Company Presentation

March 2024

Enliven THERAPEUTICS

Disclaimer

This presentation contains forward-looking statements that involve substantial risks and uncertainties of Enliven Therapeutics, Inc. ("Enliven" or the "Company"). All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, results of operations, business strategy and plans, and objectives of management for future operations, as well as statements regarding industry trends, are forward-looking statements. Such forward-looking statements include, among other things, statements regarding the potential of, and expectations regarding Enliven's product candidates and programs, including ELVN-001 and ELVN-002; Enliven's ability to advance additional programs; the expected milestones and timing of such milestones including for ELVN-001, ELVN-002 and its discovery programs; and statements regarding Enliven's financial position, including its liquidity, cash runway and the sufficiency of its cash resources. In some cases, you can identify forward-looking statements by terminology such as "estimate," "intend," "may," "plan," "potentially" "will" or the negative of these terms or other similar expressions.

We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including, among other things: Enliven's limited operating history; the significant net losses incurred since inception; the ability to raise additional capital to finance operations; the ability to advance product candidates through preclinical and clinical development; the ability to obtain regulatory approval for, and ultimately commercialize, Enliven's product candidates; the outcome of preclinical testing and early clinical trials for Enliven's product candidates, including the ability of those trials to satisfy relevant governmental or regulatory requirements and the potential that the outcome of preclinical testing and early clinical trials may not be predictive of the success of later clinical trials; Enliven's limited resources; the risk of adverse events, toxicities or other undesirable side effects; potential delays or difficulties in the enrollment or maintenance of patients in clinical trials; the decision to develop or seek strategic collaborations to develop Enliven's current or future product candidates in combination with other therapies and the cost of combination therapies; Enliven's limited experience in designing clinical trials and lack of experience in conducting clinical trials; the substantial competition Enliven faces in discovering, developing, or commercializing products; the ability to attract, hire, and retain highly skilled executive officers and employees; the ability of Enliven to protect its intellectual property and proprietary technologies; the scope of any patent protection Enliven obtains or the loss of any of Enliven's patent protection; developments relating to Enliven's competitors and its industry, including competing product candidates and therapies; reliance on third parties, contract manufacturers, and contract research organizations; and legislative, regulatory, political and economic developments and general market conditions. Information regarding the foregoing and additional risks may be found in the section entitled "Risk Factors" in documents that Enliven files from time to time with the Securities and Exchange Commission. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

The Enliven Story

Discovery process rooted in **validated biology**, **differentiated chemistry**, and **disciplined trial design**

Capital-efficient approach on **high potential programs** aiming to develop **first-in-class** or **best-in-class** candidates

ELVN-001 and ELVN-002 supported by **preclinical evidence** of an **improved therapeutic index**

Multiple **near-term milestones** in lead programs targeting **large** and **attractive markets**

Experienced team with a track record of inventing and developing **multiple FDA-approved cancer therapies**

Strong balance sheet expected to provide cash runway into late 2026

Highly Distinguished & Industry-Leading Team

Leadership Team

Sam Kintz, MBA
Co-founder and CEO
abbvie
Genentech
A Member of the Roche Group

Joe Lyssikatos, PhD
Co-founder and CSO
ARRAY BIOPHARMA
Genentech
A Member of the Roche Group

Anish Patel, PharmD
Co-founder and COO
abbvie
pharmacyclics
An AbbVie Company

Helen Collins, MD
CMO
FivePrime
GILEAD

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CFO, Head of
Corporate Development
Goldman Sachs

Galya Blachman, PhD
Chief Legal Officer,
Head of BD
5AM VENTURES
abbvie

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blueprint MEDICINES
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FivePrime
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AVIDITY BIOSCIENCES

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GILEAD

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Bristol Myers Squibb
Jazz Pharmaceuticals

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Oregon Health &
Science University

Lori Kunkel, MD
Loxo Oncology,
Pharmacyclics

Kevin Koch, PhD
Array Biopharma,
Edgewise Therapeutics

Leadership Team with Broad Range of Experience and Success

World-Renowned Chemists

- Inventor or co-inventor of over **20 product candidates** that have advanced to clinical trials

Precision Oncology and Kinase Inhibitor Experts

- Led or been involved with the discovery, development, or commercialization of over **60 kinase inhibitor programs**

Leaders with a Track Record of Success

- Significant experience building and/or leading research, development, and commercial operations

FDA-Approved Drugs Co-Invented by Enliven Chemists

MEKTOVI® (binimetinib) 15 mg tablets

Koselugo™ (selumetinib) 10 mg & 25 mg capsules

TUKYSA® tucatinib 50 mg | 150 mg tablets

Retevmo™ selpercatinib capsules 40 mg · 80 mg

Pipeline & Discovery Programs

Parallel lead product candidates:

Program	Target	Differentiation	Disease	Regimen	Discovery	IND-Enabling	Phase 1	Phase 2	Phase 3	Next Milestone	Milestone Expected
ELVN-001	BCR-ABL	Highly selective active site inhibitor w/activity against asciminib emergent mutations	CML	Monotherapy	monotherapy					Phase 1a Safety/Efficacy	2Q 2024
ELVN-002	HER2 & HER2 mutants	Irreversible, highly selective, CNS penetrant	NSCLC, other solid tumors	Monotherapy	monotherapy					Phase 1 Safety/Efficacy	2025
			HER2+ MBC and CRC	Combination	+ trastuzumab +/- chemotherapy					Phase 1a Safety/Efficacy	

Multiple discovery stage efforts ongoing at various stages

CML = Chronic myeloid leukemia. CNS = Central nervous system. CRC = colorectal cancer. IND = Investigational new drug. MBC = metastatic breast cancer. NSCLC = Non-small cell lung cancer.

Our Clinical Programs

ELVN-001

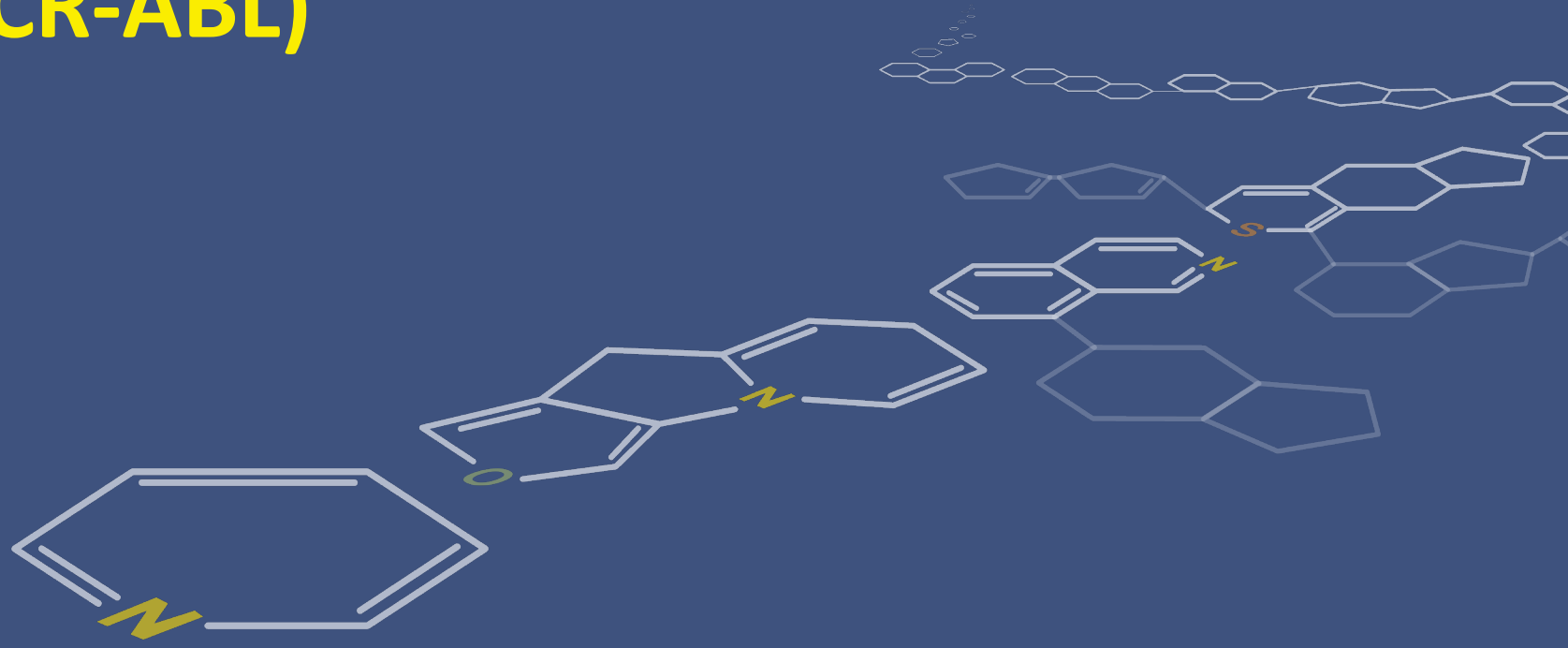
- Highly selective, active site, active form BCR-ABL inhibitor for the treatment of CML
- Designed to drive deeper responses and improve tolerability, safety and convenience compared to 1st, 2nd and 3rd Generation agents
- Precedent Phase 3 trials demonstrate a robust correlation between target coverage and 1L MMR, an established regulatory endpoint
- Significant market opportunity with >$6 billion of combined BCR-ABL TKI sales in 2022, despite generic options
- Clear need for better agents, demonstrated by successful launch of asciminib (Scemblix®), a recently approved 4th Generation TKI
- ELVN-001 has an MoA that is complementary to asciminib, and it has activity against known asciminib-resistant mutations
- Phase 1a dose escalation nearly complete in patients with CML who were resistant or intolerant to available therapies
- First clinical data disclosure expected in 2Q 2024

ELVN-002

- CNS penetrant, highly selective and irreversible HER2 and pan-HER2 mutant inhibitor
- Designed to maximize HER2 inhibition as well as enable rational combination therapies, particularly for HER2+ cancers
- Significant potential opportunity in NSCLC, CRC and MBC, especially as Enhertu® disrupts the current treatment paradigm across HER2-altered tumors leading to a new unmet need in patients who progress on, or are intolerant to, this new treatment option
- Recent clinical data with tucatinib (Tukysa®), a selective reversible HER2 TKI, suggest that dual HER2 targeting can produce clinically meaningful improvements in patients with HER2+ MBC and CRC
- Recently initiated an additional Phase 1 trial evaluating ELVN-002 combinations in HER2+ MBC and CRC based on supportive data from ongoing monotherapy Phase 1a
- Phase 1 monotherapy data and initial proof of concept combination data in HER2+ cancers expected in 2025

Precendent Phase 3 trials refer to three seperate head-to-head pivotal trials comparing the 12 month MMR rate in adults with CML between imatinib, the first generation TKI, and 2nd Generation TKIs (nilotinib, dasatinib, and bosutiinib).
1L = First line. CML = Chrionic meyloid leukemia. CRC = colorectal cancer. NSCLC = Non-small cell lung cancer. MBC = metastatic breast cancer. MMR = Major molecular response. MoA = Mechanism of action. TKI = Tyrosine kinase inhibitor.
References: Tukysa® (tucatinib) USPI.

ELVN-001 (BCR-ABL)



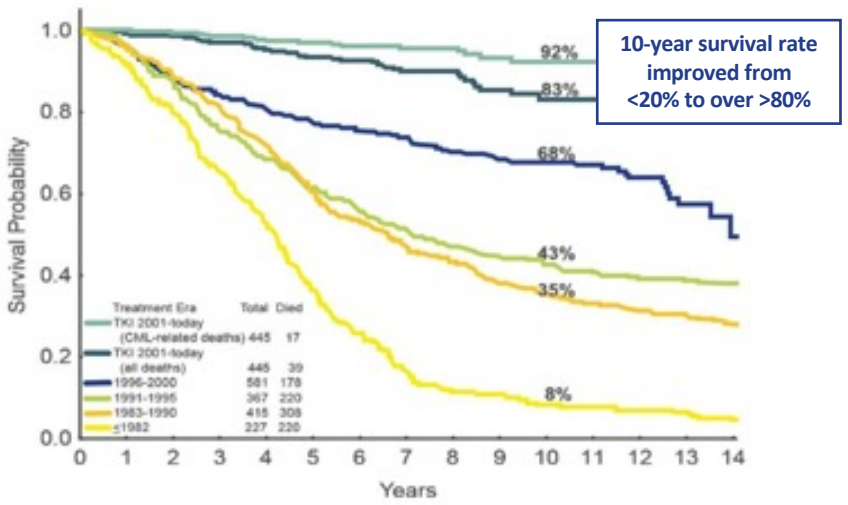
Chronic Myeloid Leukemia is Now a Long-Term Condition

As patients live longer on treatment, **quality of life** and **tolerability** have become important treatment goals

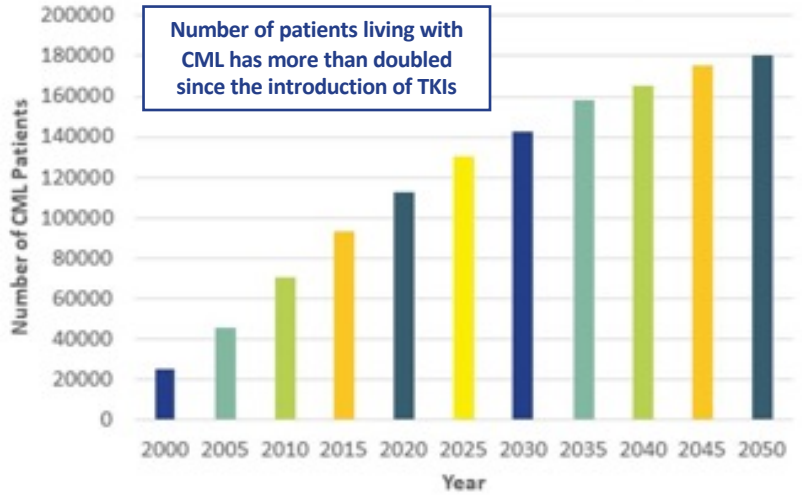
Prior to imatinib the annual CML survival rate was

<20%

CML 10-Year Survival Rate Over Time



Estimated Prevalence of CML in the US Over Time



- Prevalence is increasing globally with expected overall survival approaching age-matched controls
- CML has become a chronic disease that can require life-long TKI-treatment

Top Treatment Goals for Physicians and Patients*

1st **Maintain or improve quality of life**

2nd **Manageable side effects**

CML = Chronic myeloid leukemia. FIH = First-in-human. MMR = Major molecular response. TFR = Treatment-free reemission. TKI = Tyrosine kinase inhibitors.
References: Huang X et al. Cancer. 2012;118:3213-3127; Kantarjian et al. Chronic Myeloid Leukemia, In: Harrison's Principles of Internal Medicine. 2014.; Lang et al, EHA 2023.
*For patients who have received 2 prior therapies.

Significant Need Remains for Better Treatment Options for CML

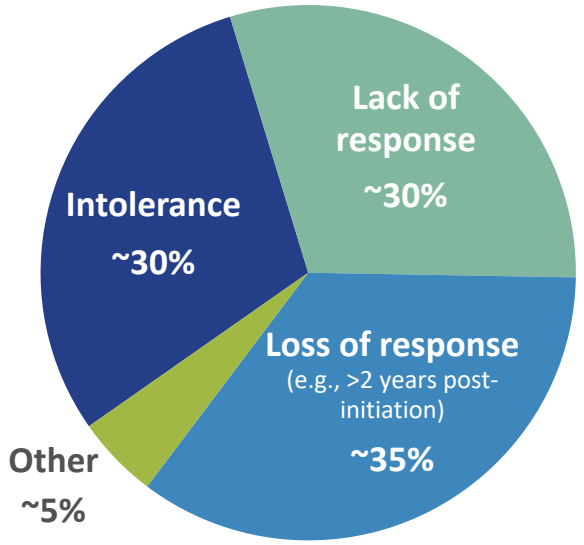
Challenges with Current Standard of Care

- Approximately **1 in 5 patients switch therapy** within the first year and **~40%** of patients switch in the first 5 years (1L & 2L)
- **Growing 3L+** patient population (>25% of CP-CML) with **limited treatment options**
- Except for asciminib, approved TKIs have **poor kinase selectivity,** resulting in tolerability issues that can impact efficacy
- **Long-term use of 2nd Generation TKIs is associated with adverse events** such as pleural effusions, GI and cardiovascular events
- Adverse events, comorbidities, restrictions with concomitant medications, and specific administration requirements may **impede long-term patient adherence**
- **Fewer than 10%** of patients successfully achieve sustained treatment-free remission (TFR)

77% of HCPs indicated need for more effective, safe, and tolerable agents for CML

Switching Dynamics Demonstrate Unmet Need

Rationale for Treatment Switching



In the US and EU3, majority of treatment switches across lines of therapy and TKIs are driven by intolerance or initial lack of molecular response (~60% combined)

1L = First line. 2L = Second line. 3L+ = Third line or later. 2nd Generation TKIs = Nilotinib, Dasatinib, Bosutinib. CML = Chronic Myeloid Leukemia. CP-CML = Chronic phase CML. GI = Gastrointestinal. TKI = Tyrosine kinase inhibitors, HCP = Healthcare professional. EU3 = France, UK, Germany.

