15% and terminal growth rate of 0%
- For 2L+ NSCLC, we est '2510 entry in the US in 2029 and EU in 2030, w/ peak sales of $386M/ $166M in US/EU by 2035 (10% PoS).
- For 1L TNBC, we est '2510 entry in the US in 2030 and EU in 2031, w/ peak sales of $75M/ $33M in US/EU by 2035 (10% PoS).
- PT $52 (DCF-based)

Upside Scenario,
$135, +563%

- Promising data from PD-(L)1xVEGF class assets in NSCLC (HARMONi and HARMONi-2), increase PoS by 5% for NSCLC
- $135 (DCF-based)

Downside Scenario,
$1, -95%

- Clinical failure of all pipeline programs
- PT: $1 (due to trading dynamic)

Sustainability Matters

- **Top Material Issue(s)**: **1) Employee Engagement, Diversity, and Inclusion.** Biotech companies face a constrained talent pool due to their reliance on highly skilled employees. Co's should prioritize competitive & equal pay, advancement opportunities, & an environment where thought diversity can drive innovation. **2) Product Quality and Safety:** Maintaining product safety and lowering manufacturing defects can help reduce costs.
- **Company Target(s):** NA
- **Qs to Mgmt**: **1)** How are you implementing DEI and employees' engagement initiative to improve employee retention? 2) What cost-saving and product quality improvement do you predict with in-house manufacturing? 3**)** What are you investing in to protect IP landscape?
- Link to Sector Framework

Catalysts

1H25: SYN-2510 China data update

1H25: Initiation of Ph 1b/2 China trial in 1L TNBC

2H25: Initiation of US trial in NSCLC

Financials: Instil Bio

Estimate changes

USD	2023A	2024E	2025E	2026E
Rev. (MM)	0.0	0.0	0.0	0.0
EPS	(24.00)	(13.41) ↓ -61%	(7.34) ↓ -436%	(6.02) ↓ -772%
Previous		(8.34)	(1.37)	(0.69)
Q1	(0.44)	(3.74)A	-	-
Previous				
Q2	(0.14)	(2.29)A	-	-
Previous				
Q3	(0.52)	(3.54)A	-	-
Previous				
Q4	(1.99)	(3.84) ↓ -412%	-	-
Previous		1.23		

Valuation metrics

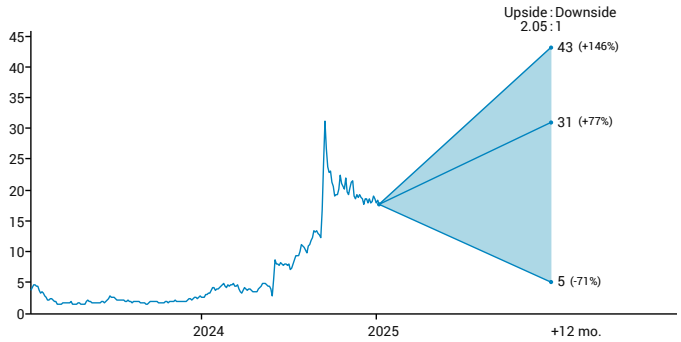
	2023A	2024E	2025E	2026E
FY P/E	NM	NM	NM	NM

The Long View: Summit Therapeutics

Investment Thesis / Where We Differ

SMMT is laser-focused on one asset: first-in-class PD-1xVEGF BsAb, Ivonescimab (ivo) in-licensed from Akeso. We see the asset as clinically de-risked as both PD-1 and VEGF are effective MOAs and Akeso has shown H2H superiority to Keytruda in 1L NSCLC and gained 1st China approval in 2L + EGFRm NSCLC. SMMT's initial focus is also on NSCLC, with three global Ph3 trials ongoing/planned. We est ~$10B risk-adj (55-65%) peak sales for ivo in NSCLC alone w/ est launch of 2L+ EGFm nsq in 2026, 1L PD-L1+ in 2027, 1L PD-L1 high in 2028. Data to date suggest ivo's best-in-class potential compared to BNTX and TIL, and we see significant upside if pursued for other indications down the road, incl PD-(L)1 approved and non-approved tumors.

Risk/Reward - 12 Month View



Base Case,
$31, +77%

• Assume a WACC of 12% and a terminal growth rate of 0%.

• For 2L+ EGFRm nsq NSCLC, we est ivo entry in the US in 2026 and EU in 2027, w/ peak sales of $297M/$131M in US/EU in 2035 (65% PoS).

• For 1L PD-L1+ NSCLC, we est ivo entry in the US in 2027 and EU in 2028, w/ peak sales of $4.4B/ $2.0B in US/EU in 2035 (55% PoS).

• For 1L PD-L1 high NSCLC, we est ivo entry in the US in 2028 and EU in 2029, w/ peak sales of $2.6B/ $1.1B in US/EU in 2035 (55% PoS).

