

The logo for Aileron, featuring the word "AILERON" in white, uppercase, sans-serif font. A green swoosh, resembling an upward-pointing arrow or a stylized wing, curves over the letters "I", "L", and "E".

AILERON

# Transforming the Experience of Chemotherapy for Cancer Patients

C O R P O R A T E   P R E S E N T A T I O N

M A R C H   2 0 2 1



## Forward Looking Statements

Statements in this presentation about Aileron's future expectations, plans and prospects, as well as any other statements regarding matters that are not historical facts, may constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to, statements about the Company's strategy and clinical development plans. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including whether Aileron's cash resources will be sufficient to fund its continuing operations for the periods anticipated; whether the Company will obtain sufficient cash resources to conduct its planned clinical trials; whether results obtained in clinical trials will be indicative of results obtained in future clinical trials; whether third-party data would be indicative of the data that would be obtained in a randomized clinical trial; whether Aileron's product candidates will advance through the clinical trial process on a timely basis, or at all; whether the results of such trials will be accepted by and warrant submission for approval from the United States Food and Drug Administration or equivalent foreign regulatory agencies; whether Aileron's product candidates will receive approval from regulatory agencies on a timely basis or at all; whether, if product candidates obtain approval, they will be successfully distributed and marketed; what impact the coronavirus pandemic may have on the timing of our clinical development, clinical supply and our operations; and other factors discussed in the "Risk Factors" section of Aileron's annual report on Form 10-K for the period ended December 31, 2020, filed on March 24, 2021, and risks described in other filings that Aileron may make with the Securities and Exchange Commission. Any forward-looking statements contained in this presentation speak only as of the date hereof, and Aileron specifically disclaims any obligation to update any forward-looking statement, whether because of new information, future events or otherwise.

# Our Opportunity To Protect Against Chemotherapy-induced Side Effects With ALRN-6924



## Regulatory and commercial pathway now established for chemoprotection

FDA approved first myeloprotective drug by GTHX, trilaciclib (COSELA™), in Feb. 2021



## ALRN-6924: best-in-class potential among chemoprotective agents (“Triple Play Efficacy”)

Clinical proof of concept demonstrated; protection against neutropenia, thrombocytopenia and anemia



## Core differentiator: p53 biomarker-enabled selective chemoprotection

50% of all cancer patients have p53-mutated cancer / Millions of patients worldwide



## Expected milestones for new randomized placebo-controlled Phase 1b in frontline NSCLC

Study start: Q2 2022 / Interim data: Q4 2021 / Topline full results: mid-2022



## Activities ongoing to accelerate entry into late-stage development in NSCLC

Strategic investments in CMC, companion diagnostic development and team scale-up

Clinical Development strategy: ultimately pursue tumor-agnostic indication based on p53 mutation

The background image is a green-tinted photograph of a modern laboratory or clinical setting. It features various pieces of medical equipment, including monitors, carts, and specialized machinery. Several people in white lab coats are visible, working at different stations. The room has a high ceiling with exposed ductwork and large pendant lights. The overall atmosphere is professional and high-tech.

# Chemoprotection May Transform Chemotherapy Like Anesthesia Transformed Surgery



# Chemotherapy Remains the Essential Backbone of the Majority of Medical Cancer Treatment, But Its Side Effects Severely Limit Its Benefits To Patients

## MILLIONS OF PATIENTS

Benefit from chemotherapy, because it prolongs life and even cures some cancers

## CHEMOTHERAPEUTIC SIDE EFFECTS

Suffered by millions of cancer patients

## CHEMOTHERAPY UNSELECTIVE

Chemotherapy cannot distinguish between cancer cells and healthy cells, causing side effects