References: HCP Qualitative & Quantitative Interviews (ClearView); Hochhaus A et al. ASH 2015; Hochhaus A et al. *Leukemia*. 2017; 31(7):1525-1531; Osorio S et al. *Ann Hematol*. 2018; 97(11):2089-2098; Rea et al. *Blood.* 2021; blood.2020009984; Baccarani M and Gale RP. *Leukemia.* 2021; 35:2199-2204; Icsluig® (ponatinib) USPI; Sprycel® (dasatinib) USPI; Tasigna® (nilotinib) USPI.; Bosulif® (bosutinib) USPI

Poor Selectivity Limits Tolerability & Efficacy of 1st, 2nd & 3rd Gen Agents

	Compound	Company	T315I Coverage	Off Target(s) & Treatment-Emergent, Non-Hematologic Adverse Events (All Gr / Gr 3+)		1L Efficacy	Drug & Administration Requirements	2022 FY Sales (USD)‡
	Imatinib (Gleevec®)	Novartis	X	c-KIT, CSFR-1, PDGFR	Peripheral Edema (20% / 0%) Nausea (41% / 2%)	28% MMR 3% MR4.5	Avoid strong CYP3A inhibitors or inducers	**$750M**
2nd Gen	**Dasatinib (Spyrcel®)**	BMS	X	SRC family, c-KIT, PDGFR-αβ	Fluid Retention (38% / 5%) Pleural effusions (28% / 3%) Diarrhea (22% / 1%)	46% MMR 5% MR4.5	Avoid strong CYP3A inhibitors or inducers, PPIs, antacids, and H2 blockers	**$2B**
2nd Gen	**Nilotinib (Tasigna®)**	Novartis	X	c-KIT, PDGFR, CSFR-1, DDR-1 (hERG Channel)	Rash (38% / <1%) Headache (32% / 3%) Nausea (22% / 2%); Diarrhea (19% / 1%) **Black Box:** QT Prolongation/Sudden Deaths	44% MMR 11% MR4.5	Avoid strong CYP3A inhibitors or inducers and PPIs; avoid food 2 hours before and 1 hour after each dose	**$2B**
2nd Gen	**Bosutinib (Bosulif®)**	Pfizer	X	SRC family	Hepatic dysfunction (45% / 27%) Diarrhea (75% / 9%) Abdominal Pain (39% / 2%)	41% MMR 7.5% MR4.5	Avoid strong CYP3A inhibitors or inducers, PPIs, antacids, and H2 blockers	**$575M**
3rd Gen	**Ponatinib (Iclusig®)**	Takeda	✓	KDR, FGFR, c-KIT, RET, FLT3, PDGFR	**Black Box:** Arterial Occlusive Events, Heart Failure, VTE, Hepatoxicity	N/A	Avoid strong CYP3A inhibitors or inducers	**$475M**
	Asciminib (Scemblix®)	Novartis	✓ **(US, high dose only)**	N/A	Hypersensitivity (32% / 2%) Hypertension (19% / 9%) Cardiovascular (13% / 3.4%)	Expected 2024	Avoid CYP2C9 substrates and certain statins; avoid food 2 hours before and 1 hour after each dose	**$500M**

A selective BCR-ABL inhibitor could yield enhanced target coverage, leading to greater efficacy and better long-term tolerability

1L = Front line. GI = Gastrointestinal. Gr = Grade. FY = Fiscal Year. MMR = Major Molecular Response. MR4.5 = Deep Molecular Response. PPI = Proton pump inhibitors. MMR and MR4.5 at 12 months. VTE = Venous thromboembolism.
‡ 2022 FY Sales (USD) B = billions, M = millions; numbers in the billions have been rounded to the nearest half billion and sales numbers in the millions have been rounded to the nearest $25 million increment from Company Investor Reports. Asciminib sales represents annualized sales based on the reported Q4 2023 sales figure of $125 million.

References: 1. Gleevec® (imatinib) USPI; 2. Sprycel® (dasatinib) USPI; 3. Kantarjian H et al. *NEJM*, 2010; 362(24):2260-70; 4. Cortes JE et al. *J Clin Oncol*. 2016; 34(20):2333-40; 5. Tasigna® (nilotinib) USPI; 6. Saglio G et al. *NEJM* 2010; 362(24):2251-9; 7. Hochhaus A et al. *Leukemia*. 2016; 30(5):1044-54; 8. Bosulif® (bosutinib) USPI. 9. Cortes JE et al. *J Clin Oncol*, 2012; 30(28):3486-92; 10. Iclusig® (ponatinib) USPI; 12. Scemblix® (asciminib) USPI.

Review of Asciminib (Scemblix®), 4th Generation Allosteric TKI

Observations

- Asciminib's **strong launch** demonstrates the **large market** size and **need for better agents**
- However, unmet needs still exist. In ASCEMBL, only **1.2% of patients discontinued due to PD/death, but due to lack of efficacy/AE:**
  - ~30% of patients discontinue by week 48
  - **~50% of patients discontinue** by week 96
- Asciminib has limitations:
  - **Resistance mutations** in both the allosteric binding site and the ATP pocket result in loss of activity
  - **Drug-drug interactions** require avoiding drugs that are CYP2C9 substrates (up to 20% of commonly prescribed medications)
  - **Requires fasting** 2 hours before and 1 hour after each dose
  - **Substrate for efflux transporters** (PgP & BCRP), which may contribute to **lack of efficacy**
  - Treatment of **T315I mutations requires 5x dose** resulting in more dose reductions (23%), increased pancreatic & liver enzyme elevation

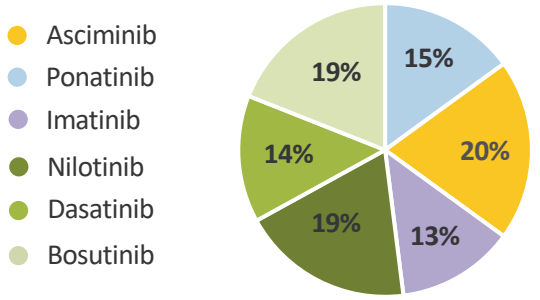
Scemblix's Robust Launch Continues to Demonstrate Patient Need for More Effective and Tolerable Agents

US 3L+ Approval	Q4 2021
EU 3L+ Approval	Q3 2022
1L Data Readout	H1 2024

$125M
4Q23 Sales

$500M of annualized sales

Current 3L+ Market Dynamics



~$2B
implied market size in 3L+ alone

AE = Adverse event. ATP = Adenosine triphosphate. PD = Progressive disease. TKI = Tyrosine kinase inhibitor. ASCEMBL: A phase 3, open-label, randomized study of asciminib vs bosutinib in CML after 2 or more prior TKIs.
References: Hochhaus et al. ASH 2020; Cortes et al. ASH 2020; ASH 2021; Scemblix (Asciminib) USPI; ASCO 2022; Eadie et al Oncotarget 2018; Pharmaceogent Genomics, 2010 Apr; 20(4):277-281]; November 2023 Novartis R&D Investor Event. HCP Qualitative & Quantitative Interviews (ClearView).
Note: Current Scemblix information and 3L+ Markey Dynamics based on November 2023 Novartis R&D Investor Event. Estimated 3L+ market size calculated using Scemblix Q3 23 annualized sales and 20% market penetrance. Sales numbers in the billions have been rounded to the nearest billion.

Our Strategy and Initial Positioning in an Evolving CML Market

	Treatment Paradigm			Market Insights	Market Size (U.S.)
1L (50%)	**1st Gen TKI** Imatinib 28% MMR	**2nd Gen TKIs** Nilotinib, Dasatinib, Bosutinib ~45% MMR		**~50% of patients start on 2nd Gen TKIs**, driven by faster & deeper molecular responses **Further improvements in efficacy or tolerability** may still allow for **new entrants in 1L** setting	~30K+
2L (30%)	**2nd Gen TKIs** ~35% MMR	**2nd Gen TKIs** ~20-25% MMR	**ELVN-001** 30-40%+ MMR Target*	HCPs consistently express high interest in prescribing **novel agents with improved safety/tolerability and efficacy in 2L+**	~18K+
3L+ (20%)	**2nd Gen TKI** Bosutinib ~20% MMR	**3rd & 4th Gen TKIs** Ponatinib 35% MMR Asciminib ~33% MMR		Asciminib has the potential to become the **preferred option in earlier lines of therapy** HCPs report up to **~25% of patients end up back on imatinib** in 3L+ setting	~12K+
T315I	**3rd Gen TKI** Ponatinib 58% MMR	**4th Gen TKI** High Dose Asciminib 58% MMR**	**ELVN-001** >50% MMR Target*	A **more tolerable choice for T315I patients** has the potential to displace ponatinib High dose asciminib is now an option only in the US, but **risks remain** (e.g., liver enzyme elevation)	~2K+

< $500M USD > $2B USD

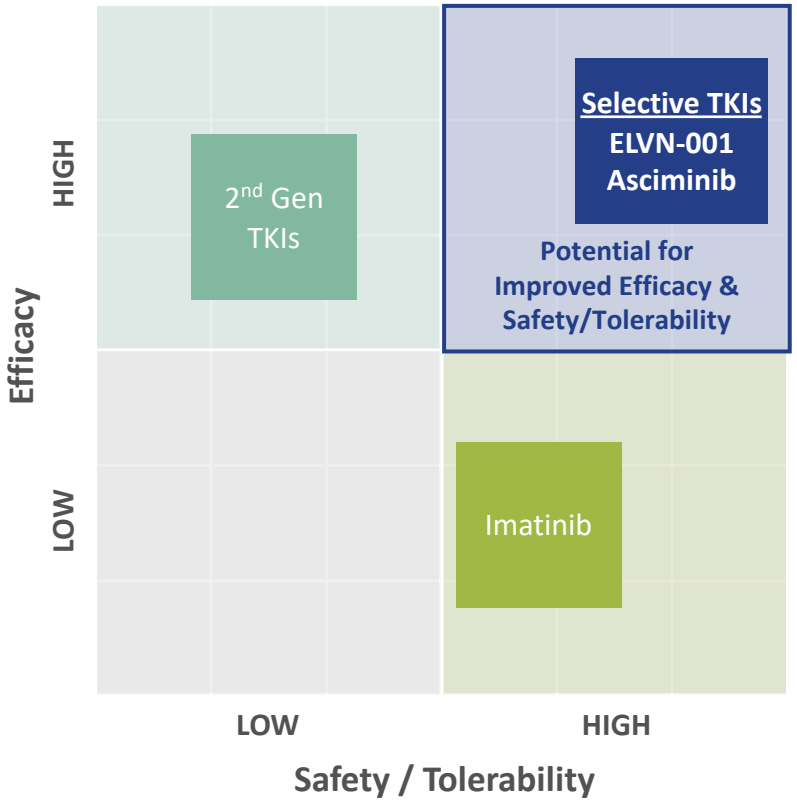
1L = First line. 2L = Second line. 2L+ = Second or later line. 3L+ = Third or later line. 2nd Gen TKIs = Nilotinib, Dasatinib, Bosutinib. CML = Chronic Myeloid Leukemia. MMR = Major Molecular Response at ~12 months. HCP = Health Care Provider.
*Depending on patient population; **Ponatinib-naïve patients (n = 21)

References: HCP Qualitative & Quantitative Interviews (ClearView); Gleevec® (imatinib) USPI; Tasigna® (nilotinib) USPI; Sprycel® (dasatinib) USPI; Bosulif® (bosutinib) USPI; Icsluig® (ponatinib) USPI; Scemblix® (asciminib) USPI; Hochhaus et al. ASH 2020; Cortes JE et al. *Blood.* 2020; 136(Supplement1):47-50.

ELVN-001 Potential Positioning in Future CML Treatment Paradigm

Limitations of Current Treatment Paradigm

(if data supports)



Future Treatment Paradigm

(if data supports)

1L	**1st Gen TKI** Imatinib	**4th Gen TKI** Asciminib
2L	**4th Gen TKI** Asciminib	**ELVN-001**
3L+	**ELVN-001**	

Market Insights & Assumptions

Asciminib could capture significant 1L market share given potentially superior efficacy compared to imatinib & **improved tolerability compared to 2nd Gen TKIs**

ELVN-001 is well-positioned to follow asciminib given its **unique binding mode and complementary MoA** (ATP-site/active form vs. allosteric/inactive form)

With more early line use of asciminib, there may be a significant **need for treatment options with improved efficacy & tolerability** in later lines

- Additionally, an **opportunity may exist to compete directly with asciminib across lines of therapy** based on differentiated efficacy, tolerability or administration requirements

1L = First line. 2L = Second line. 2L+ = Second line. 3L+ = Third or later line. Gen = Generation. 2nd Gen TKIs = Nilotinib, Dasatinib, Bosutinib. CML = Chronic Myeloid Leukemia. MoA = Mechanism of action. TKI = Tyrosine kinase inhibitor.
References: HCP Qualitative & Quantitative Interviews (ClearView).
Note: Illustrative current and future treatment paradigm.

ELVN-001 Clinical Focus and Target Product Profile

Our Opportunity

Drive Deeper Responses | **Improve Tolerability** | **Enhance Safety & Convenience**

Target Product Profile

- Activity against native BCR::ABL1, T315I, and known asciminib-resistant mutations
- **Highly selective:** No/minimal clinically relevant off-target toxicity
- **Efficacy**: MMR greater than approved TKIs driven by an enhanced therapeutic window
- **Tolerability**: Fewer dose reductions & discontinuations
- **Safety**: No black box warnings; no edema, effusions, reduced GI toxicity
- **No restrictions** with concomitant medications

Phase 1a/b: Dose Escalation in Late Line

- Patients with CML who have exhausted all available treatment options
- Seek to demonstrate improved therapeutic window & efficacy (BCR::ABL1 transcript level reductions) in highly resistant/intolerant disease

Phase 1b: Expansions

- Begin enrolling earlier lines of patients
- Seek to demonstrate the potential for improved tolerability and efficacy compared to 2nd Gen TKIs
- Generate data supportive of an early line pivotal study

Current Goal: Early Line H2H vs Physician's Choice

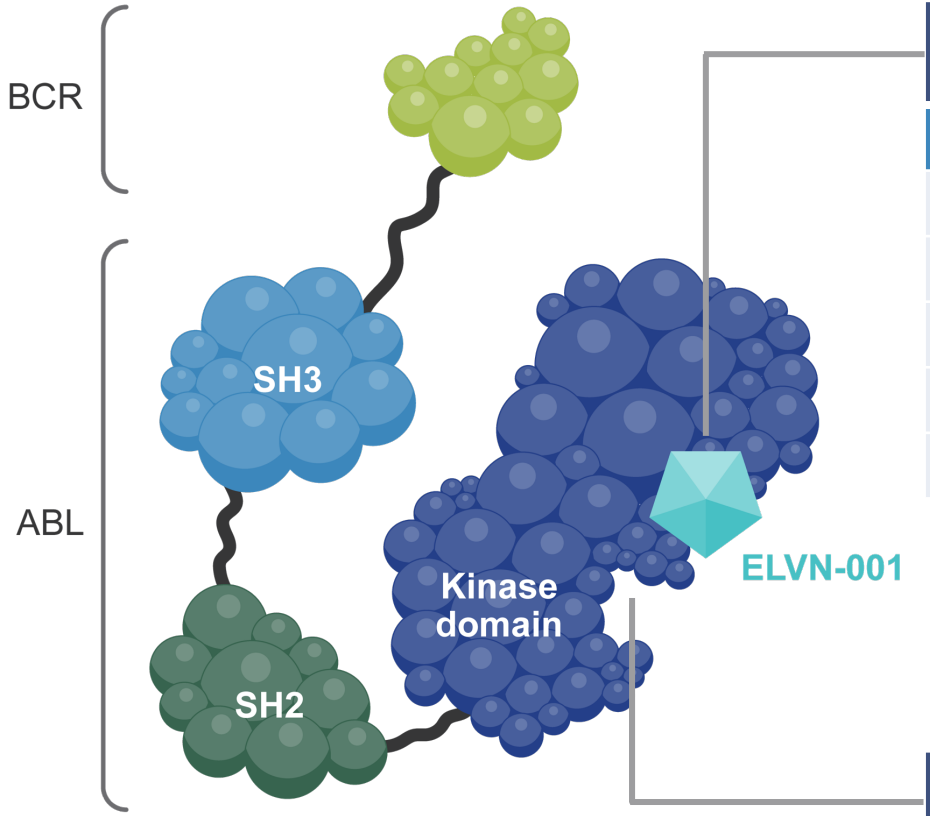
- Superiority based on 6m and 12m MMR in CP-CML
- Better overall tolerability, fewer dose reductions & discontinuations vs. approved agents

Optionality: 4L+ and T315I mutation

- Single-arm study; precedent for approval in late line based on CCyR/MR2 (ponatinib, OPTIC study)
- T315I mutation in ponatinib or asciminib progressed, intolerant, or ineligible

CCyR = Complete cytogenetic response. CML = Chronic Myeloid Leukemia. CP-CML = Chronic phase CML. H2H = Head-to-head. M = Month. MMR = Major molecular response. MR2 = BCR::ABL1 < 1%. TKI = Tyrosine kinase inhibitor.

ELVN-001 is a Selective Active Site, Active Form Inhibitor of BCR::ABL1



ATP-BINDING SITE

DRUG	BINDING CONFORMATION
ELVN-001	**Active**
BOSUTINIB	Active
DASATINIB	Active
IMATINIB	Inactive
NILOTINIB	Inactive
PONATINIB	Inactive

MYRISTOYL POCKET

DRUG	BINDING CONFORMATION
ASCIMINIB	**Inactive**

Key Attributes of ELVN-001:

- Type 1 small molecule inhibitor of BCR::ABL1 targeting the ATP-binding site of the ABL1 kinase domain that binds to a unique P-loop “folded-in” active conformation of ABL1
- Unique binding mode confers exquisite selectivity against the broader kinome
- Broad activity against multiple clinically important BCR::ABL1 mutations, including T315I, and those that confer resistance to asciminib
- Unlike all the approved TKIs, ELVN-001 is not a substrate for the common drug efflux transporters, PgP and BCRP, which may play a role in resistance to TKIs in CML

ATP = Adenosine triphosphate. CML = Chronic Myeloid Leukemia. TKI = Tyrosine kinase inhibitors.

References: Braun T. et al. *Cancer Cell* 2020 2020 Apr 13;37(4):530-542; Qiang W et al., Mechanisms of Resistance to the BCR-ABL1 Allosteric Inhibitor Asciminib; Leukemia 2017.

ELVN-001 Has a Differentiated and Attractive Profile for CML

IC_{50} values (nM)	Asciminib	Ponatinib	Nilotinib	ELVN-001
KCL-22 (BCR-ABL^{wt}) cytotox IC_{50} (50% human serum)	7	1	90	19
KCL-22 (BCR-ABL^{T315I}) cytotox IC_{50} (50% human serum)	>1,150	14	>10,000	131
K-562 (BCR-ABL^{wt}) cytotox IC_{50} (50% human serum)	85	4	228	65
K-562 pCRKL IC_{50} (100% human serum)	**N/A**	**36**	**1,080**	**112**
HL-60 cytotox IC_{50} (10% FBS)	12,200	366	5,050	3,550
Human Hepatocyte stability, extraction ratio	64	62	62	**0**
Plasma Protein Binding (% unbound)	~2	< 1	< 1	40
CYPs (% inhibition @ 10 µM)	All < 50%	All < 50%	2C8, 2C9, 3A4, 2C19 > 50%	All < 50%
hERG IC_{50} (µM)	25	2.3	0.13	>30
BCRP Substrate	Yes	Yes	Yes	**No**

Strong correlation to MMR in humans

BCRP may play a role in CML resistance to TKIs

- **Good potency** in the presence of human serum against native BCR-ABL and T315I (smaller potency shift compared to ponatinib & asciminib)
- Designed for safe and flexible use including **reduced risk of DDIs**, appropriate for a chronic disease setting
- Predicted human PK will enable **maximal target coverage** through the full dosing window

CML = Chronic Myeloid Leukemia. DDI = Drug-drug interaction. TKI = Tyrosine kinase inhibitors.
Note: IC values represent an average derived from multiple runs internally with a minimum of two independent experiments. ADMET data were generated internally or obtained from literature including NDAs. Results of a head-to-head comparison may differ from those set forth herein.