• Price Target: $31 (DCF-based)

Upside Scenario,
$43, +146%

• Positive data from ivo in 2L+ EGFRm NSCLC (HARMONi) in mid-2025, increase PoS by 25%, and increase PoS by 15% for 1L PD-L1+ and 1L PD-L1 high NSCLC

• Price Target: $43 (DCF-based)

Downside Scenario,
$5, -71%

• For 1L PD-L1+ NSCLC, ivo does not show OS benefit in China HARMONi2 trial. PoS is lowered to 10% for HARMONi-7 and HARMONi-3 trial.

• Negative data from ivo in 2L+ EGFRm NSCLC (HARMONi) in mid-2025, lower PoS to 0.

• PT: $5 (DCF-based)

Sustainability Matters

- **Top Material Issues(s)**: **1) Product Quality & Safety:** as the company is actively developing potentially transformative and novel treatments, it will need to ensure safety of its products in clinical trial participants as well as safe delivery of its products to trial sites. **2) Access & Affordability:** company will need to carefully balance access/affordability of its product(s) and profitability once its product(s) is approved and marketed in the future.
- **Company Target(s)**: Company has not yet disclosed its ESG commitment targets.
- **Qs to Mgmt:** 1) What human resources programs or initiates does SMMT have in place to attract talent with diverse backgrounds, experiences and perspectives? 2) How does SMMT work to safeguard the safety of patients in clinical trials?
- Link to Sector Framework

Catalysts

- **Early 2025**: Initiate global Ph3 HARMONi-7 trial in 1L PD-L1 high NSCLC
- **Mid 2025**: Topline data from global Ph3 HARMONi trial in 2L+ EGFRm NSCLC
- **YE25/Early26 (E)**: OS data from China Ph3 HARMONi-2 trial in 1L PD-L1+ NSCLC
- **YE25/Early26 (E)**: Topline data from China Ph3 HARMONi-6 trial in 1L sqNSCLC

Financials: Summit Therapeutics

Estimate changes

USD	2023A	2024E	2025E	2026E
Rev. (MM)	0.0	0.0	0.0	(82.9)
Cons. Rev.	-	0.0	0.0	21.8 ↓ -66%
Previous				63.9
Cons. EPS	-	(0.29) ↑ +3%	(0.41) ↓ -8%	(0.63) ↓ -17%
Previous		(0.30)	(0.38)	(0.54)
EPS	(0.99)	(0.31)	(0.43)	(0.70)
Q1	-	(0.06)A	-	-
Q2	-	(0.09)A	-	-
Q3	-	(0.08)A	-	-
Q4	-	(0.09)	-	-

Valuation metrics

	2023A	2024E	2025E	2026E
FY P/E	NM	NM	NM	NM
EV/Rev				NM
P/Rev				NM

Company Description

Summit Therapeutics

Summit Therapeutics, Inc. is a biopharmaceutical company, that focuses on the discovery, development, and commercialization of patient, physician, caregiver, and societal-friendly medicinal therapies intended to improve quality of life, increase potential duration of life, and resolve serious unmet medical needs. The firm conducts clinical programs focusing on Clostridioides Difficile Infection (CDI). Its lead product, Ridinilazole, is an orally administered small molecule antibiotic that is in Phase III clinical trials for the treatment of CDI. The company was founded in 2003 and is headquartered in Miami, FL.

Instil Bio

Founded in 2018, Instil Bio was looking to harness tumor-infiltrating lymphocytes (TILs) to develop novel cell therapeutics for the treatment of cancer. The company's lead pipeline program, ITIL-306, is a next-gen genetically engineered TIL for FOLR1 expressing solid tumors, including ovarian, NSCLC and RCC. ITIL-306 uses a co-stimulatory platform (CoStAR) to enhance TIL activation in the tumor environment. In 2023, TIL abandoned its tumor infiltrating lymphocyte programs. In Aug 2024, TIL in-licensed two assets from ImmuneOnco to develop IMM2510 (PD-L1xVEGF BsAb) and IMM27M (next-gen anti-CTLA-4 antibody) outside of China.

Company Valuation/Risks

Summit Therapeutics

We arrive at a $31 price target based on a DCF valuation model that assumes a WACC of 12%, a terminal growth rate of 0%, and outstanding shares of 737M, driven by sales of ivonescimab. Risks: Clinical, regulatory and/or commercial failure. Competitive, manufacturing and/or financing risks.

Instil Bio

Our $52 PT is DCF-based (WACC 15%). Risks include clinical, regulatory, and commercial.

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Investment Recommendation Record

(Article 3(1)e and Article 7 of MAR)

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- Akeso Inc. (9926 HK: HK$59.35, BUY)
- BioNTech SE (BNTX: $120.21, BUY)
- Bristol-Myers Squibb Co (BMY: $56.68, BUY)
- Merck & Co Inc (MRK: $99.72, BUY)
- Roche (ROG SW: CHF257.50, HOLD)
- Summit Therapeutics Inc (SMMT: $17.47, BUY)

Distribution of Ratings

			IB Serv./Past12 Mos.		JIL Mkt Serv./Past12 Mos.	
	Count	Percent	Count	Percent	Count	Percent
BUY	2097	59.90%	381	18.17%	127	6.06%
HOLD	1227	35.05%	98	7.99%	22	1.79%
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