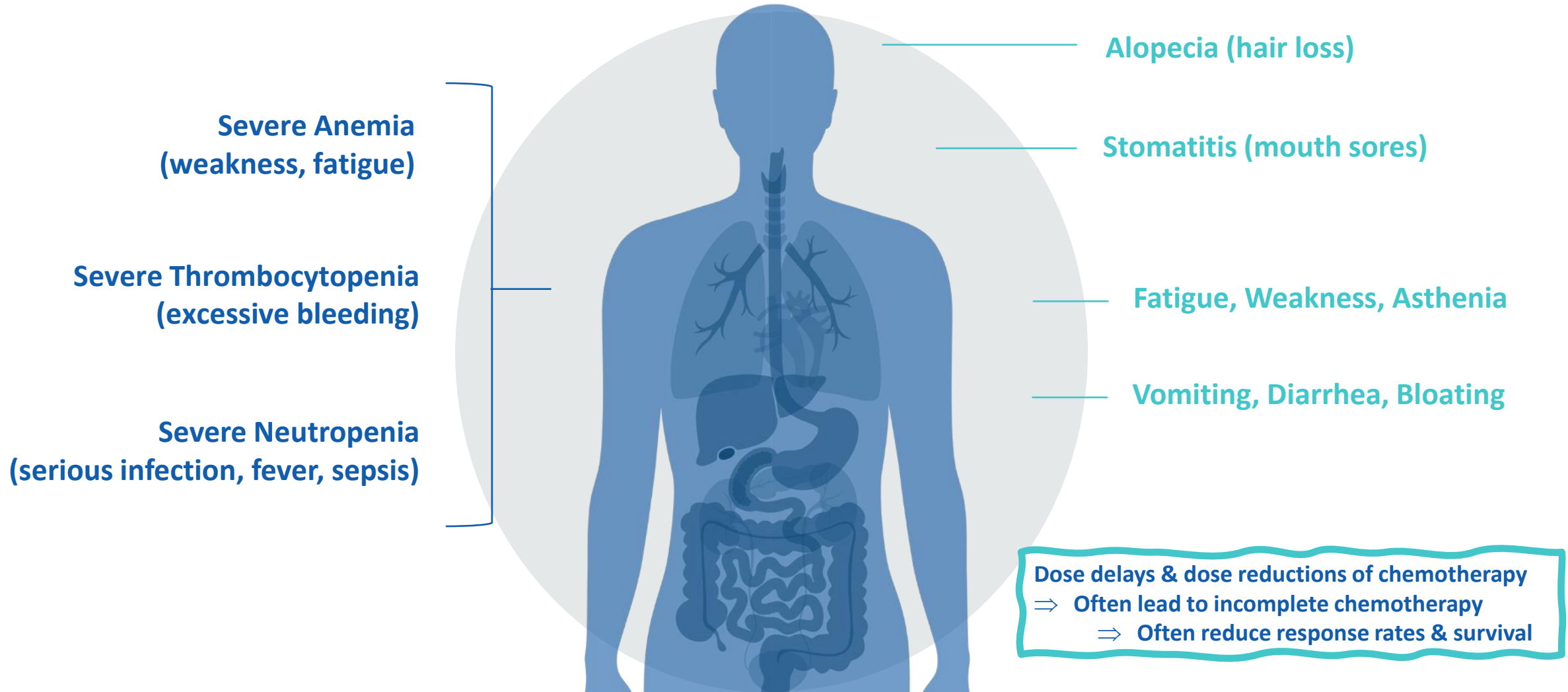
### TODAY'S APPROACH:

#### Resignation / Side Effects Accepted

- Multiple drugs; typically address only one toxicity
- Often ineffective; associated with harmful toxicities
- No options for some side effects (like hair loss)