ELVN-001 is Selective for ABL1

- ELVN-001 has a **very selective kinase profile**
  - Clean against key off-target kinases in cells compared to 2nd and 3rd Gen TKIs
  - 372 kinases screened at 1 µM compound (100 µM ATP)
  - Kinases with >50% inhibition selected for IC_{50} determination
  - >100x window vs. all but 2 kinases profiled
- ELVN-001 is also very clean (>10 µM) in an *in vitro* safety panel of >130 receptors

Cellular Phosphorylation IC_{50} (nM)

	cKIT	FLT3wt	PDGFRb	VEGFR2	cSRC
ELVN-001	>10,000	>10,000	>10,000	>10,000	>10,000
Ponatinib	30	3.8	89	4.8	630
Nilotinib	200	>10,000	720	2,900	>10,000
Dasatinib	0.6	>1,000	7.1	>1,000	10
Bosutinib	1,000	4,700	7,900	>10,000	16

ELVN-001 (100 µM ATP)

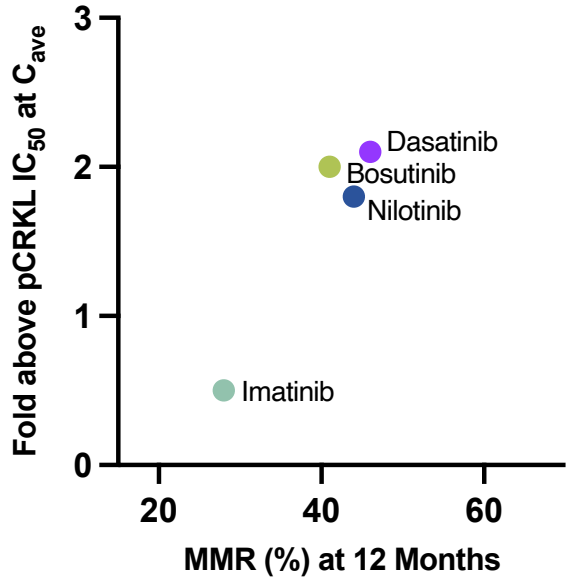
Kinase	IC_{50} (nM)
ABL1	**1**
ABL2/ARG	31
TRKC	41
TNIK	110
LOK/STK10	183
LRRK2	486
FGR	550
ACK1	698
FYN	725
HGK/MAP4K4	973
LCK	>1,000

Large window for ABL2/ARG may result in a favorable safety profile

2nd Gen = Nilotinib, Dasatinib, Bosutinib. 3rd Gen = Ponatinib. ATP = Adenosine triphosphate. TKI = Tyrosine kinase inhibitors.
Reference: Abl kinases are required for vascular function, Tie2, and angiopoietin-1-mediated survival. Pendergast et al. *PNAS*. 2013;110(30):12432-7.
Note: IC values used to calculate fold shift represent an average derived from multiple runs internally with a minimum of two independent experiments.

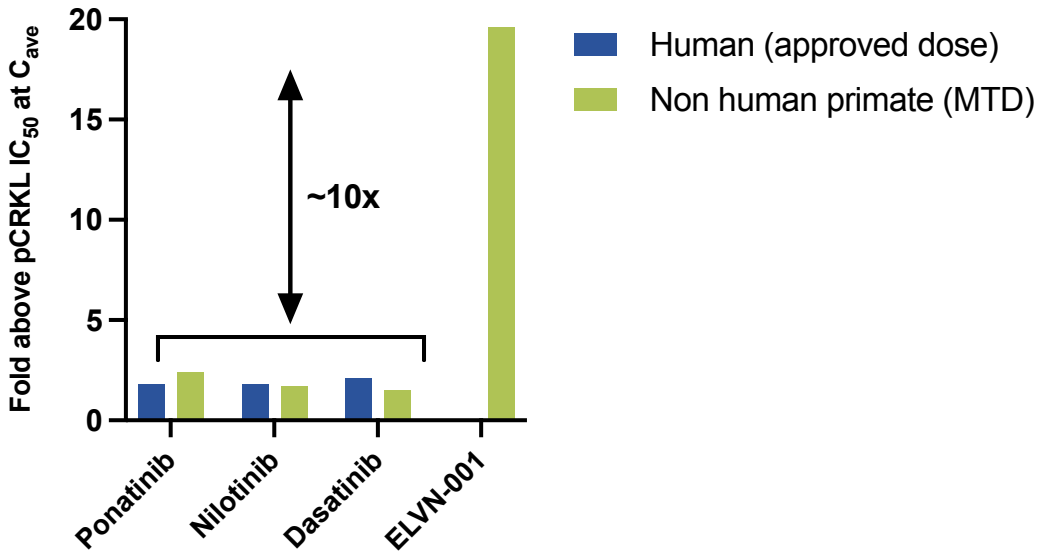
ELVN-001 Potentially Affords an Improved Therapeutic Index

Target Coverage at C_{ave} vs. 1L MMR



- Clear correlation between target coverage of the approved active site agents and 1L MMR at 12 months (from H2H pivotal studies)
- Phosphorylated CRKL or pCRKL IC_{50} represents a robust pharmacodynamic marker for BCR-ABL inhibition

Therapeutic Index vs. NHP Safety Margin



- Toxicology studies with other ABL TKIs show that the maximum tolerated drug exposure is similar between non-human primates and humans*
- Data suggests ELVN-001 has the potential for a significantly greater therapeutic index than approved active site TKIs

1L = First line. CRKL = Crk like protein. H2H = Head to head. MMR = Major molecular response. MTD = Maximum tolerated dose. NHP = Non-human primate.
NHP data for ponatinib, nilotinib, and dasatinib were obtained from the data reported for the maximum tolerated dose (MTD) in their respective NDAs. NHP data from 28-day GLP tox study for ELVN-001 at 5 mg/kg, a well-tolerated, no adverse event dose (NOAEL).
*No data for bosutinib in NHPs available.
y-axis: mean C_{ave} plasma concentration at the human approved dose (or NHP MTD) divided by K562 pCRKL IC_{50} in 100% human serum; C_{ave} = steady state plasma exposure area under the curve, AUC (ng*hr/mL), divided by 24 hours
Note: IC values represent an average derived from multiple runs internally with a minimum of three independent experiments.
References: Human PK References: (Imatinib) Peng et al. *J Clin Oncol*. 2004; 22:935-942. DOI: 10.1200/JCO.2004.03.050; (Nilotinib) Tasigna® USPI; (Bosutinib) Bosulif® USPI; (Dasatinib) Spyrcel® USPI; (Ponatinib) Iclusig® USPI.
MMR References: (Bosutinib) Cortes JE et al. *J Clin Oncol*. 2012; 30(28):3486-92; (Nilotinib and Imatinib) Saglio G et al. *NEJM*. 2010; 362(24):2251-9; (Dasatinib) Kantarjian H et al. NEJM, 2010; 362(24):226.

BCR::ABL1 Mutations Conferring Resistance to Asciminib (ASCEMBL)

ELVN-001 maintains activity against the emerging BCR::ABL1 mutations known to confer resistance to asciminib; and activity against T315I similar to ponatinib

Emerging BCR-ABL mutations upon discontinuation due to lack of efficacy or progressive disease

	Asciminib (n=39)	Bosutinib (n=30)
No mutations	22 (56%)	20 (67%)
ATP Binding Site	M244V (n=3), E355G, F359V, T315I	T315I, V299L
Myristoyl Binding Pocket	A337T (n=3), P465	None

Fold Shift from BCR::ABL1 wt (Ba/F3 Cells)

	T315I	M244V	A337T	E355G	F359C	F359V	P465S
Asciminib	96	611	173	>2380	>2380	>2380	>2380
ELVN-001	**4**	**2**	**1**	**4**	**3**	**2**	**2**
Dasatinib	2935	2	1	3	4	2	2
Bosutinib	113	3	1	4	5	5	4
Ponatinib	3	2	1	3	5	5	2
Imatinib	>20	3	1	8	18	10	4
Nilotinib	>341	2	1	5	33	21	3
Vodobatinib	445	2	1	3	10	7	2
Olverembatinib	5	2	1	3	6	6	2

Most frequent mutation at baseline and end of treatment in patients that switched off asciminib in ASCEMBL*

*ASCEMBL: A phase 3, open-label, randomized study of asciminib vs bosutinib in CML after 2 or more prior TKIs. CML = Chronic myeloid leukemia. TKI = Tyrosine kinase inhibitor.

References: Rea et al., Blood (2021) 138 (21): 2031–2041.

Note: IC values represent an average derived from multiple runs internally with a minimum of two independent experiments.

ELVN-001 Clinical Development Strategy

Phase 1

- CP-CML patients who have failed or are intolerant to all available therapies
- T315I mutation

GOALS

- Demonstrate potential for efficacy superior to 1st & 2nd Gen TKIs (at least as good as asciminib & ponatinib) at well tolerated dose(s)
- Identify dose(s) for Phase 1b and beyond

Phase 1b / 2

- Begin enrolling early line patients
- Continue late line single arm & T315I single arm

GOALS

- Establish PoC for deep, durable and tolerable responses in earlier lines of CML
- Demonstrate efficacy and safety profile suitable for initiating an early line pivotal study

Registrational / Phase 3

- Initiate early line H2H vs. Physician's Choice
- Potentially file on 4L+ and T315I single arm data

GOALS

- Initiate early line H2H study for broad label accelerated approval in CP-CML
- Consider pursuing accelerated approval in late line CP-CML and/or T315I CML

4L+ = Fourth line or later. CML = Chronic Myeloid Leukemia. CP-CML = Chronic-phase CML. H2H = Head-to-head. MMR = Major molecular response. PoC = Proof of concept. TKI = Tyrosine kinase inhibitor.

ELVN-001 || Current Status

Ongoing Phase 1a in Late Line CML

- Phase 1a dose escalation is nearly complete
- Inclusion: patients who are resistant/intolerant to available therapies for “their CML”
  - Most enrolled patients had been heavily pretreated
  - All enrolled patients had received at least one 2nd Gen or later TKI, and many had received ponatinib and/or asciminib
- Generally, two types of patients have enrolled:
  - Patients who had achieved a molecular response but could not tolerate prior TKIs. For these patients, a key benefit and **potential driver of commercial use is maintaining or improving molecular response with better tolerability**
  - Patients with high or increasing baseline BCR::ABL1 transcripts who had not responded or lost response to prior TKIs. For these patients, achieving a **decline in transcript levels supports early proof of concept**
- Given the **robust correlation between target coverage and MMR established by other TKIs in early lines of therapy**, we hope to demonstrate that ELVN-001 can achieve the same or greater target coverage as 2nd Gen TKIs, while also having an improved tolerability profile compared to 2nd Gen TKIs
- We expect to have enrolled >20 patients in an efficacious dose range at the time of first data disclosure; and expect that 10-20 patients will have been treated for >3 months

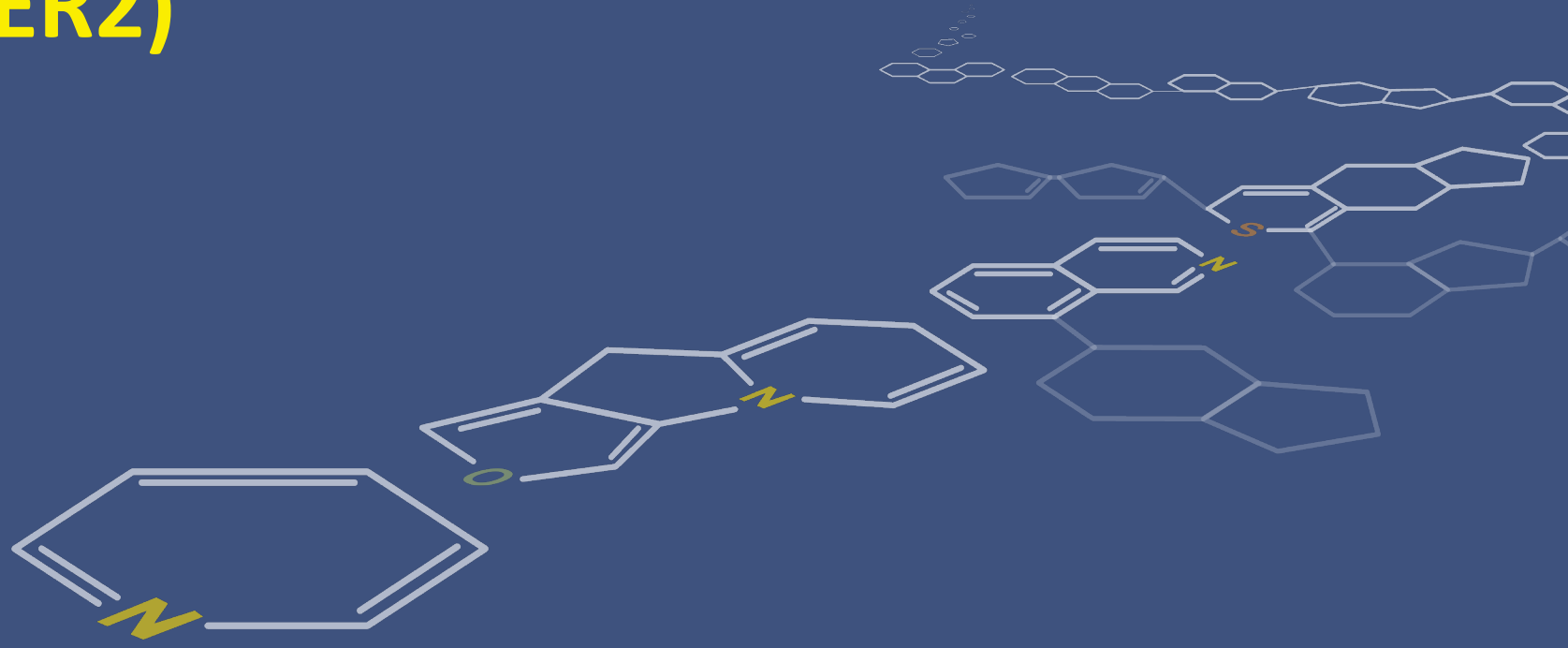
Key Benchmarks for Late Line CML

- In the 3L setting (post-imatinib and a 2nd generation TKI), the efficacy benchmark is 20-30% MMR by 6 months
  - In 4L & 5L, 2nd Gen TKI efficacy falls off rapidly, for example:
    - 0% 6-month MMR in 5L bosutinib
    - 16% 6-month MMR for 5L asciminib
- MMR is a high-bar in TKI-resistant CML
  - In patients with CML resistant to non-ponatinib TKIs, only 3/28 (~10%) achieved MMR by 6-months in the asciminib Phase 1 study
- Post-ponatinib responses are even lower with available therapies
  - In asciminib’s Phase 1, the MMR rate in patients resistant to ponatinib was 0/4 by 6 months, and only 1/8 in T315I CML
- In addition to MMR, 1-log reductions in BCR::ABL1 can support proof of concept of efficacy
  - For example, in asciminib’s Phase 1 ~20% of patients with baseline BCR::ABL1 transcript levels >10% achieved levels <1% by 6 months

3L = Third line. 4L = Fourth line. 5L = Fifth line. 2nd Gen TKIs = Nilotinib, Dasatinib, Bosutinib. CML = Chronic Myeloid Leukemia. MMR = Major molecular response. TKI = Tyrosine kinase inhibitor.

References: Rea D et al. Blood. 2021;blood.2020009984. DOI: 10.1182/blood.2020009984. Hughes, et al NEJM 2019. Mauro, et al. Leukemia 2023.

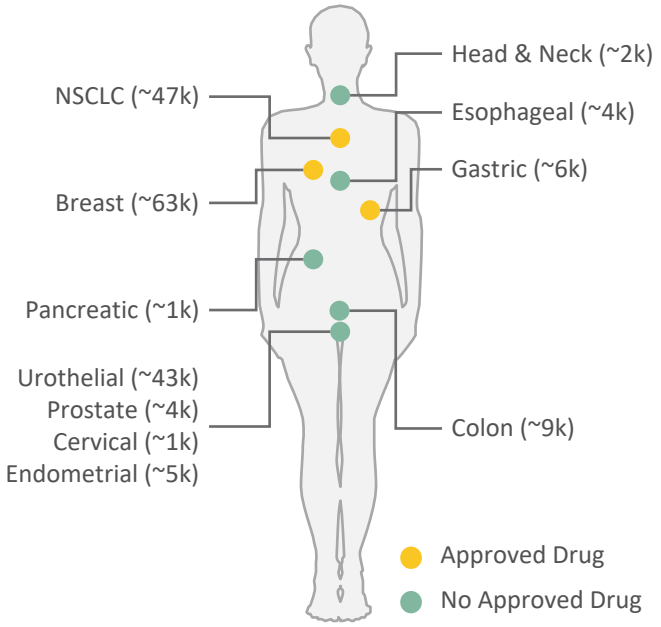
ELVN-002 (HER2)



Substantial Opportunity in HER2-altered Patient Populations

Reshuffling of Treatment Paradigm Could Create a Significant Post-Enhertu® Opportunity Across HER2-altered Cancers

U.S. Incidence of HER2-altered Tumors



WW HER2+ Sales	2022A	2028E
PERJETA	$4.3B	$2.5B
Herceptin trastuzumab	$2.3B	$0.9B
Kadcyla trastuzumab emtansine	$2.2B	$0.9B
ENHERTU fam-trastuzumab deruxtecan-nxki	$1.6B	$10.3B
PHESGO	$0.8B	$2.0B
TUKYSA tucatinib	$0.4B	$1.2B
Total	**~$12B**	**~$18B**

Multi-billion-dollar market opportunity post-Enhertu® with **~25% of patients receiving Enhertu® progressing within 12-months and up to 50% of patients developing brain metastases**

Multiple Early-Line Settings Without Entrenched Drugs

- Lack of approved drugs for key tumors harboring HER2 mutations (e.g., 1L NSCLC) and HER2 amplified or overexpressing tumors (e.g., NSCLC and CRC)
- Trial timing opens the window for multiple fast-follower and follow-on opportunities

Key HER2 1L Trials

MBC			
Compound	**Company**	**Stage**	**Timing**
ENHERTU fam-trastuzumab deruxtecan-nxki	Daiichi-Sankyo	Phase III Ongoing	Initiated in Apr '21

HER2 Mutant NSCLC			
Compound	**Company**	**Stage**	**Timing**
ENHERTU fam-trastuzumab deruxtecan-nxki	Daiichi-Sankyo	Phase III Ongoing	Initiated in Dec '21
Zongertinib	Boehringer Ingelheim	Phase III Ready	Initiating in 2024

CRC			
Compound	**Company**	**Stage**	**Timing**
TUKYSA tucatinib	Seagen	Phase III Ongoing	Initiated in Oct '22

1L = First line. CRC = Colorectal cancer. HER2-altered = HER2 amplification/overexpression and HER2 mutant. MBC = Metastatic breast cancer. NSCLC = Non-small cell lung cancer.

