

# Summit Therapeutics (SMMT)

## Investment Research Report

Update: November 25, 2025

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## Executive Summary

**Ticker:** NASDAQ: SMMT | **Market Cap:** \$14.4B | **Price:** \$19.28

Summit Therapeutics is developing **ivonescimab**, a first-in-class bispecific antibody targeting PD-1/VEGF for NSCLC. The company has demonstrated clinical superiority vs Keytruda (HARMONi-2) and met primary PFS endpoint in 2L EGFR+ setting (HARMONi). BLA filing expected Q4 2025/Q1 2026. Post-\$500M financing provides runway through 2027.

**Price Target Range:** \$25-\$35 (Base Case, +30% to +82% upside)

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## 1. Company Overview

Summit Therapeutics (NASDAQ: SMMT) is a biopharmaceutical company focused on innovative oncology therapies. The pipeline centers on **ivonescimab (AK112/SMT112)**, developed in partnership with Akeso Biopharma.

### Partnership Structure

- **Summit:** Exclusive rights for USA, Canada, Europe, Japan
- **Akeso:** Rights for China and Greater China
- **Trials:** Separate in China (HARMONi-A, HARMONi-2) and global (HARMONi)

### Target Market: EGFR-Mutated NSCLC

- Represents 10-15% of lung cancer cases in USA
  - ~40,000 new patients annually
  - Post-osimertinib progression → limited treatment options
  - Poor prognosis: median OS 14 months with standard care
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## 2. Ivonescimab: Bispecific Mechanism

### Structure & Mechanism

**Ivonescimab** is a tetravalent bispecific antibody simultaneously blocking:

1. **PD-1/PD-L1:** Immune checkpoint inhibition
2. **VEGF/VEGFR:** Anti-angiogenic mechanism

## Rationale for Dual-Targeting

<b>Benefit</b>	<b>Mechanism</b>
<b>Immuno-metabolic synergy</b>	VEGF blockade normalizes vasculature → improves T cell infiltration → enhances anti-PD-1
<b>Integrated PK</b>	Coordinated exposure without variability of separate combinations
<b>Safety advantage</b>	Low hemorrhagic events (<1% grade ≥3) vs traditional PD-1 + bevacizumab

## 3. Clinical Data: HARMONi Trials

### HARMONi Trial (Global - 2L EGFR+ NSCLC)

#### Study Design:

- 553 patients with EGFR-mutated NSCLC post-osimertinib progression
- Randomization: Ivonescimab + chemo vs placebo + chemo
- Primary endpoint: PFS | Co-primary: OS

#### Results (September 2025):

<b>Endpoint</b>	<b>Ivonescimab + Chemo</b>	<b>Placebo + Chemo</b>	<b>HR (95% CI)</b>	<b>p-value</b>
<b>Median PFS</b>	6.8 months	4.4 months	0.52 (0.40-0.68)	<0.001
<b>Median OS</b>	16.8 months	14.0 months	0.79 (0.60-1.03)	0.057 (NS)
<b>ORR</b>	45%	34%	—	—
<b>DCR</b>	94%	89%	—	—

**Interpretation:** Primary PFS endpoint met with 48% risk reduction. OS shows 21% reduction in mortality risk (trend positive) but did not reach statistical significance at interim (39% data maturity).

## HARMONi-2 Trial (China - 1L PD-L1+ NSCLC)

### Study Design:

- 398 treatment-naïve patients with PD-L1+ NSCLC
- Head-to-head: Ivonescimab monotherapy vs Pembrolizumab (Keytruda)
- Primary endpoint: PFS

### Results (March 2025, Lancet Oncology):

Endpoint	Ivonescimab	Pembrolizumab	HR (95% CI)	p-value
Median PFS	11.1 months	5.8 months	0.51 (0.38-0.69)	<0.0001
ORR	50.0%	38.5%	—	0.034
DCR	89.9%	70.5%	—	—

**Significance:** First demonstration of PFS superiority vs pembrolizumab monotherapy in 1L PD-L1+ NSCLC—49% risk reduction.