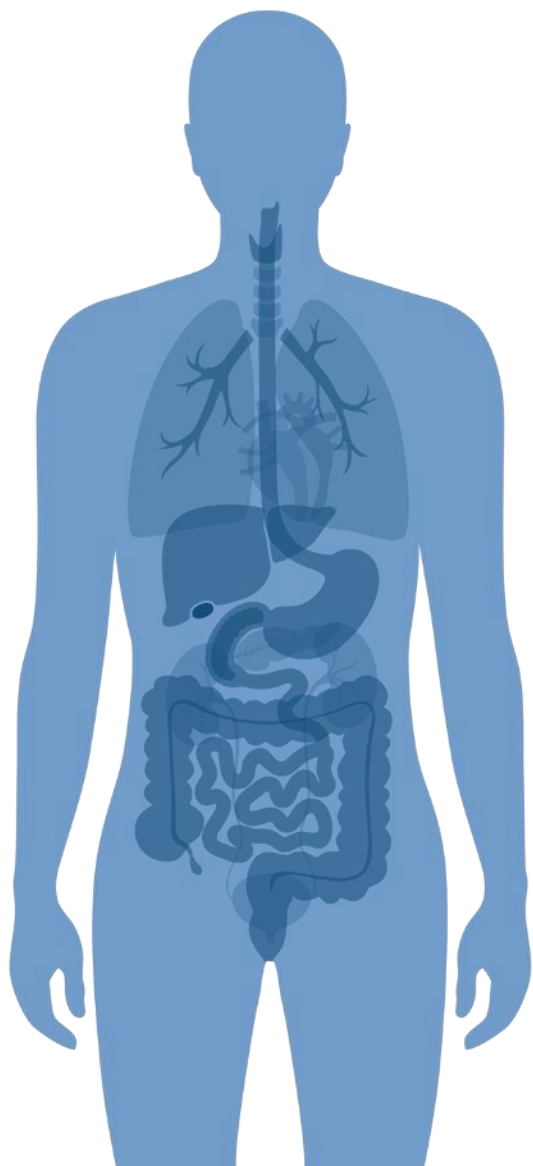
# Chemotherapy's Lack Of Selectivity Causes Side Effects – From Unpleasant To Life-Threatening

ALRN-6924 harnesses a universal mechanism common to normal cells to protect them against chemotherapy side effects



# Poor Standard Of Care For Management Of Bone Marrow Toxicities

Opportunity for ALRN-6924 to be Best in Class Medicine to Protect Against Chemotherapy Side Effects



## SEVERE ANEMIA

**Standard of Care:** "EPOs" (e.g., Aranesp®/Epogen®); Blood transfusions

### Clinical Issues:

- EPOs: promote tumor growth and thrombo-embolic events (black box warning ⚠)
- Limited efficacy
- Transfusions: risk of infection; limited supply

## SEVERE NEUTROPENIA

**Standard of Care:** G-CSF (e.g. Neulasta® /Neupogen®)

### Clinical Issues:

- Can promote tumor growth, can cause spleen rupture and bone pain

## SEVERE THROMBOCYTOPENIA

**Standard of Care:** No drugs used as standard of care – platelet transfusions instead

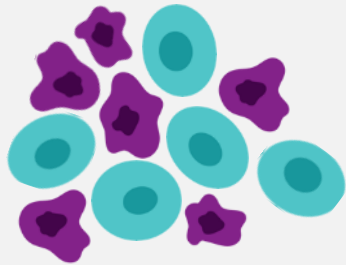
### Clinical Issues:

- Effects limited to 2-5 days maximum
- Patients can become transfusion-refractory
- Transfusion-related risk of infection; limited supply

# Basic Principles To Successfully Protect Against Chemotherapy-induced Side Effects

## CURRENT PARADIGM:

Chemotherapy targets both healthy cells and cancer cells that are cycling (undergoing cell division process)



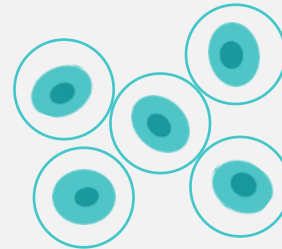
Normally, both healthy cells and cancer cells are destroyed by chemotherapy

PARADIGM  
SHIFT

## AILERON PARADIGM:

Temporarily pause cycling in healthy cells, shielding them

No interruption of cycling in p53-mutant cancer cells, thus not protecting cancer cells from chemotherapy