References: EvaluatePharma. Cancer Metastasis Rev (2015) 34:157–164. Oncologist. 2019 Dec; 24(12): e1303–e1314. Seer, National Cancer Institute.

Significant Opportunities for ELVN-002 in a Rapidly Evolving Landscape

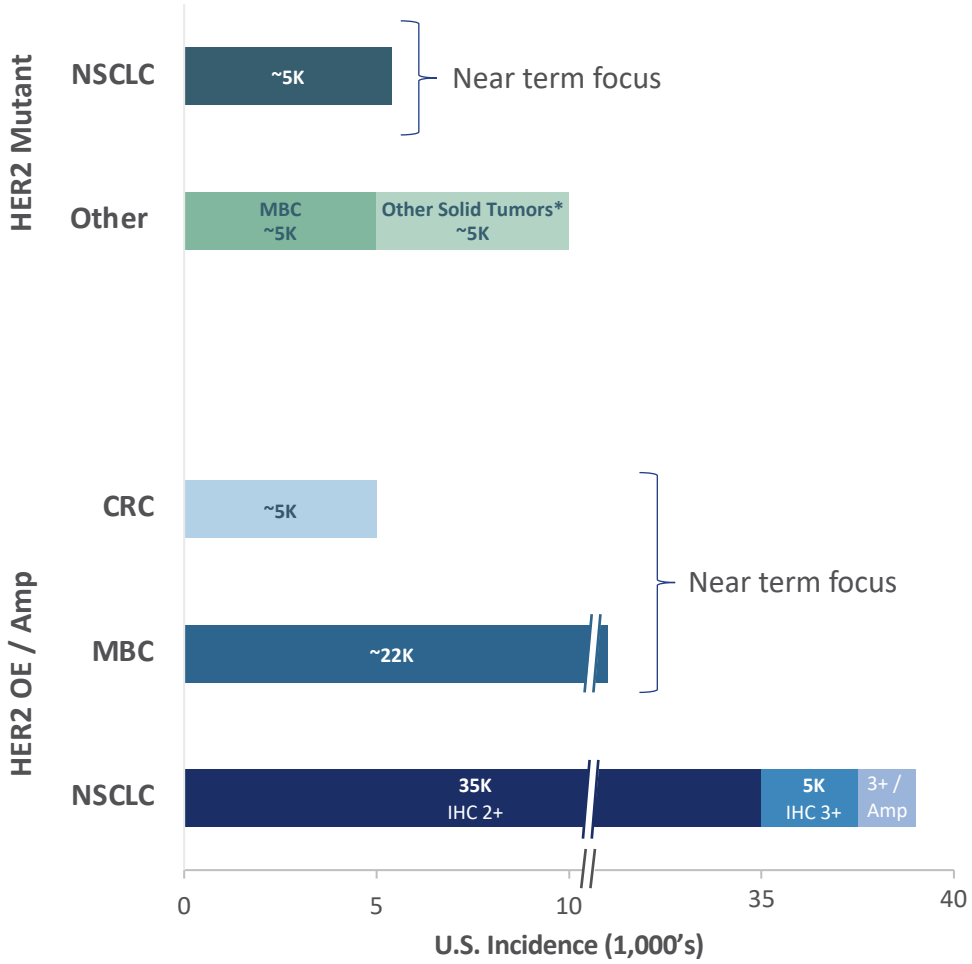
HER2 Mutant NSCLC and Other HER2 Mutant Cancers

- Approximately 3% of NSCLC patients harbor HER2 mutations, for which there are **no approved TKIs**
- Currently there is a **high unmet need** in this indication, but the landscape is evolving as ADCs and multiple investigational TKIs emerge
- Other HER2 mutant cancers represent a **larger market** with **limited treatment options**

HER2 Amplified or Overexpressing Cancers

- Largest potential market opportunity, with **nearly 70K addressable patients**
- As Enhertu® disrupts earlier lines of therapy in a broad set of indications, a **follow-on TKI combination** opportunity exists
- **Tukysa® (tucatinib) is generating >$400M annualized revenue** with a 2L+ HER2+ MBC label in combination with trastuzumab + chemotherapy (capecitabine)
- Recent tucatinib data shows **dual HER2 targeting without the need for chemotherapy** has clinical benefit in HER2+ CRC
- Additionally, recent tucatinib + Kadcyla® data in HER2+ MBC **supports a larger opportunity in MBC** and the **rationale for ADC + TKI combinations more broadly**
- Currently, **no targeted therapies are approved for HER2+ NSCLC**

U.S. Market Size Estimates (approximate)



*Other cancers include prostate, endometrial, gastric, stomach, hepatobiliary, etc.
2L+ = Second line or later. ADC = Antibody drug conjugate. CRC = Colorectal cancer. IHC = Immunohistochemistry. TKI = Tyrosine kinase inhibitors. NSCLC = Non-small cell lung cancer. MBC = Metastatic breast cancer. OE = Overexpressing. Amp = Amplified.
Reference: National Cancer Institute. SEER*Stat software. Bethesda, MD: National Cancer Institute, Surveillance Research Program; Robichaux et al. *Cancer Cell.* 2019;36(4):444-457.e7.
Note: Tukysa® annualized revenue calculated based on $102 million of revenue in Q3 2023

ELVN-002: Opportunity for a CNS Penetrant, Selective and Irreversible Pan-Mutant HER2 TKI

Current HER2 TKI Landscape & Limitations

- The **high degree of structural homology** between EGFR and HER2 makes it difficult to design HER2-selective inhibitors
- Tucatinib is the **only approved HER2-selective TKI,** but is a **reversible inhibitor and only achieves IC_{90} coverage in ~40% of patients**
- Tucatinib also **lacks potency against key mutations** in NSCLC and breast cancer
- Most approved and investigational **irreversible TKIs** are **dual EGFR/HER2 inhibitors** and are **dose-limited by EGFR-driven toxicity**
- Current HER2 TKIs potentially **leave room for further improvement in addressing brain metastases**

Our HER2 Candidate: ELVN-002

- Designed to **irreversibly inhibit HER2 and multiple key HER2 mutations** in NSCLC and breast cancer, including HER2 YVMA and L755, and
- Selectively inhibit HER2 while **sparing EGFR** to prevent EGFR-related toxicities, with the potential for **improved efficacy** across HER2-driven cancers
- Deliberately **designed to enable rational combination therapies**, particularly for HER2+ cancers
- Demonstrated **superior pre-clinical activity** in HER2-amplified **subcutaneous and intracranial models**, and an **improved safety margin** in NHPs compared to tucatinib

ELVN-002 was designed to achieve an improved therapeutic index compared to current approved and investigational TKIs in the broad HER2 population, including HER2 mutant and amplified / overexpressed tumors.

CNS = Central nervous system. NSCLC = Non-small cell lung cancer. TKI = Tyrosine kinase inhibitor. NHP = non-human primate.

References: Tucatinib NDA; Moulder SL et al. Data from a Completed Phase 1 Study to Assess the Safety, Tolerability and PK of ARRY-380 - an Oral Inhibitor of HER2. SABCS, December 8-12, 2010, San Antonio, TX.

ELVN-002 Clinical Focus and Target Product Profile

Our Opportunity

Drive Durable Responses | **Well Tolerated** | **CNS activity**

Target Product Profile

- **Activity against:**
  - HER2 mutant NSCLC (e.g., Exon 20 IM) and breast cancer (e.g., L755x)
  - HER2 amplified and/or overexpressed tumors (breast, CRC, NSCLC, etc.)
  - Brain metastases
- **Selective:** does not inhibit wild-type EGFR
- **Safety/tolerability**: minimal GI and skin toxicity (avoid EGFR-toxicity)
- **Combinable** with SOC including ADCs across HER2-driven tumors

Phase 1a Dose Escalation in solid tumors with HER2 alterations

- Monotherapy in HER2-altered solid tumors
- Evaluate the combination with ADCs in HER2+ breast cancer and HER2 NSCLC

Phase 1b in HER2 mutant NSCLC

- Complete Phase 1b, establish monotherapy dose
- Consider 2L+ single-arm study with potential to support accelerated approval

Phase 1 in HER2 Overexpressed/Amplified MBC & CRC

- Initiation of additional Phase 1 trial in combination with trastuzumab +/- chemotherapy
- Expected FPI for Phase 1a in mid-2024

Multiple Indication Opportunities

- Driving proof of concept for mono/combo therapy in multiple tumors (mutant NSCLC, HER2+ breast and CRC)
- With additional indications to explore (HER2+ NSCLC and other HER2-driven solid tumors)

ADC = Antibody drug conjugate. CRC = Colorectal cancer. IM = Insertion mutations. CNS = Central nervous system. FPI = First patient in. GI = Gastrointestinal. IM = insertion mutations. NSCLC = non-small cell lung cancer. MBC = Metastatic breast cancer.
SOC = Standard of care. TKI = Tyrosine kinase inhibitors.

ELVN-002 Potently Inhibited HER2 & HER2 Mutants While Sparing EGFR

IC_{50} values (nM)	Pyrotinib	Tucatinib	Compound (I) WO2023066296*	Zongertinib	ELVN-002
BT474 $HER2^{WT}$ pHER2 IC_{50} (10% FBS)	13	12	19	30	8.5
Beas2b $HER2^{S310F}$ pHER2 IC_{50} (10% FBS)	1.4	9.6	6.4	2	1.8
Beas2b $HER2^{L755S}$ pHER2 IC_{50} (10% FBS)	4.5	47	12	5.4	3.5
Beas2b $HER2^{YVMA}$ pHER2 IC_{50} (10% FBS)	4.5	74	20	1.5	3.4
BT474 $HER2^{WT}$ pHER2 IC_{50} (50% human serum)	**40**	**37**	**134**	**164**	**18**
Beas2b $HER2^{S310F}$ pHER2 IC_{50} (100% human serum)	**51**	**304**	**903**	**433**	**17**
Beas2b $HER2^{YVMA}$ pHER2 IC_{50} (100% human serum)	**220**	1,650	**273**	**145**	**28**
BT474 ($HER2^{wt}$) cytotox IC_{50}	2.3	23	58	7.8	3.9
NCI-N87 ($HER2^{wt}$) cytotox IC_{50}	2.6	37	65	3.8	3.3
Ba/F3 $HER2^{L755S}$ cytotox IC_{50}	3.7	245	323	11	4.8
Ba/F3 $HER2^{YVMA}$ cytotox IC_{50}	3.5	107	229	6.5	5.9
H2073 ($EGFR^{wt}$) pEGFR IC_{50}	6.4	>10,000	218	2,030	2,160
A431 ($EGFR^{wt}$) pEGFR IC_{50}	10	>7,690	980	2,200	1,700
A431 ($EGFR^{wt}$) cytotox IC_{50}	75	>10,000	8,360	9,360	*3,530*
Human Hepatocyte stability, extraction ratio (%)	74	76	83	42	22
Kinetic Solubility pH 7.4 (µM)	< 0.1	9.3	108	< 0.07	260

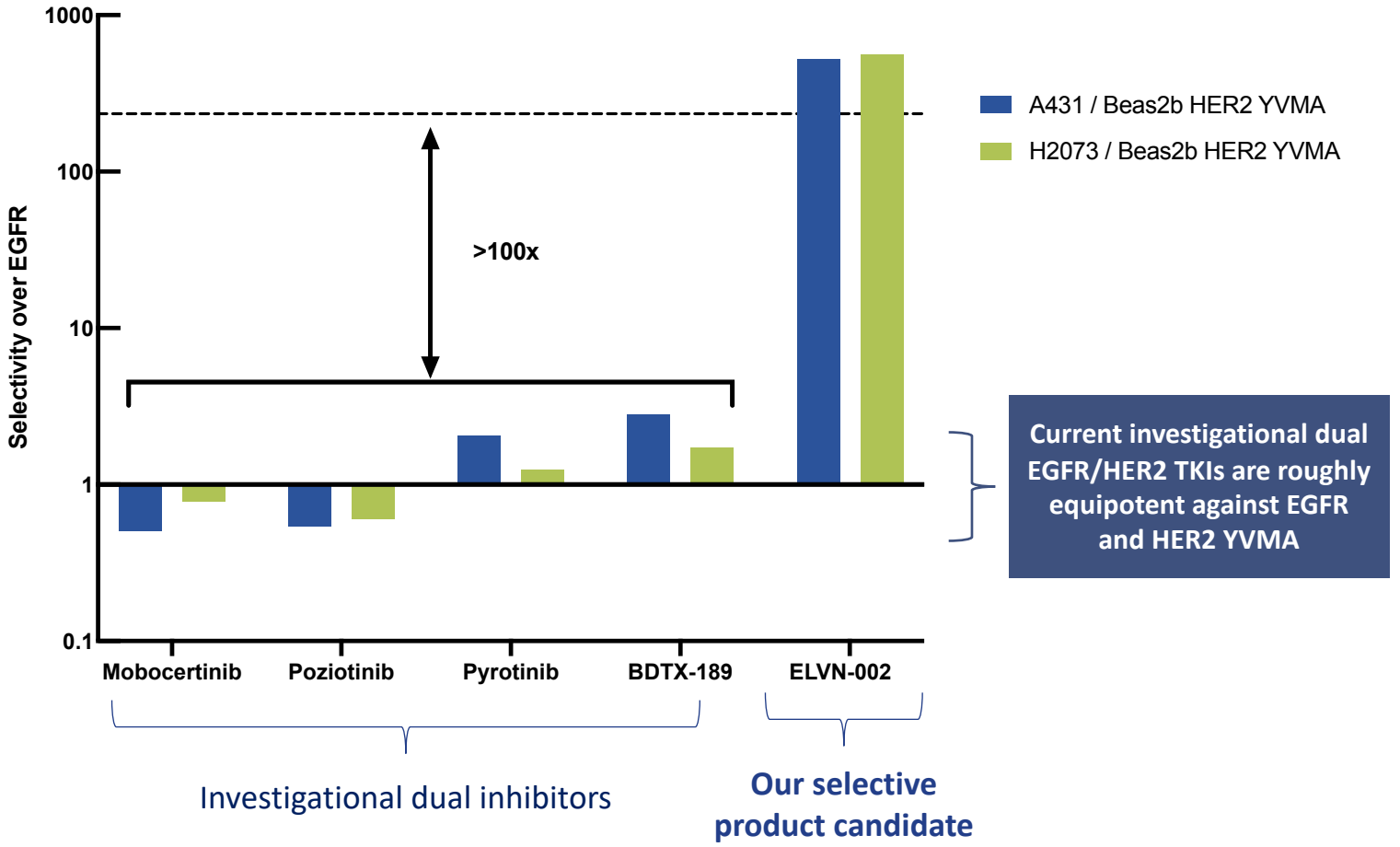
ELVN-002 has differentiated potency in human serum, particularly vs. $HER2^{WT}$

ELVN-002 maintains potency vs. major single-point and E20IM mutations

ELVN-002 has exceptional drug like properties and PK profile**

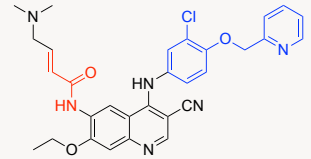
FBS = fetal bovine serum. E20IM = Exon 20 insertion mutations. PK = Pharmacokinetic.
*This compound, which is disclosed in WO2023066296, may be the same, or similar to, ZN-1041, which was sold to Roche by Zion Pharma in 2023 and is being developed for the treatment of HER2+ cancers, including breast cancer.
**Based on non-clinical results/data.
Note: IC values represent an average derived from multiple runs internally with a minimum of two independent experiments. ADMET data were generated internally.

ELVN-002 was >100x More Selective for HER2 YVMA Over EGFR Compared to Dual EGFR/HER2 TKI Competitors



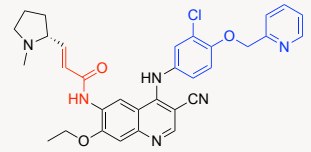
Current investigational dual EGFR/HER2 TKIs are roughly equipotent against EGFR and HER2 YVMA

Lack of Differentiation Across Next Generation TKIs



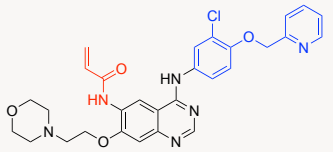
Neratinib

Poor efficacy & tolerability in HER2 mutant setting



Pyrotinib

Phase 1b/2
19% ORR in HER2 mutant NSCLC, poor tolerability



BDTX-189

Poor efficacy & tolerability in HER2 mutant setting

ORR = Overall response rate. NSCLC = Non-small cell lung cancer. TKI = Tyrosine kinase inhibitor.
Note: IC values represent an average derived from multiple runs internally with a minimum of two independent experiments.