### Safety Profile

Adverse Event	Ivonescimab	Comparator
Grade ≥3 AE	48%	42%
Grade ≥3 hemorrhage	<1%	<1%
Grade ≥3 hypertension	4%	1%
Discontinuations for AE	5%	4%

**Assessment:** Manageable safety profile, comparable to standard therapies, low serious hemorrhagic events.

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## 4. Competitive Landscape

### NSCLC Checkpoint Inhibitor Market

**Global market size:** ~\$90B oncology immunotherapy (2025); ~\$20B NSCLC-specific

Drug	Company	Target	Approvals	2024 Sales
Keytruda	Merck	PD-1	1L, 2L, adjuvant	~\$25B
Opdivo	BMS	PD-1	1L combo, 2L	~\$8B
Tecentriq	Roche	PD-L1	1L combo	~\$3B
Imfinzi	AstraZeneca	PD-L1	Stage III, 1L	~\$3B
<b>Ivonescimab</b>	<b>Summit/Akzo</b>	<b>PD-1/VEGF</b>	<b>Pre-approval</b>	<b>Pre-commercial</b>

### Ivonescimab Competitive Positioning

#### Potential Advantages:

- Superior efficacy vs Keytruda (PFS HR 0.51)
- Differentiated dual mechanism (no approved competitor)
- Acceptable safety profile

#### Competitive Challenges:

- Keytruda dominates >50% market share in 1L NSCLC
- High switching costs; physician inertia
- Biosimilars arriving 2028-2029
- Next-gen therapies: ADCs (Enhertu, Dato-DXd), CAR-T emerging

## 5. Financial Analysis Q3 2025

### Balance Sheet & Cash Position

Parameter	Q1 2025	Q2 2025	Q3 2025
<b>Cash &amp; Equivalents</b>	\$361.3M	\$297.9M	\$238.6M
<b>Total Assets</b>	\$381.2M	\$318.4M	\$259.1M
<b>Total Liabilities</b>	\$44.8M	\$47.2M	\$51.3M
<b>Stockholders' Equity</b>	\$336.4M	\$271.2M	\$207.8M
<b>Quarterly Burn</b>	—	~\$63M	~\$59M
<b>Runway (months)</b>	~15	~14	~12

### Post-Q3 Financing (November 2025):

- \$500M private placement at \$18.74/share
- Pro-forma cash: ~\$738M
- Runway extended to Q4 2027
- Dilution: ~3.5% (26.7M new shares)

### Operating Expenses

Expense (\$M)	Q1 2025	Q2 2025	Q3 2025
<b>R&amp;D (GAAP)</b>	\$51.2	\$208.0	\$131.1
<b>G&amp;A (GAAP)</b>	\$15.6	\$360.4	\$103.1
<b>Total GAAP</b>	\$66.8	\$568.4	\$234.2
<b>Non-GAAP OpEx</b>	\$55.7	\$89.6	\$103.4

*Note: Q2 spike due to \$478M one-time stock-based compensation charge. Non-GAAP reflects recurring operational expenses.*

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## 6. Catalyst Timeline

### Near-Term (Q4 2025 - Q1 2026)

#### 1. BLA Filing FDA

- Indication: 2L NSCLC EGFR-mutated post-osimertinib
- Fast Track status already granted
- Impact: Confirms path to US commercialization, significant de-risking

#### 2. Overall Survival Data Update (HARMONi)

- Current: OS trend positive (HR 0.79, p=0.057)
- Next interim: Q4 2025/Q1 2026 with more data maturity
- Importance: Significant OS would strengthen FDA approval case

#### 3. HARMONi-GI3 Trial Initiation

- Colorectal cancer indication
- Timeline: Late 2025
- Pipeline diversification beyond NSCLC

### Medium/Long-Term (2026-2027)

- **FDA Approval Decision:** ~6-10 months post-BLA (mid-2026)
  - **Commercial Launch USA:** Late 2026 (if approved)
  - **EU Regulatory Filing:** EMA submission 2026
  - **Japan Regulatory Filing:** PMDA submission 2026-2027
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## 7. Risk Analysis

### Clinical & Regulatory Risks

#### Overall Survival Non-Significance

Current OS interim (HR 0.79,  $p=0.057$ ) did not reach statistical significance. FDA may require significant OS for full approval or grant conditional approval requiring confirmatory trial.