Healthy cells always have normal p53 thus can be protected



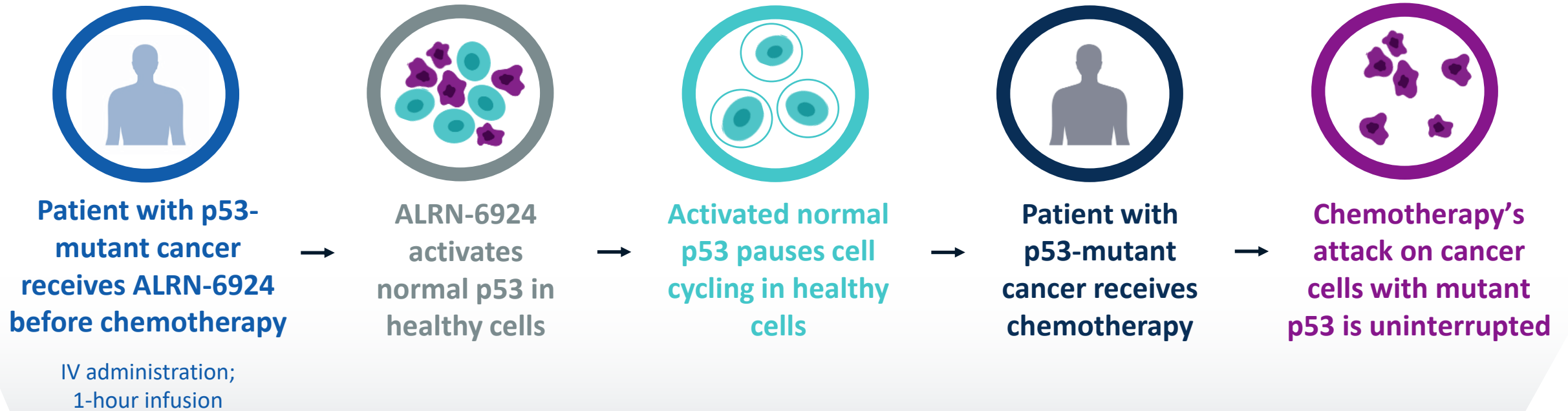
Cancer cells with mutant p53 are not protected

## A COUNTERINTUITIVE APPROACH:

Treat healthy cells, not cancer cells



# Healthy Normal Cells Have Normal p53. Normal p53 Is Activated By ALRN-6924, Which Pauses Cell Cycle In Normal Cells, But Not In Cancer Cells With Mutant p53



Selective chemoprotection of healthy cells (always normal p53)