ELVN-002 Had Favorable Mutant Coverage Compared to Tucatinib

	Ba/F3 HER2 Mutation	Proliferation IC50 [nM]		Proliferation IC_{50} Fold over	
		Tucatinib	ELVN-002	Tucatinib	ELVN-002
	wild-type	29	6	1	1
	P95	33	11	1	2
HER2 Exon20 Insertion Mutations	A775-G776-ins-C	24	2	1	0.2
	A775-G776-ins-YVMA	225	11	8	2
	A775-G776-ins-YVMS	510	15	18	2
	A775-G776-ins-SVMA	157	6	5	1
	A775-G776-ins-VVMA	294	12	10	2
	A775-G776-ins-MMAY	287	7	10	1
	A775-G776-ins-YVMA-R678Q	642	14	22	2
	G776VC	499	17	17	3
	G776-del-ins-IC	1104	41	38	7
	G776-del-ins-LC	88	13	3	2
	G776-del-ins-VV	1239	34	43	5
	G776-V777-del-ins-CVC	209	13	7	2
	G776-Del-ins-AVGC	438	14	15	2
	V777-G778-ins-GC	20	5	1	1
	P780-Y781-ins-GSP	29	3	1	1
Common HER2 Point Mutations	S310F	11	3	0.4	0.5
	S310Y	12	3	0.4	0.5
	R678Q	29	5	1	1
	L755S	418	8	14	1
	L755P	1284	21	44	3
	D769N	7	2	0.3	0.3
	V773M	64	4	2	1
	V777L	11	3	0.4	1
	T798M	3412	194	118	32
	L869R	148	2	5	0.4
	L869R/T798I	2524	43	87	7
	V842I	21	4	1	1
	BaF3 parental cell line	>10000	>10000	>10000	>10000
	EGFR	>10000	>10000	>10000	>10000

YVMA: 71% E20IM NSCLC

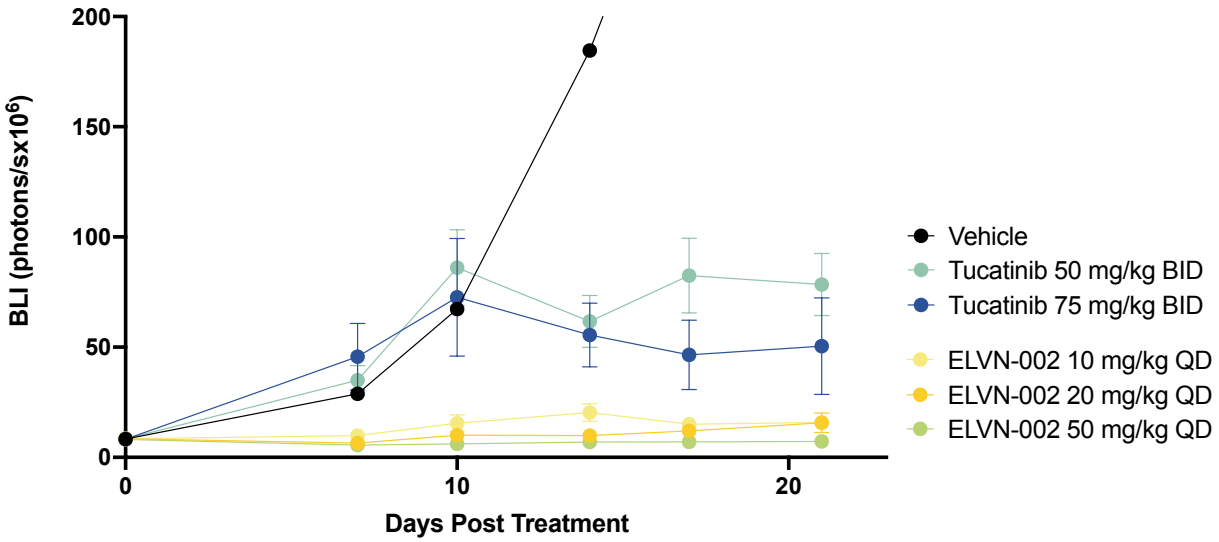
VC: 11% E20IM NSCLC

22% $HER2^{mut}$ MBC

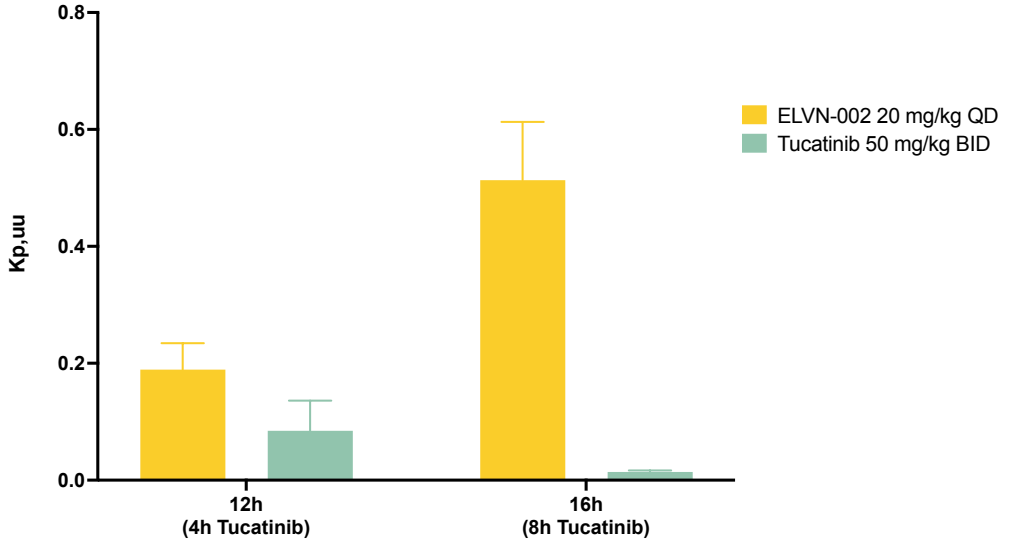
E20IM = Exon 20 insertion mutations. NSCLC = Non-small cell lung cancer. MBC = Metastatic breast cancer.
Note: IC values represent an average derived from multiple runs internally with a minimum of two independent experiments.

ELVN-002 Demonstrated Robust CNS Anti-Tumor Activity in NCI-N87 HER2^{WT} Intracranial Model at Well-Tolerated Doses

NCI-N87 HER2^{wt} Intracranial (CNS) Model



Tucatinib vs. ELVN-002 Brain Exposure



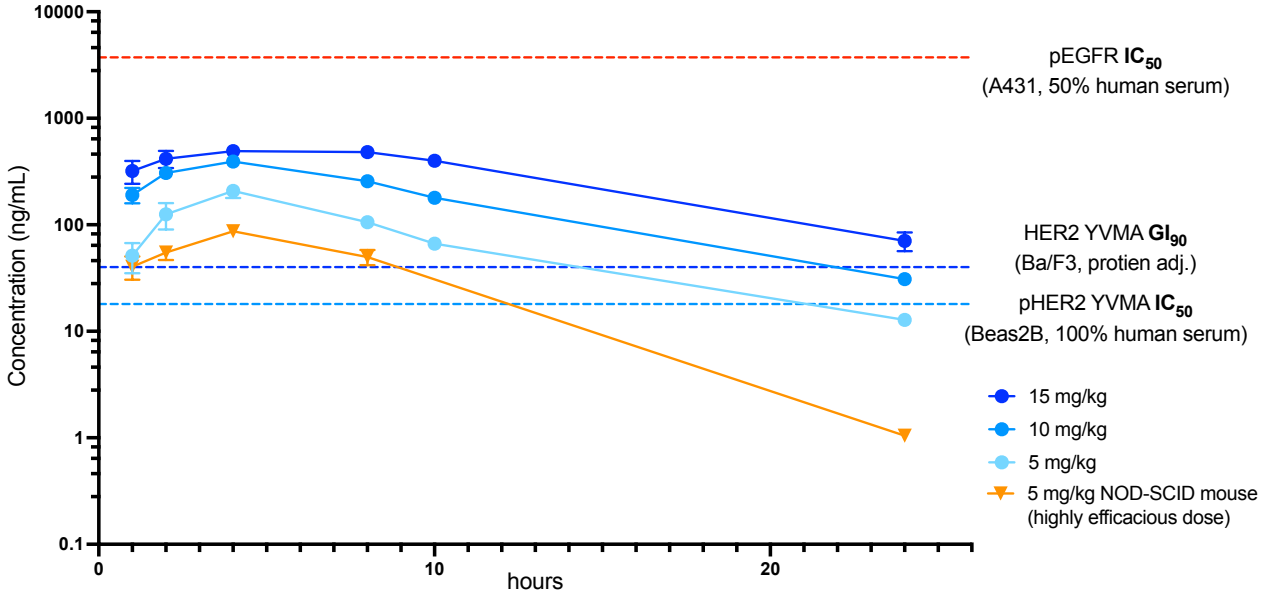
- **ELVN-002 yielded sustained tumor regressions** in the NCI-N87 intracranial model, and all doses were well tolerated
- **Tucatinib's exposure in patients at its approved dose is ~4.5x and ~12x lower than** in mice treated with 50 mg/kg and 75 mg/kg BID, respectively
- ELVN-002 exhibited **superior CNS anti-tumor activity at up to ~100x lower exposures** compared to tucatinib in this model
- **ELVN-002 achieved significant free-drug exposure** in mouse brain across a plasma concentration range that we estimate will be clinically relevant

BID = Twice a day. QD = Once a day. CNS = Central nervous system.

Mouse brain exposures: Steady state Kp,uu for ELVN-002 and tucatinib in non–tumor-bearing BALB/c nude mice (n=3). Measurements were taken after 5 days of dosing at timepoints corresponding to estimated clinically relevant plasma concentrations. Tucatinib was dosed BID and measurements were made at 12h and 16h; however, Kp,uu levels were even lower than at 4h and 8h, respectively. Kp,uu = Free brain concentration (total brain concentration adjusted for brain tissue binding)/Free plasma concentration (total plasma concentration adjusted for protein binding).

ELVN-002 Achieved a Wide Safety Margin in Preclinical Species

ELVN-002 28-day GLP Tox NHP TK



ELVN-002 Safety Margin at NHP NOAEL

Dose (mg/kg)	Fold vs. Highly Efficacious Exposure	Fold vs. Tucatinib TGI-matched exposure
5	2	5
10	5	12
15	**8**	**22**

NHP NOAEL

Based on preclinical exposures (AUC), ELVN-002 had a >10x larger safety margin compared to tucatinib in NHPs (HER2 amp setting)

- At its 28-day NOAEL, **ELVN-002 had a wide safety margin** in non-human primates (NHPs) and even wider safety margin in rats
- At its approved dose, **tucatinib only achieves IC_{90} all day (over 24 hours) in ~40% of patients**
- Due to its larger safety margin, irreversible inhibition and improved PK profile, we believe **ELVN-002 has the potential to achieve better target inhibition and improved efficacy compared to tucatinib**

Amp = amplification. AUC = area under the curve. GLP = Good lab practices. NHP = Non-human primate. NOAEL = No observed adverse event level. TGI = Tumor growth inhibition. TK = toxicokinetics or PK from tox study. PK = Pharmacokinetics.
Highly Efficacious Exposure equals the total AUC of ELVN-002 at 5 mg/kg in NOD-SCID mouse, which yielded robust tumor regression in a HER YVMA xenograft
To determine Fold vs. Tucatinib TGI-matched exposure, we use the AUC of ELVN-002 at 2.5 mg/kg in Nude mouse, a dose that roughly matches the TGI of Tucatinib at 20 mg/kg BID measured in an NCI-N87 xenograft model. Protein adj. = GI_{90} value divided by the fraction unbound in serum.
ELVN-002 NHP data shown are measured averages from Day 1 TK male animals in a 28-day GLP tox study
References: Tucatinib NDA; Moulder SL et al. Data from a Completed Phase 1 Study to Assess the Safety, Tolerability and PK of ARRY-380 - an Oral Inhibitor of HER2. SABCS, December 8-12, 2010, San Antonio, TX.

ELVN-002 Clinical Development Strategy

Phase 1a

- HER2 mutant (e.g., Exon 20 IM)
- HER2 amplified or overexpressed

GOALS

- Demonstrate potential for efficacy at well tolerated dose(s)
- Identify dose(s) for Phase 1b and beyond

Phase 1b / 2

- Late line HER2 mutant NSCLC
- Explore combinations (e.g., ADCs, chemotherapy, trastuzumab) in HER2+ CRC and MBC

GOALS

- Establish PoC for HER2-mutant NSCLC and evaluate intracranial activity
- Explore potential beyond NSCLC in other HER2-altered solid tumors (e.g., MBC, CRC, etc.)
- Demonstrate the potential for best-in-class efficacy and tolerability for combination therapies

Registrational / Phase 3

- Initial registrational studies as mono or combination therapy in NSCLC, CRC and MBC

GOALS

- Consider registrational options for HER2 mutant NSCLC
- Initiate registrational studies in combination therapies in HER2+ MBC and CRC

ADC = Antibody drug conjugate. CRC = Colorectal cancer. IM = Insertion mutation. MBC = Metastatic breast cancer. NSCLC = Non-small cell lung cancer. PoC = Proof of concept.

ELVN-002 || Current Status

Monotherapy Dose Escalation

- Investigator reported responses (including unconfirmed) in patients with both HER2+ and HER2 mutant tumors, including in patients who progressed on Enhertu and in patients with brain metastases, at doses that were well tolerated
- At the clinically predicted optimal monotherapy dose (n=30), based on current Phase 1a data:
  - The most common reported (>10%) treatment-related AEs, were headache (37%), nausea (33%), vomiting (27%) and diarrhea (27%)
    - No ≥ Grade 4; Grade 3: headache (10%), nausea (7%), vomiting (3%), diarrhea (0%)
    - Of note, only Grade 1/2: AST/ALT (3%/0%), rash (3%)
  - Compared to tucatinib, ELVN-002 had >10x better target coverage based on pharmacokinetics in cancer patients and preclinical HER2+ efficacy of ELVN-002

Combination in HER2+ MBC and CRC

Rationale

- Preclinical and clinical data suggest that dual HER2 targeting results in clinically meaningful improvements in patients with HER2+ MBC and CRC
- Tucatinib + trastuzumab + capecitabine demonstrated a survival advantage in HER2+ MBC
- Tucatinib + trastuzumab produced durable responses in HER2+ CRC (DOR ~12.4 months)

Overview

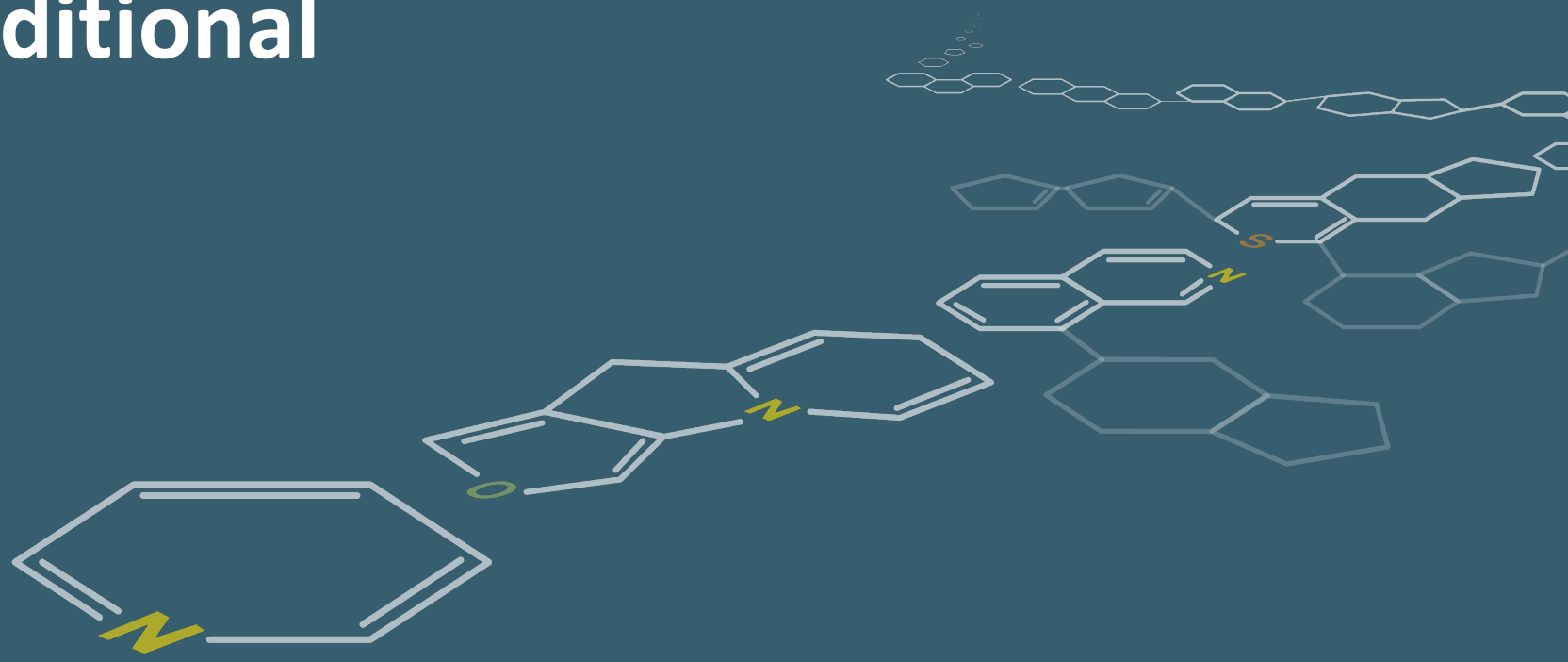
- Open-label, multicenter, multi-part, global Phase 1a/b trial of ELVN-002 in combination with trastuzumab +/- chemotherapy
- Designed to evaluate safety, tolerability, PK, and preliminary efficacy in patients with advanced stage HER2+ tumors
- First site activated for Phase 1 combination trial in HER2+ CRC and MBC, FPI expected in Q2 2024

Phase 1 monotherapy data and initial proof of concept combination data in HER2+ cancers expected in 2025

Target coverage is defined by the mean total drug exposure (area under the curve, AUC) achieved in cancer patients at the indicated dose divided by the mean AUC at the dose in head-to-head preclinical efficacy models that elicits ~100% tumor growth inhibition. Drug exposure of tucatanib in cancer patients was obtained from its NDA and was not obtained from head-to-head clinical trials in cancer patients.
ALT = Alanine transaminase. AST = Aspartate aminotransferase. CRC = colorectal cancer. DOR = duration of response. FPI = First patient in. MBC = metastatic breast cancer. PK = Pharmacokinetic. AE = Adverse event. NDA = New drug application.
References: 1. Oh, DY et al., Nat Rev Clin Oncol 2020. 2. Cocco E. et al. *Pharmacol Ther*. 2019; 2. SEER 2022; 4. Dai WF et al., JAMA New Open 2022; 5. Murthy RK et al., NEJM 2020; 6. Tukysa® (tucatinib) USPI.