#### Population Differences

HARMONi-2 conducted in China. Results may not fully replicate in USA/European populations due to differences in tumor biology, PD-L1 expression, prior standard of care.

#### Long-Term Safety Signals

VEGF-related toxicities (hypertension, proteinuria, thromboembolism, bleeding) may emerge with prolonged follow-up or larger populations post-approval.

### Competitive Risks

#### Keytruda Market Dominance

50% market share in 1L NSCLC with entrenched prescribing habits. Switching requires robust OS data + pricing/reimbursement advantages.

#### Competing Bispecifics

Roche (tiragolumab + bevacizumab), BMS, and AstraZeneca pursuing similar PD-1/VEGF combinations.

#### Next-Generation Therapies

ADCs (Enhertu approval 2024, Dato-DXd Phase 3) and CAR-T emergence may redefine NSCLC standards within 3-5 years.

### Financial & Operational Risks

#### Future Dilution

\$500M raise created ~3.5% dilution. Delayed commercialization or additional trials could require further raises.

#### Manufacturing Dependency

Summit relies on Akeso for production. Supply chain issues or partnership rupture could block US commercialization.

#### Pre-Revenue Status

No commercial revenue until potential 2026 launch. \$60M quarterly burn requires perfect execution on BLA/approval timeline.

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## 8. Valuation & Price Targets

### Methodology

Probability-weighted DCF incorporating:

- Peak sales NSCLC scenarios
- 12% discount rate, 2% terminal growth
- Risk-adjusted Probability of Success (PoS)
- Comparable biotech company multiples

### Price Target Scenarios (12-Month)

▣ **Bear Case:** \$8–\$12

**Downside:** -38% to -58% | **Probability:** 15%

#### Key Assumptions:

- OS final result neutral/negative (HR >0.85)
- FDA requires confirmatory trial (3-5 year delay)
- Safety issues emerge (bleeding, cardiovascular toxicity)
- Commercialization underperforms
- Peak sales <\$500M

**Catalysts:** FDA rejection, intense competition, macro downturn

▣ **Base Case:** \$25–\$35

**Upside:** +30% to +82% | **Probability:** 60%

#### Key Assumptions:

- OS trend maintained (HR 0.75–0.80, non-significant)
- FDA conditional or standard approval (10–12 months post-BLA)
- 15–20% market share in 2L EGFR+ NSCLC
- \$15K/month pricing (parity with Keytruda)
- Peak sales \$2–3B (2031–2033)

**Rationale:** Execution to plan, normal market development, no major surprises

▣ **Bull Case:** \$50–\$70

**Upside:** +159% to +263% | **Probability:** 25%

#### Key Assumptions:

- OS becomes statistically significant (HR <0.75, p<0.05) by Q1 2026
- FDA accelerated approval (6 months post-BLA)
- Becomes new standard; 25–30% market share
- Label expansions: 1L NSCLC, combinations, other indications
- Peak sales \$5–7B (2030–2032)

**Catalysts:** OS significance Q1 2026, BLA filing Q4 2025, FDA approval mid-2026, strong launch

## Analyst Consensus

Metric	Value
Average Price Target	\$31.14
Upside Implied	+61.5%
Range	\$12 – \$44
Rating Distribution	11 Buy, 1 Strong Buy, 6 Hold

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## 9. Investment Thesis

### Bull Case:

- Clinical data demonstrates efficacy vs market-leading Keytruda
- Large, underpenetrated 2L EGFR+ NSCLC market (~40K patients/year US)
- Differentiated dual mechanism with acceptable safety
- Strong cash position post-\$500M raise
- Multiple near-term catalysts (BLA, OS update, approval)

### Bear Case:

- OS data currently not statistically significant
- Keytruda entrenched dominance; switching difficult without clear OS benefit
- Clinical efficacy in China may not translate to Western populations
- Pre-revenue company with \$60M quarterly burn
- Competitive pipeline advancing (ADCs, next-gen combos)

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