No protection of cancer cells with p53-mutation

# Potential Path to Tumor-Agnostic Indication for ALRN-6924

## Small Cell Lung Cancer (SCLC) (Topotecan)

### Phase 1b Completed

- Achieved proof of concept

### Healthy Volunteer Study

- Results to be submitted for presentation in 2H21

## Non-Small Cell Lung Cancer (NSCLC) (1<sup>st</sup> line carboplatin + pemetrexed +/- immune checkpoint inhibitor)

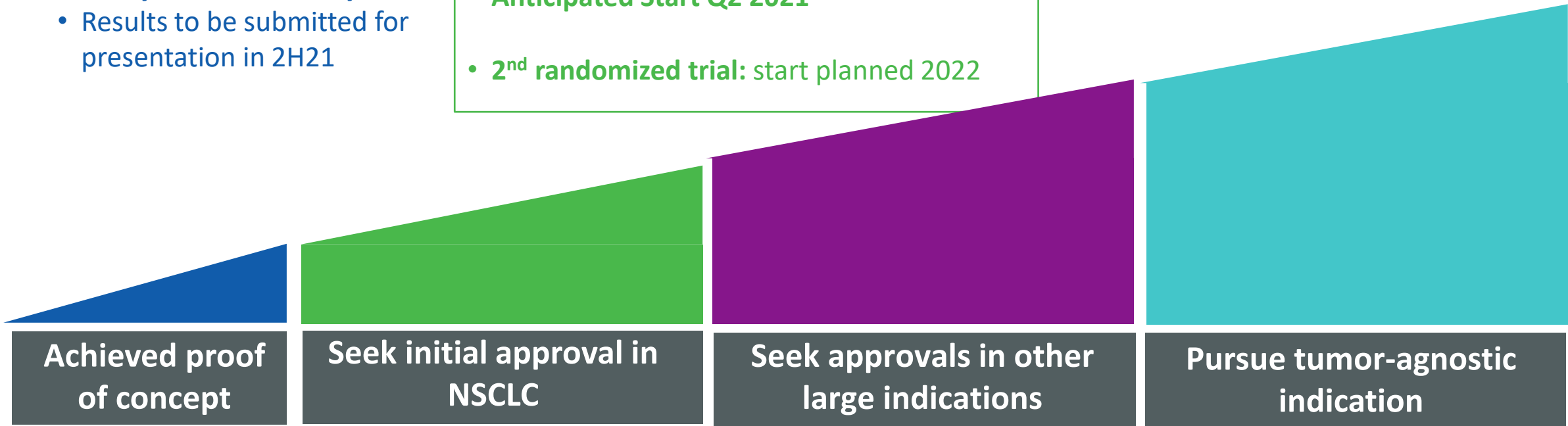
### Registration Program<sup>†</sup>

- Randomized, Placebo-Controlled Phase 1b (N=60 patients)
- Anticipated Start Q2 2021
- 2<sup>nd</sup> randomized trial: start planned 2022

## Gastrointestinal (GI) and Other Cancers (Chemotherapies TBD)

### Registration Program<sup>†</sup>

- Start of trials planned for 2022



<sup>†</sup> Future trials are subject to clinical, regulatory, financial and other considerations

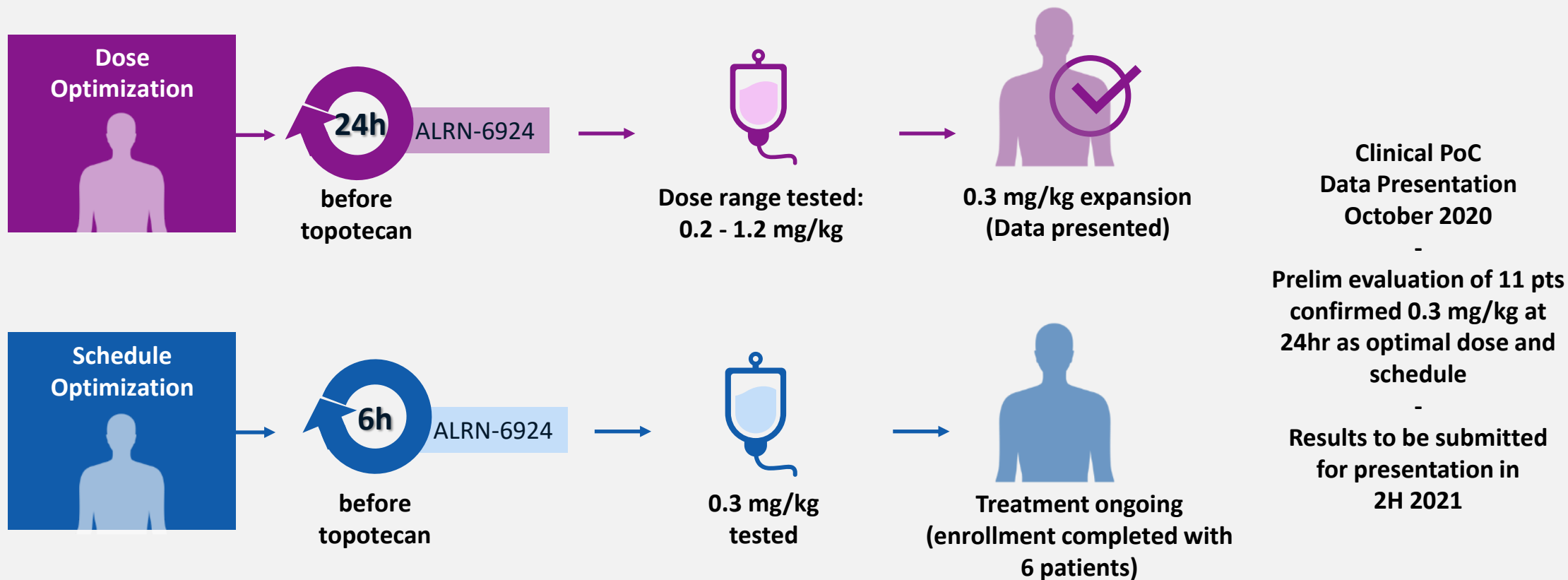
# **ALRN-6924 Phase 1b Trial**

## Design & Results

Data presented in late-breaking poster presentation at  
EORTC-NCI-AACR conference (October 24, 2020)