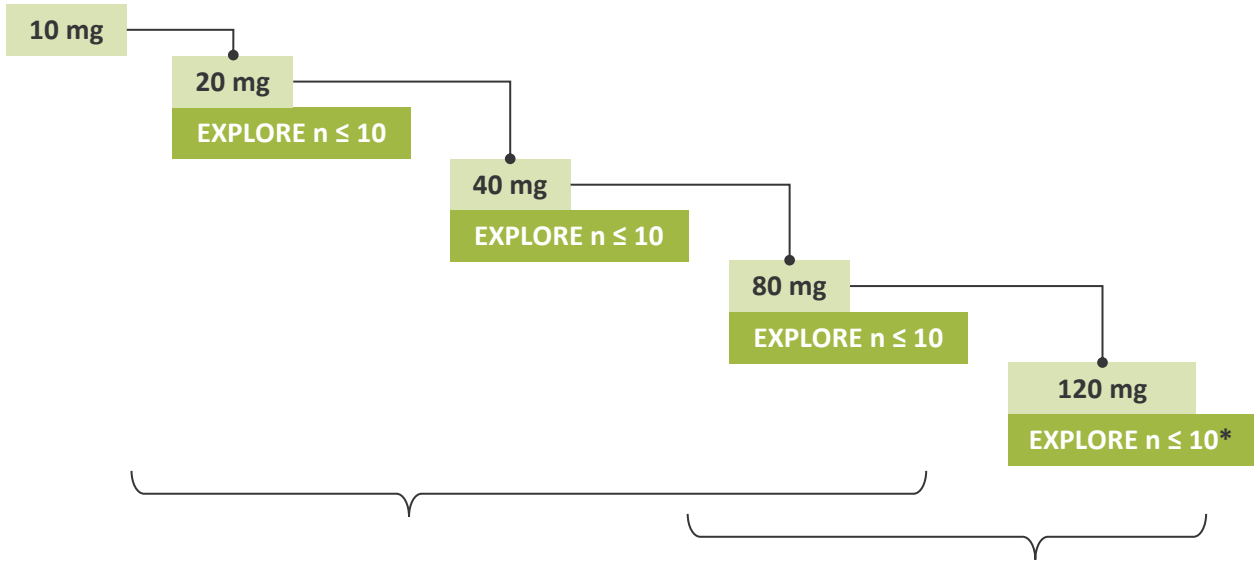
Appendix

ELVN-001 Additional Information



Phase 1 Trial Design/Execution: ELVN-001-101

KEY INCLUSION CRITERIA	Chronic Phase CML (CP-CML) Failed or intolerant (per PI) to available therapies known to be active for treatment of their CML
STUDY DESIGN	Phase 1a dose escalation, exploration Phase 1b expansion, randomized at 2 dose levels Phase 1b T315I single arm expansion
TREATMENT ARMS	Monotherapy
SITES	US, Australia, S. Korea, France, Spain, Germany
DOSING	QD (once daily)
ENDPOINTS	Primary: AEs, ECGs, laboratories Secondary: PK parameters, molecular response (qPCR)
# OF PATIENTS	Phase 1a mono: up to 30 (+ up to 50 exploratory) Phase 1b mono: up to 40 (20 per arm)

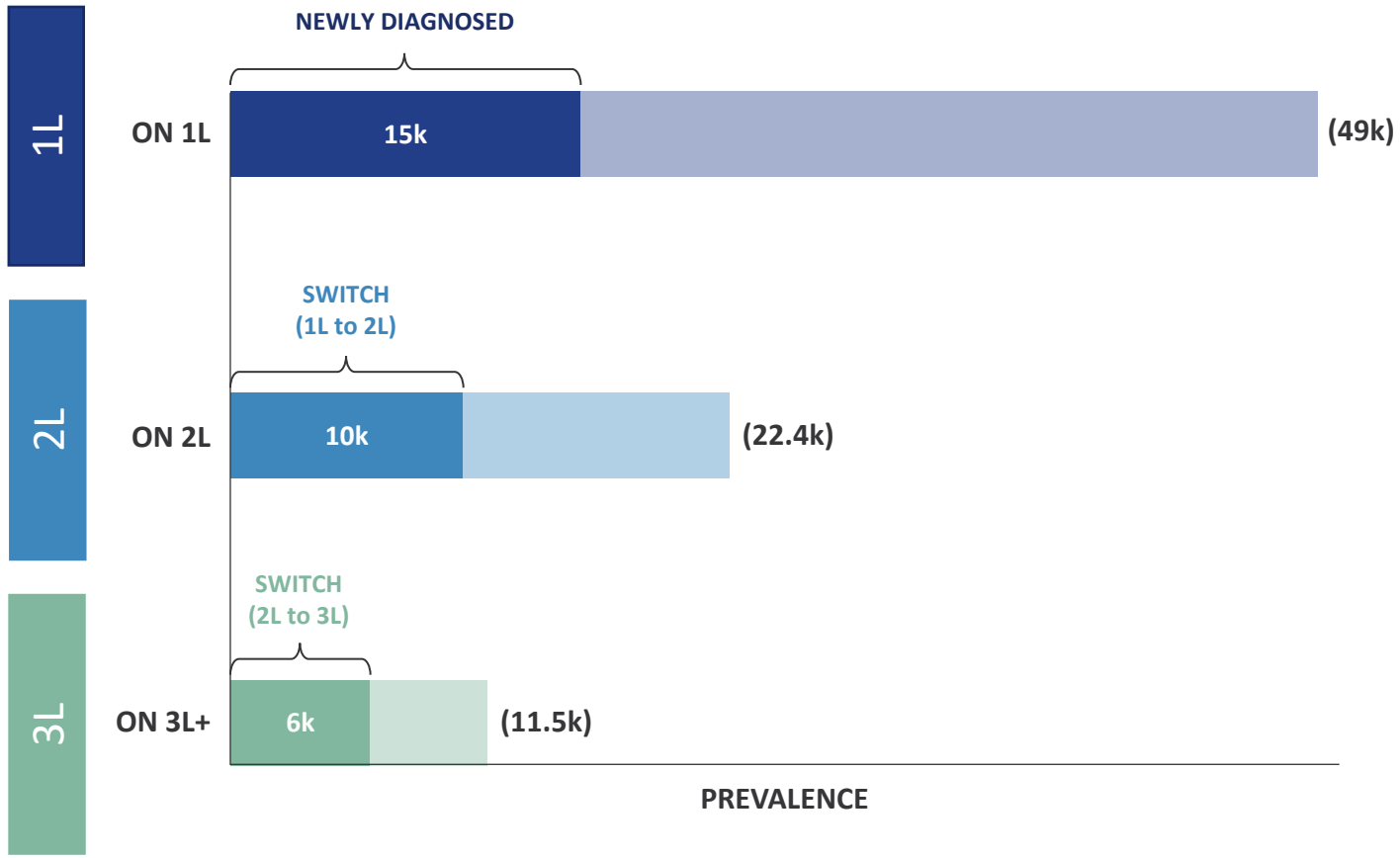


*highly resistant CML

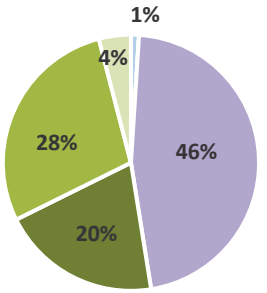
AE = Adverse events. ECG = electrocardiogram. QD = Once Daily. CML = Chronic myeloid leukemia. CP-CML = Chronic phase CML. RDE-1,2,3 = Recommended dose for expansion 1,2,3. PI = Principal investigator. PK = Pharmacokinetic. qPCR = Quantitative polymerase chain reaction.

Treatment Paradigm in CML

CML Patient Population

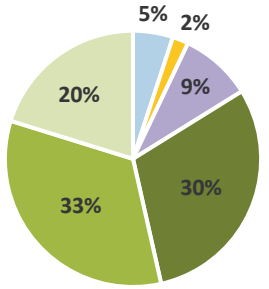


CML Treatment Landscape



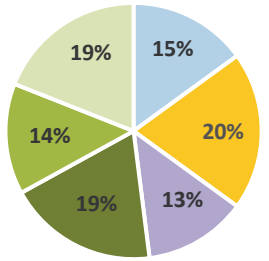
1L

~50% of patients are treated with imatinib, and the other ~50% with 2nd Gen TKIs



2L

Nearly all patients receive 2nd Gen TKIs (mainly nilotinib or dasatinib)



3L+

>50% of patients receive 2nd Gen TKIs

Scemblix · Ponatinib · Imatinib

2nd Generation TKIs { Nilotinib · Dasatinib · Bosutinib

1L = First line. 2L = Second line. 3L+ = Third line or later. CML = Chronic myeloid leukemia. Gen= Generation. TKI = Tyrosine kinase inhibitor.

References: November 2023 Novartis R&D Investor Event. HCP Qualitative & Quantitative Interviews (ClearView).

Evolving Chronic Myeloid Leukemia Market Dynamics

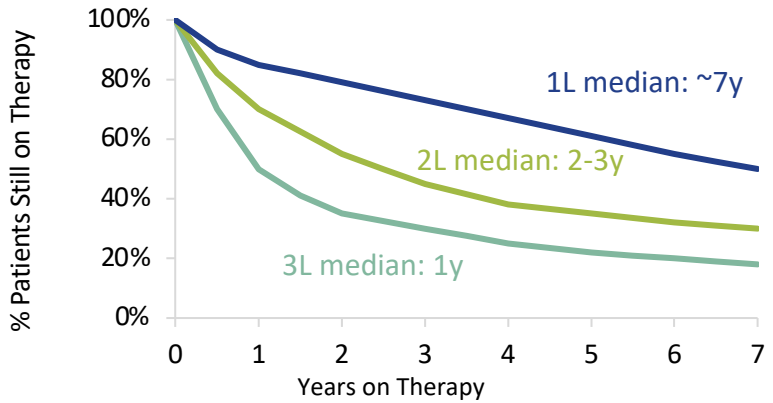
Current Market

- **Growing patient population:** due to improved survival, some patients are required to be **on TKIs for decades**
- Patients **frequently switch therapies due to liabilities of the existing approved drugs**, including poor tolerability due to off-target effects and inability to dose to maximal efficacy
- Nevertheless, the six approved drugs (despite multiple generics) drive **annual sales of >$6B,** with **every drug achieving ~$500M** in sales and multiple drugs achieving sales of ~$2B

Our Vision

- New drugs with **better tolerability and efficacy** profiles further drive increased switching rates and gain rapid adoption (similar to the HIV market)
- Additional focus from patients and doctors on **deeper molecular responses** as well as **tolerability and convenience** factors for long-term treatment
- Chronic nature of CML allows doctors to **freely switch** between therapies, with limited consequences, thereby **blurring lines of therapy**

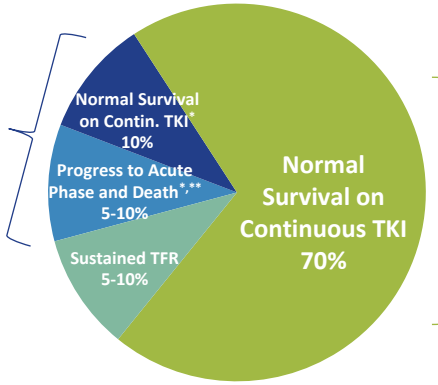
Treatment Duration for SOC by Line of Therapy



CML is a chronic disease requiring many years (even decades) of treatment

Current Outcomes in CML

Treatment decisions are guided by **mutation status,** etc. in only **15-20%** of patients who develop BCR-ABL mutations or other molecular abnormalities

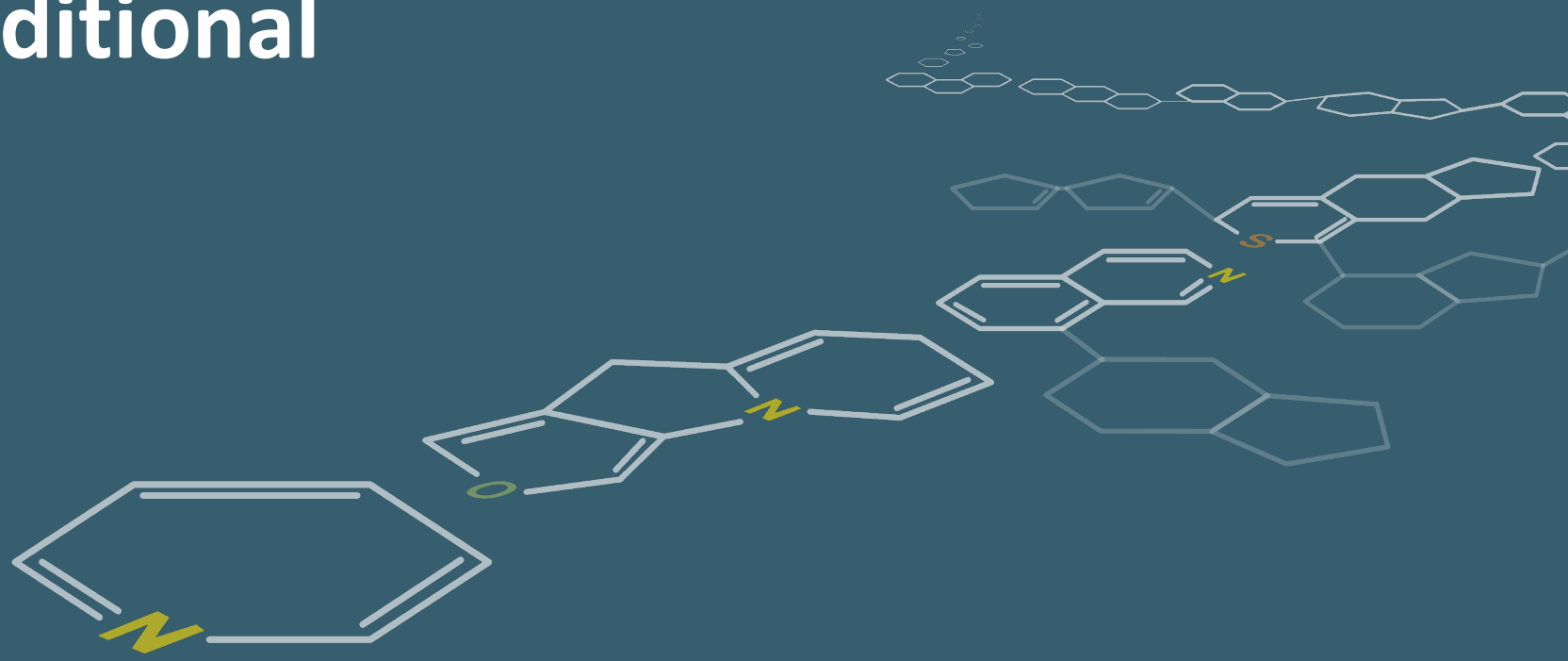


Treatment decisions guided **holistically** based on individual patient (co-meds, co-morbidities, tolerability, etc.) for **>70%** patients

10% overall share (by patients) equates to >$1 billion market opportunity in the U.S. alone†

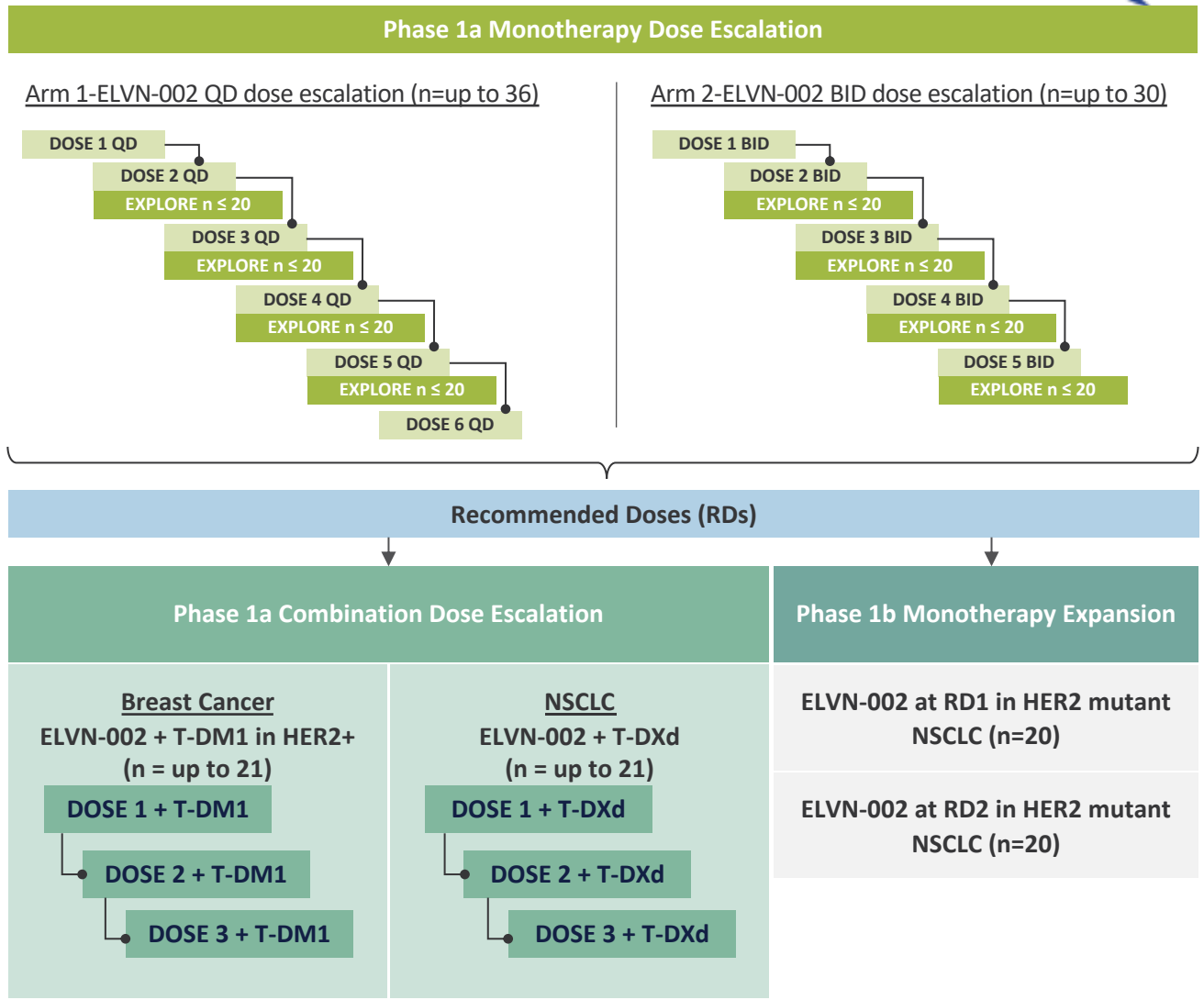
*Develop BCR/ABL Mutations **Develop other molecular abnormalities. † Assumes current branded pricing
CML = Chronic Myeloid Leukemia. SOC = Standard of care. TFR = Treatment free remission. TKI = Tyrosine kinase inhibitor. Normal survival refers to the expected survival of the age-matched general population.
References: Kantarjian HM, et al. *Leukemia*. 2021 Feb; 35(2): 440-453; Hochhaus A et al. *NEJM* 2017; 376:917-927; Hochhaus, A. et al. *Leukemia* 34, 2125–2137 (2020); Giles, et al. *Leukemia* 27, 107–112 (2013); Hochhaus, A. et al. *ASH* 2020; Baccarani M and Gale RP. *Leukemia.* 2021; 35:2199-2204.

ELVN-002 Additional Information



Phase 1 Trial Design/Execution: ELVN-002-001

KEY INCLUSION CRITERIA	No appropriate therapy Local testing for HER2 mut, amp, overexpression Measurable disease No prior HER2 TKI (Phase 1b only)
STUDY DESIGN	**Monotherapy:** • Phase 1a dose escalation, exploration in any HER2-altered solid tumor (e.g., HER2 mutant, Amp, 3+ Overexpression) **Ph 1b expansion, randomized at 2 dose levels in HER2 mutant NSCLC** **Combination:** • Phase 1a dose escalation with T-DXd in HER2 mutant NSCLC • Phase 1a dose escalation with T-DM1 in HER2+ MBC
SITES	US, Australia, S. Korea, Taiwan, France, Spain, Italy
DOSING	QD and BID
ENDPOINTS	Primary: DLTs, AEs, ECGs, laboratories Secondary: cORR, DoR, PK parameters
# OF PATIENTS	**Phase 1a mono: up to 36 (+ up to 60 exploratory)** • Up to 10 patients per dose per tumor type **Phase 1b mono: 40** **Phase 1a combo: up to 21 in each arm**



Amp = amplification. QD = Once Daily. BID = Twice Daily. RD = Recommended Dose. RP2D = Recommended Phase 2 Dose. T-DXd = fam-trastuzumab deruxtecan. T-DM1 = ado-trastuzumab emtansine. AE = Adverse events. DLT = Dose limiting toxicity. ECG = electrocardiogram. cORR = Confirmed objective response. DoR = Duration of response. PK = Pharmacokinetic. NSCLC = Non-small cell lung cancer. MBC = Metastatic breast cancer. TKI = Tyrosine kinase inhibitor.

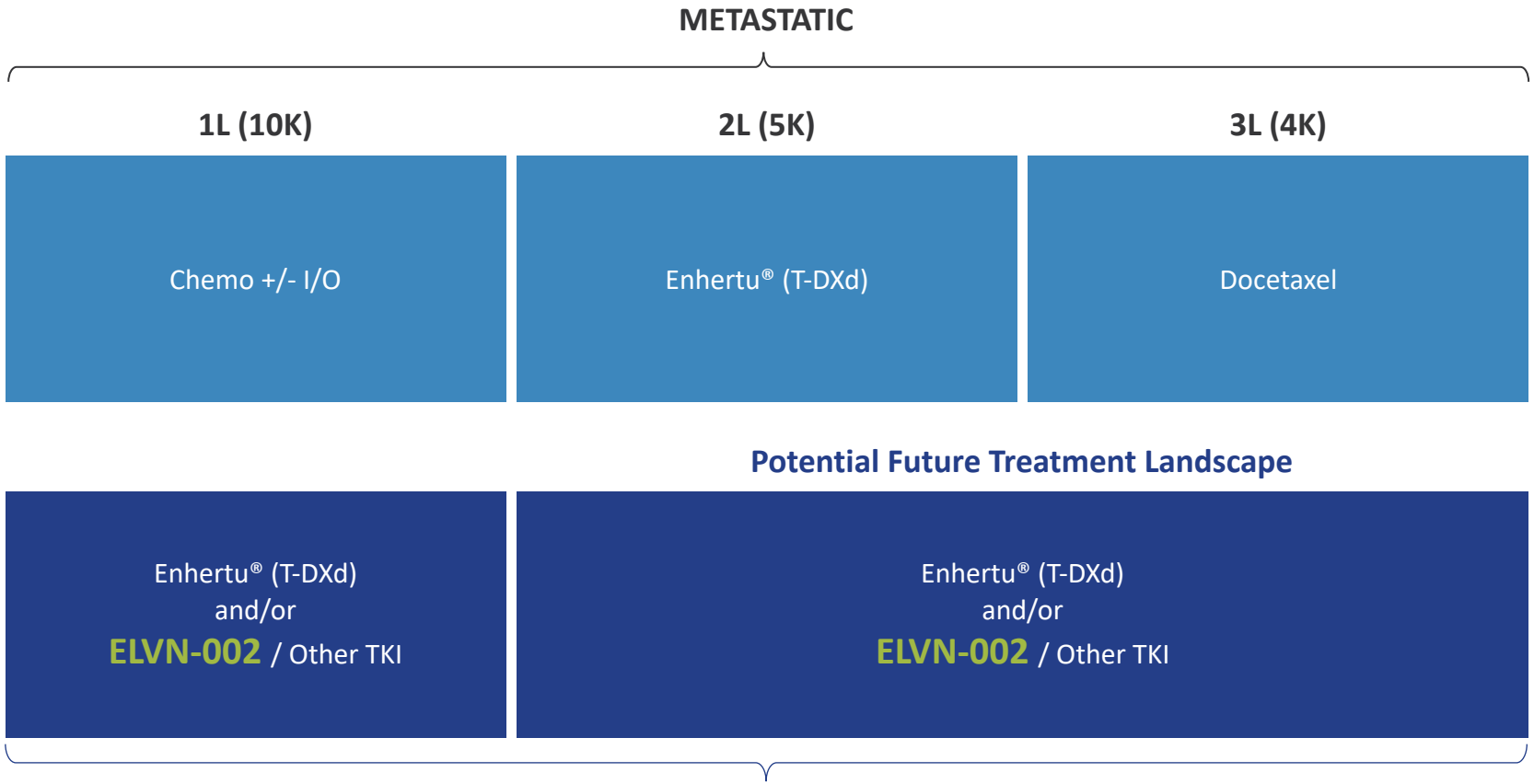
HER2 Mutant NSCLC Landscape: No Approved Selective TKIs

Compound	Company	Stage	MoA	Selectivity over $EGFR^{WT}$	HER2 mut NSCLC Efficacy	Safety / Tolerability
CURRENT & POTENTIAL FUTURE STANDARD OF CARE						
Platinum-doublet[1]	N/A	N/A	Chemo	N/A	ORR: ~25-35% mPFS: 4-7m	Gr 3+ Neutropenia: 19% All Grade Nausea: 52%; Constipation, diarrhea, vomiting, cough, dyspnea, decreased appetite (20-30% each)
Trastuzumab deruxtecan (Enhertu®)[2]	Daiichi Sankyo	FDA Approved (2L+)	HER2-ADC topoisomerase payload	HER2-specific	ORR: 58% DOR: 8.7m	Gr 3+ Neutropenia: 16% All Grade Nausea (61%), Anemia (34%), Fatigue (32%) Black Box Warning: 12% ILD/pneumonitis (all grades)
INVESTIGATIONAL TKIs						
Pyrotinib[3]	Jiangsu HengRui Medicine	Phase 3 (H2H vs. Docetaxel)	Irreversible, EGFR/HER2	≤ 1x	ORR: 19% mPFS: 5.6m	Gr 3+: Diarrhea (17%) All Grade Diarrhea (86%); Fatigue (58%); Anemia (36%); Dizziness (33%); Decreased appetite (32%, Hand-foot syndrome (32%); Nausea (32%)
Zongertinib (BI-1810631)[4]	Boehringer Ingelheim	Phase 1b	Irreversible, HER2	> 100x	ORR: 74% (n=23) 62% ≤2 LOT No prior ADC	Grade 3+: 10% total; AST / ALT increase (2.4% each) All Grade Diarrhea (29%); Rash (21%); AST increase (10%); ALT increase (7%)
BAY 2927088[5]	Bayer	Phase 1a	Reversible, EGFR/HER2	claims EGFR mutant specific over wt	ORR: 60% (n=20) (Exon 20 only)	Grade 3+: 25% total, 15.8% diarrhea, All Grade Diarrhea 75%; Paronychia 25%; dry skin 22.4%; dermatitis acneiform 21.1%

2L+ = Second or later line of therapy. AE = Adverse event. CRL = Complete Response Letter. DOR = Duration of response. Gr = Grade. ILD = Interstitial lung disease. m = Months. N/A = Not applicable. NSCLC = Non-small cell lung cancer. ORR = Overall response rate. mPFS = Median progression free survival. TKI = Tyrosine kinase inhibitor. MoA = Mechanism of action. ALT = Alanine transaminase. AST = Aspartate aminotransferase. ADC = Antibody drug conjugate. NSCLC = Non-small cell lung cancer. Mut = Mutant. H2H = head to head.

References: 1. Wang et al. *BMC Cancer* (2018) 18:326; 2. Enhertu® (fam-trastuxumab deruxtecan) USPI; 3. Song et al. *BMC Medicine* (2022) 20:42; 4. Ruiter G et al., ESMO 2023; 5. Loong et al., ESMO 2023

HER2 Mutant NSCLC Present and Potential Future Landscape



PRESENT

FUTURE

1L = First line. 2L = Second line. 3L = Third line. NSCLC = Non-small cell lung cancer. T-DXd = fam-trastuzumab deruxtecan. TKI = Tyrosine kinase inhibitor. I/O = immuno-oncology therapy (e.g., PD-1, PD-L1). PD-1 = Programed cell death protein 1. PD-L1 = Programed cell death ligand 1.
Note: incidence numbers in parentheses represent estimated epidemiology across G7 (US, EU5, JP) using the November 9, 2023 AstraZeneca presentation and Eng J et al. Lung Cancer. 2016 Sep;99:53-6.

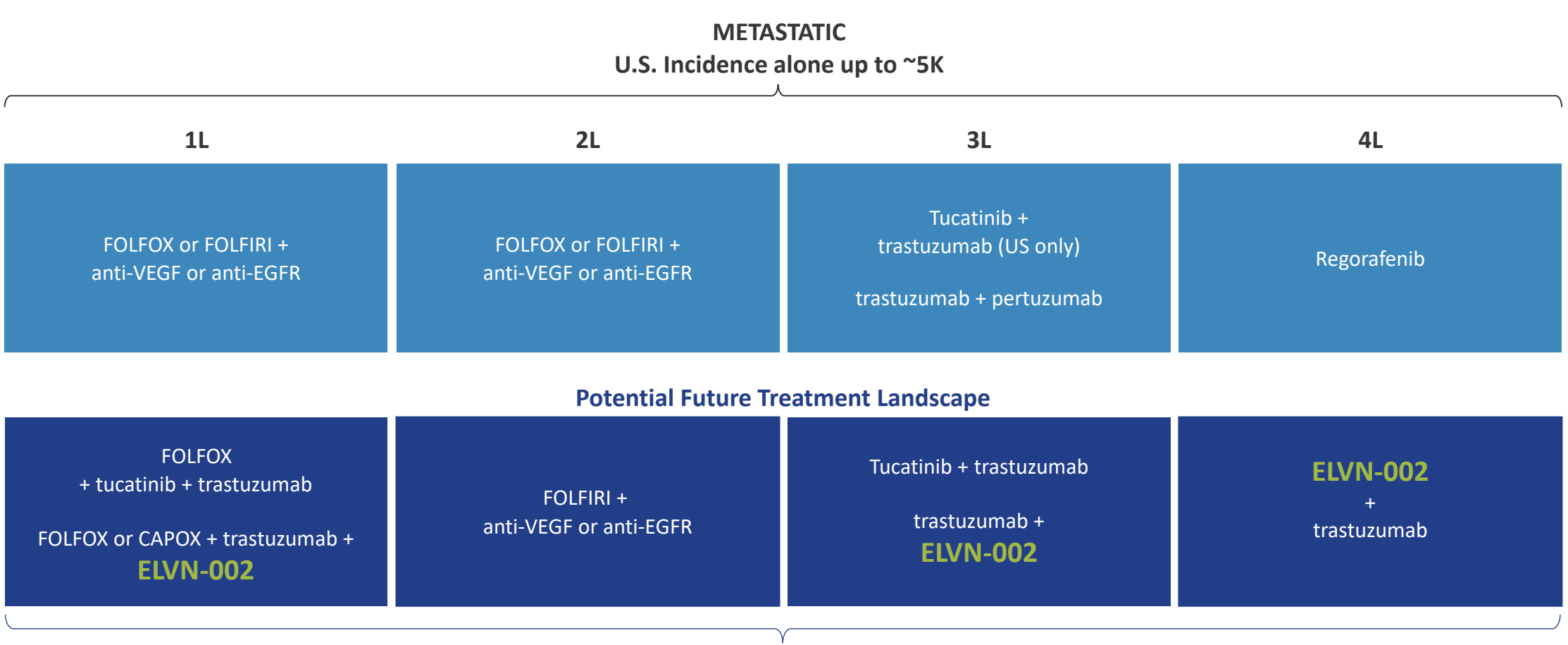
HER2+ Colorectal Landscape

Compound	Company	MoA	Clinical Usage	HER2+ CRC Efficacy	Safety / Tolerability
CHEMOTHERAPY					
FOLFOX / FOLFIRI[1,2]	N/A	Chemo	1L	ORR: 50-60% mPFS: 10-12m mOS: 25-30m	Gr 3+: Neutropenia (15%) All Grade: Neutropenia (43%); Anemia, Leukopenia (33% each)
TYROSINE KINASE INHIBITORS					
Tukysa® (tucatinib + trastuzumab)[3]	Seagen	Reversible, HER2 TKI	2L+	ORR: 38% DoR: 12.4m	Gr 3+: Diarrhea (3.5%); Abdominal Pain, Back Pain, Fatigue (2.3% each) All Grade: Diarrhea (65%); Fatigue (44%); Nausea (35%)
Regorafenib[4]	Bayer	Multi-kinase TKI	3L	ORR: 1% mPFS: 2m mOS: 6.4m	Gr 3+: Hand-foot skin reaction (17%); Fatigue (15%) All Grade: Increased AST (65%); Increased ALT (45%); Proteinuria (84%) **Black Box:** Hepatotoxicity
ANTIBODY DRUG CONJUGATES					
Enhertu® (fam-trastuzumab deruxtecan)[5]	Daiichi Sankyo	HER2-ADC topoisomerase payload	Investigational (5.4mg/kg)	ORR: 38% DoR: 5.5m mPFS: 5.8m	Gr 3+: Neutropenia (16.9%); Fatigue (9.6%); Nausea (8.4%) All Grade: ILD (8.4%); Nausea (58%); Fatigue (46%); Neutropenia (30%)

1L = First line of therapy. 2L = Second line of therapy. 2L+ = Second or later line of therapy. 3L+ = Third or later line of therapy. AE = Adverse event. ADC = Antibody drug conjugate. AST = Aspartate aminotransferase. ALT = Alanine transaminase. DoR = Duration of response. ORR = Overall response rate. mPFS = Median progression free survival. mOS = Median overall survival. TKI = Tyrosine kinase inhibitor. Tx or Txt = Treatment. MoA = Mechanism of action. ILD = Interstitial lung disease. Gr = Grade. Chemo = Chemotherapy.

References: 1. Zhang H, Y et al. Medicine; 2. Wang F et al, Clin Cancer Res. 2022; 3. Tuksya® (tucatinib) USP; 4. Stivarga® (regorafenib) USPI; 5. Raghav et al., DESTINY-CRC02 ASCO 2023.

HER2+ CRC Present and Potential Future Landscape



1L = First line. 2L = Second line. 3L = Third line. 4L = Fourth line. ADC = Antibody drug conjugate. CRC = Colorectal cancer. T-DXd = fam-trastuzumab deruxtecan. TKI = Tyrosine kinase inhibitor.

References: SEER database.; Takegawa N et al. Clin Colorectal Cancer 2015; Valtorta E et al. Mod Pathol. 2015. Atreya et al., ASCO 2017.

HER2 Breast Landscape: No Irreversible, Highly Selective TKI Option

Compound	Company	MoA	Clinical Usage	HER2+ MBC Efficacy	Safety / Tolerability
ANTIBODY DRUG CONJUGATES					
Enhertu® (fam-trastuzumab deruxtecan)[1]	Daiichi Sankyo	HER2-ADC topoisomerase payload	2L	ORR: 80% mPFS: 28.8m	Gr 3+: Neutropenia: 20% All Grade: ILD (11%); Nausea (72%); Alopecia, Anemia, Vomiting (30-40% each)
Kadcyla® (ado-trastuzumab emtansine)[1]	Roche	HER2-ADC DM1 toxin payload	2L	mPFS: 6.8m ORR: 35%	Gr 3+: Thrombocytopenia: 25% All Grade: Nausea, Fatigue, AST/ALT increase (20-30% each)
TYROSINE KINASE INHIBITORS					
Tukysa® (tucatinib + ado-trastuzumab emtansine)[2]	Seagen	Reversible, HER2 TKI	3L+ (CNS mets)	ORR: 42% mPFS: 9.5m mOS: NR	Gr 3+: AST / ALT Increase (16.5% each); Anemia (8.2%); Thrombocytopenia (7.4%) All Grade: Nausea (65%); Diarrhea (57%); Fatigue (49%)
Tukysa® (tucatinib + trastuzumab + capecitabine)[3]	Seagen	Reversible, HER2 TKI	3L+ (CNS mets)	ORR: 40.6% mPFS: 7.8m mOS: 21.9m	Gr 3+: PPE / Diarrhea (12-13% each) All Grade: Diarrhea (80%); PPE (63%); Fatigue, Nausea (~50% each)
Tucatinib (single agent)[4,5]	Seagen	Reversible, HER2 TKI	N/A	ORR: 11% CBR: 22% (med prior tx: 6)	Gr 3+: ALT increase (4%); Rash (4%); Diarrhea (0%) All Grade: Diarrhea (26-33%); Nausea (33%); Fatigue (18%)
CHEMOTHERAPY					
Xeloda® (capecitabine)[6]	Roche	Chemo	3L+	ORR: 25% DoR: 5m	Gr 3+: Diarrhea (15%); PPE (11%); Nausea, Vomiting (4% each) All Grade: PPE / Diarrhea (57% each); Nausea (53%); Vomiting (37%)

1L = First line of therapy. 2L = Second line of therapy. 3L+ = Third or later line of therapy. ADC = Antibody drug conjugate. AST = Aspartate aminotransferase. ALT = Alanine transaminase. DoR = Duration of response. Gr = Grade. ILD = Interstitial lung disease. NR = Not reached. N/A = Not applicable. ORR = Overall response rate. mPFS = Median progression free survival. PPE = Palmar-plantar erythrodysesthesia. mOS = Median overall survival. TKI = Tyrosine kinase inhibitor. MBC = Metastatic breast cancer. MoA = Mechanism of action.

References: 1. Cortes J et al. *N Engl J Med* 2022; 386:1143-1154; 2. Hurwitz, S et al. SABCS 2023; 3. Murthy RK et al. *N Engl J Med* 2020; 382:597-609; 4. Moulder S et al. *Clin Cancer Res*; 23(14); 5. Stricker et al. *ESMO* 2022; 6. Xeloda® USPI, 2015.

HER2+ Breast Cancer Present and Potential Future Landscape

NEOADJUVANT/ADJUVANT (105K)

Neoadjuvant

taxane + trastuzumab + pertuzumab (THP)

Post-neoadjuvant

T-DM1

Adjuvant

taxane + trastuzumab + pertuzumab

METASTATIC

1L (25K)	2L (18K)	3L (13K)	4L (11K)
THP	T-DXd	T-DM1 (+/- tucatinib**) *or* Tucatinib + trastuzumab + capecitabine	Neratinib + capecitabine *or* Lapatinib + capecitabine *or* trastuzumab + chemo*

Potential Future Treatment Landscape

1L (25K)	2L (18K)	3L (13K)	4L (11K)
T-DXd +/- pertuzumab	Taxane + trastuzumab + **ELVN-002**	T-DM1 + **ELVN-002**	trastuzumab + chemo + **ELVN-002**

Sequencing will be based on patient needs and prior therapies

PRESENT

FUTURE

1L = First line. 2L = Second line. 3L = Third line. 4L = Fourth line. T-DXd = fam-trastuzumab deruxtecan. T-DM1 = ado-trastuzumab emtansine.
*Capecitabine, eribulin, gemcitabine, navelbine; **Recently announced "positive" trial.
Note: incidence numbers in parentheses represent estimated epidemiology across G7 (US, EU5, JP) using the November 9, 2023 AstraZeneca presentation and Dumbrava EEI et al, JCO Precis Oncol. 2019 Oct 21.

HER2 OE/AMP NSCLC Landscape: No Approved Targeted Therapies

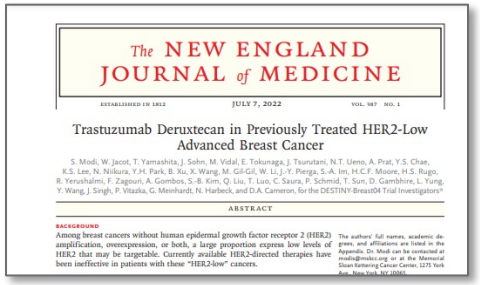
Compound	Company	MoA	Clinical Usage	HER2+ NSCLC Efficacy	Safety / Tolerability
CHEMOTHERAPY + IMMUNOTHERAPY					
Keytruda® (pembrolizumab) + chemotherapy[1]	Merck	PD-1	1L (unselected pop.)	ORR: 48% mPFS: 8.8m mOS: NR	Gr 3+: Anemia, Lymphopenia, Neutropenia (~20% each) All Grade: Anemia (85%); Lymphopenia, Neutropenia, Fatigue (40-60%)
Doxetaxel[2]	N/A	Chemotherapy	3L+ (unselected pop.)	ORR: 12% DoR 5.6m mPFS: 4.2m	Gr 3+: Neutropenia (27%); Febrile Neutropenia (10%); Leukopenia (8%) All Grade: Fatigue (29%); Nausea 26%; Alopecia (25%); Diarrhea (23%)
TYROSINE KINASE INHIBITORS					
Pyrotinib[3]	Jiangsu HengRui Medicine	Irreversible, EGFR/HER2 TKI	Investigational (NGS AMP)	ORR: 17-22% DoR: 7.2m mPFS 4.7-6.3m	Gr 3+: Diarrhea (7%); Vomiting (7%) All Grade: Diarrhea (92%); Anemia (48%); Nausea, fatigue (37% each),
ANTIBODY DRUG CONJUGATES					
Enhertu® (fam-trastuzumab deruxtecan)[4]	Daiichi Sankyo	HER2-ADC topoisomerase payload	Investigational (IHC 2+ or 3+)	ORR: 25% DoR: 6m PFS: 5.4m	Gr 3+ Neutropenia: 16% All Grade Nausea (61%), Anemia (34%), Fatigue (32%) Black Box Warning: 12% ILD/pneumonitis (all grades)

1L = First line of therapy. 3L+ = Third or later line of therapy. ADC = Antibody drug conjugate. DoR = Duration of response. Gr = Grade. IHC = Immunohistochemistry. ILD = Interstitial lung disease. NE = Not evaluable. NR = Not reached. NGS = Next generation sequencing. ORR = Overall response rate. OE = Overexpression. AMP = amplification. mPFS = Median progression free survival. mOS = Median overall survival. TKI = Tyrosine kinase inhibitor. MoA = Mechanism of action. NSCLC = Non-small cell lung cancer. PD-1 = Programed cell death protein 1. Pop = Population.

References: 1. Keytruda® (pembrolizumab) USPI; 2. Borghaei H et al., NEJM 2015; 3. Song et al, Clin Cancer Res 2022; 4. Nakagawa K el al. WCLC 2022.

The HER2+ Post-Enhertu® Market is Growing Appreciably

Trastuzumab Deruxtecan (Enhertu®) Is Augmenting the Canonical HER2+ Population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Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

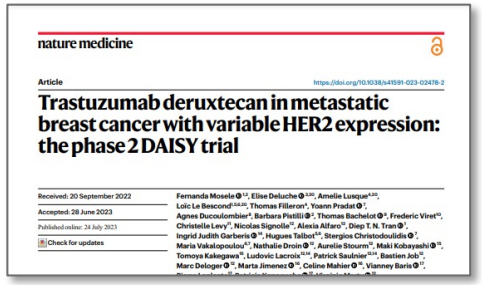
ABSTRACT

BACKGROUND

Among breast cancers without human epidermal growth factor receptor 2 (HER2) amplification, overexpression, or both, a large proportion express low levels of HER2 that may be targetable. Currently available HER2-directed therapies have been ineffective in patients with these "HER2-low" cancers.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Modi can be contacted at modis@mskcc.org or at the Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

DESTINY-Breast04 trial established Enhertu® as the new SOC post 1L chemo in HER2-low MBC


nature medicine

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Trastuzumab deruxtecan in metastatic breast cancer with variable HER2 expression: the phase 2 DAISY trial

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DAISY trial demonstrated encouraging activity in HER2-low & HER2-non-detected MBC

The Advent of HER2-Low Identification Efforts Further Broadens HER2+ Patient Population

1) Deep learning-based image analysis to produce a HER2 Quantitative Continuous Score (QCS), a novel approach to better identify patients with low-level expression who may benefit from a HER2-directed therapy
2) Other AI-mediated approaches designed to detect 'true' HER2 expression in spite of IHC classification through the use of H&E-stained tissue samples
3) Supplementing mass spec-standardized HER2 array with quantitative immunofluorescence to increase sensitivity of genetic amplification beyond conventional assays

Post-Enhertu® Market Is Substantial and Represents a Land Grab Opportunity

Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer

J. Cortés, S.-B. Kim, W.-P. Chung, S.-A. Im, Y.H. Park, R. Hegg, M.H. Kim, L.-M. Tseng, V. Petry, C.-F. Chung, H. Iwata, E. Hamilton, G. Curigliano, B. Xu, C.-S. Huang, J.H. Kim, J.W.Y. Chiu, J.L. Pedrini, C. Lee, Y. Liu, J. Cathcart, E. Bako, S. Verma, and S.A. Hurvitz, for the DESTINY-Breast03 Trial Investigators*

	12-Mo Progression-free Survival (95% CI) %
Trastuzumab Deruxtecan	75.8 (69.8 – 80.7)
Trastuzumab Emtansine	34.1 (27.7 – 40.5)

Hazard ratio for disease progression or death, 0.28 (95% CI, 0.22-0.37) P<0.001

Multi-billion-dollar market opportunity post-Enhertu® with ~25% of patients receiving Enhertu® progressing within 12-months and 50% of patients developing brain metastases

Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Guideline Update

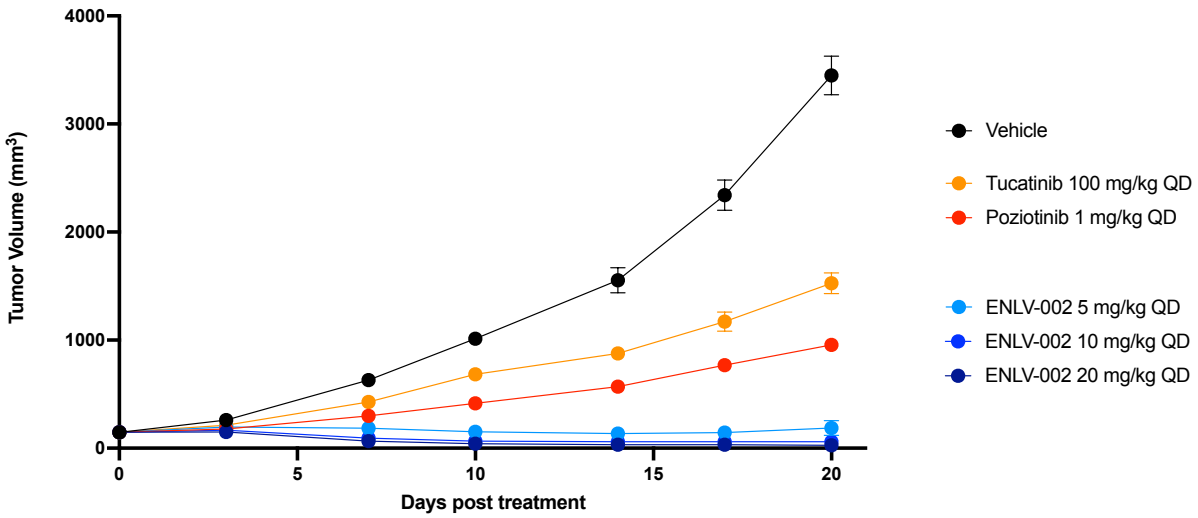
"Trastuzumab, pertuzumab, and taxane for first-line treatment and trastuzumab deruxtecan for second-line treatment are recommended. **In the third-line setting, clinicians should offer other HER2-targeted therapy combinations. There is a lack of head-to-head trials; therefore, there is insufficient evidence to recommend one regimen over another."**

1L = First line. ASCO = American society of clinical oncology. H&E = Hematoxylin and eosin. IHC = Immunohistochemistry. SOC = Standard of care. MBC = Metastatic breast cancer.

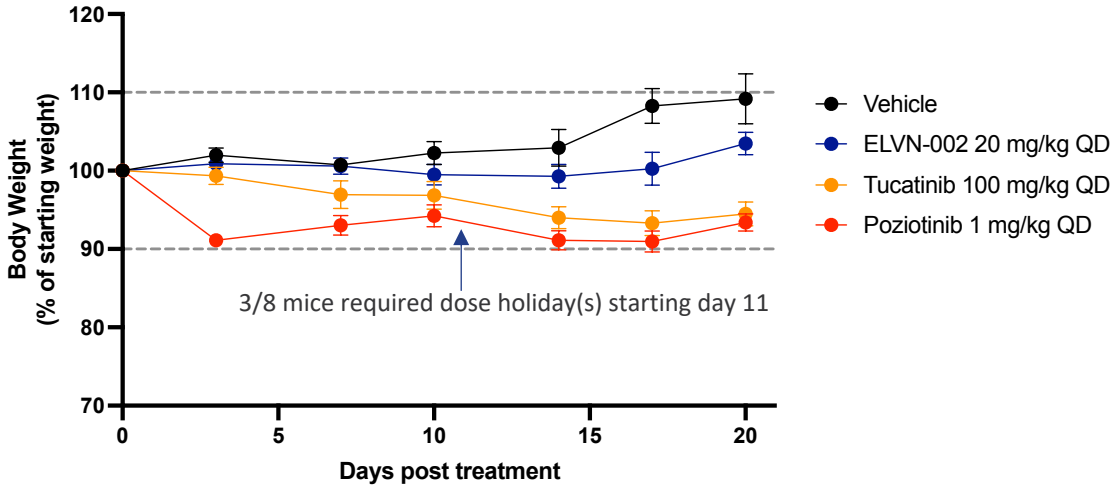
References: Zhang H, et al. Cancers (Basel). 2022 Dec 25; Cortés J, et al. N Engl J Med. 2022; Journal of Clinical Oncology 40, no. 23 (August 10, 2022) 2612-2635.

ELVN-002 Demonstrated Robust Anti-Tumor Activity in Beas2b HER2 YVMA Xenograft Model at Well-Tolerated Doses

Beas2b HER2 YVMA Xenograft TGI



Beas2b HER2 YVMA Xenograft Body Weight Change

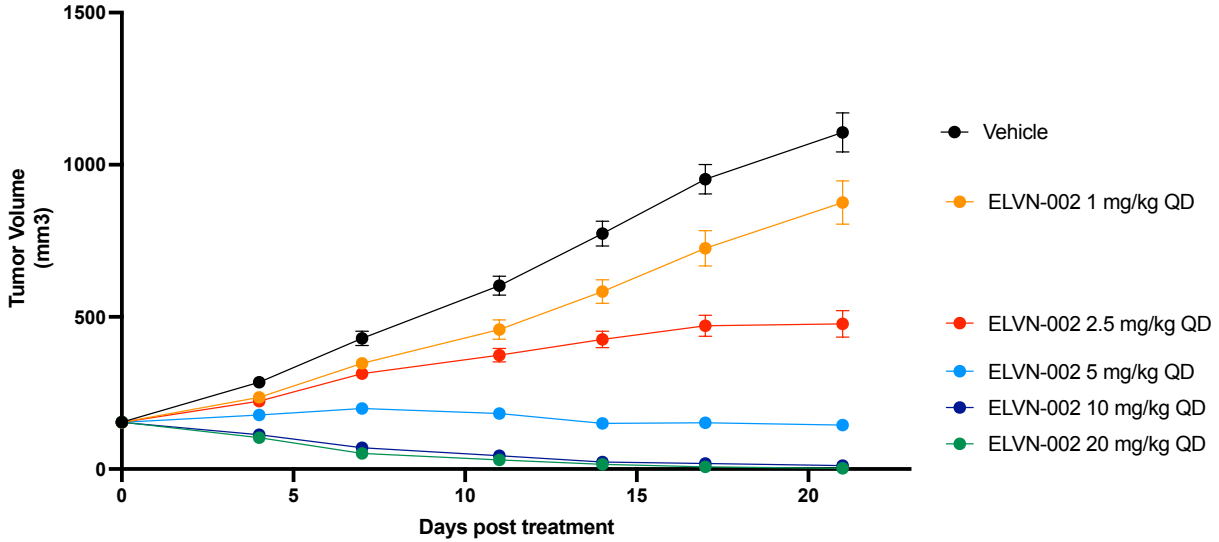


- **Poziotinib's MTD** in this model was 1 mg/kg, and this dose yielded an exposure **~8x its human exposure** at 16 mg QD
- **ELVN-002 yielded deep tumor regressions**, and all doses tested were **well-tolerated**
- **Minimal TGI** vs. YVMA observed with **tucatinib** treatment up to **~14x its human exposure** at 300 mg BID

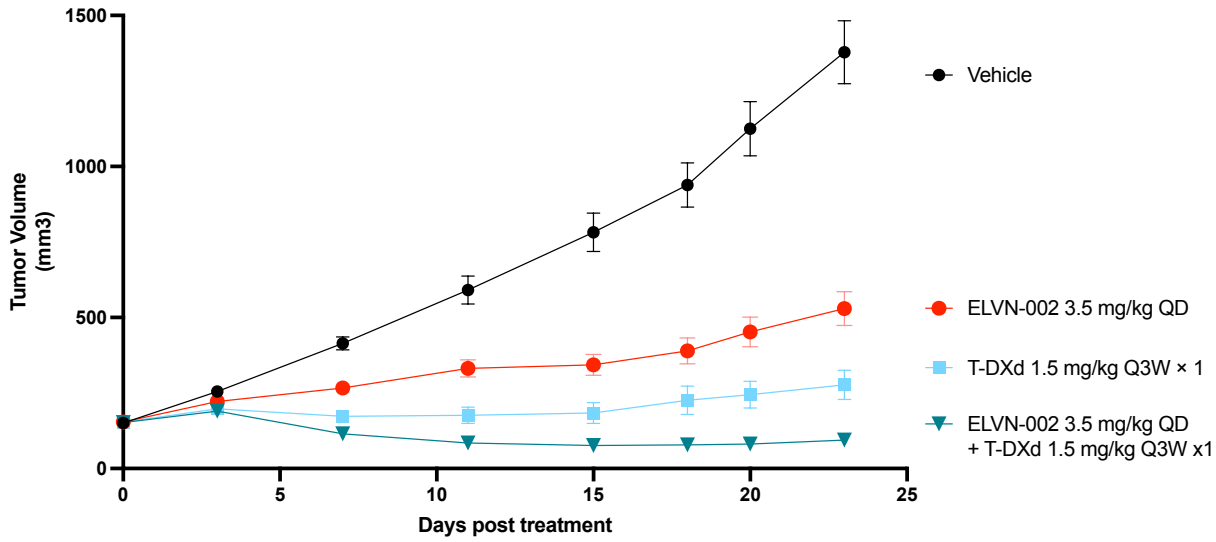
BID = Twice a day. MTD = Maximum tolerated dose. TGI = Tumor growth inhibition. QD = Once a day.

ELVN-002 Demonstrated Robust Anti-Tumor Activity & Additive Activity in Combination with Enhertu® at Well-Tolerated Doses

NCI-N87 HER2^{wt} Xenograft TGI: ELVN-002 Mono



NCI-N87 HER2^{wt} Xenograft TGI: Enhertu® Combo



- **ELVN-002 yielded deep tumor regressions** in the NCI-N87 xenograft model, and all doses tested were **well-tolerated**
- **Low dose ELVN-002 combined with Enhertu® resulted in additive activity** and deep tumor regressions in the same model
- **In contrast to reversible inhibitors** like tucatinib, irreversible inhibitors have been shown mechanistically to drive increased receptor internalization, and there is both **preclinical and clinical precedent for additive activity upon combining irreversible TKIs with ADCs in HER2-driven settings**

ADC = Antibody drug conjugate. TGI = Tumor growth inhibition. QD = Once a day. Q3W = Every 3 weeks. T-DXd = fam-trastuzumab deruxtecan.

References: Li et al. Cancer Disc 2020; Abraham et al. J Clin Oncol 2019.