# ALRN-6924 Proof-Of-Concept Phase 1b SCLC Study Schema



Protocol highlights: Topotecan ( $1.5 \text{ mg/m}^2$ ) administered on days 1 through 5 of every 21-day treatment cycle. Prophylactic G-CSF treatment not permitted in cycle 1; Hb  $>9 \text{ g/dL}$ , ANC  $>1500/\mu\text{L}$ , Platelets  $>100\text{k}/\mu\text{L}$  at baseline

## ALRN-6924 Clinical Results: Key Takeaways

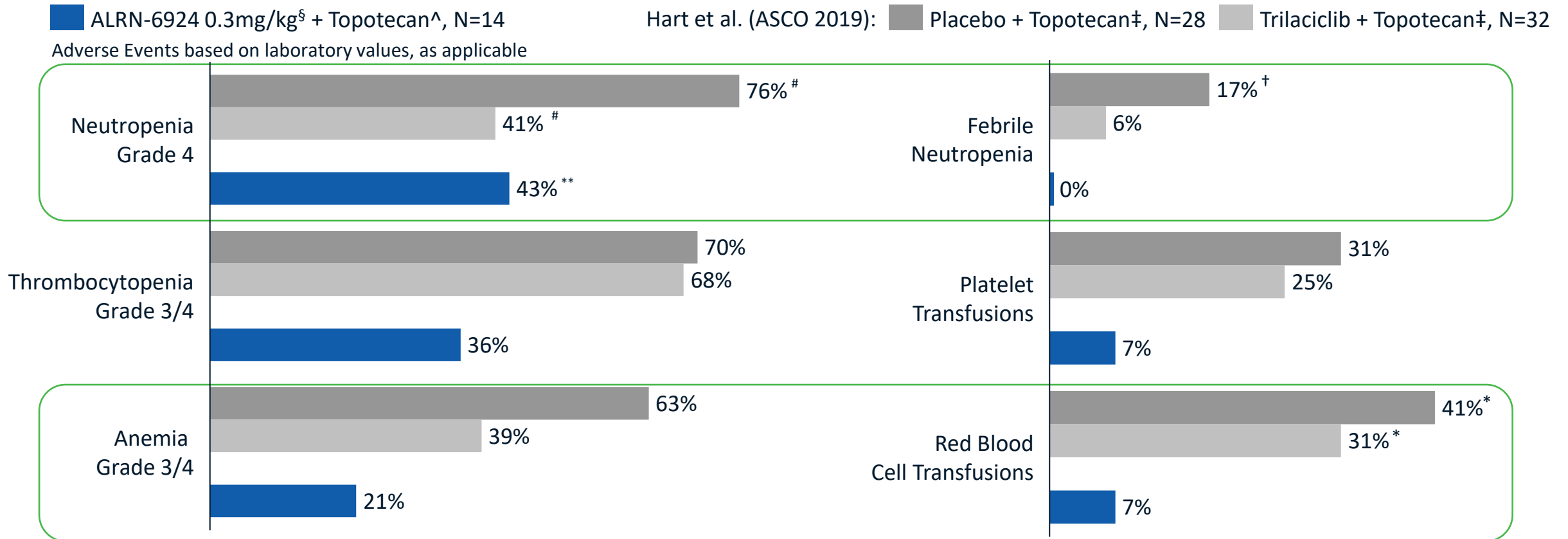
Meaningful reductions of multiple chemotherapy-induced hematologic toxicities as well as fewer RBC transfusions and platelet transfusions

Chemoprotection for normal cells without protecting cancer cells

Fewer dose reductions of chemotherapy  
=> potential for improved efficacy

# ALRN-6924: “Triple-play Efficacy” for Reduction of Neutropenia, Thrombocytopenia, and Anemia, as well as Fewer Transfusions in SCLC Patients Receiving Topotecan<sup>^</sup>

Results of ALRN-6924 Phase 1b Trial and Results of Trilaciclib Trial in SCLC Patients Receiving Topotecan Presented by Hart et al. (ASCO 2019)



<sup>^</sup> ALRN-6924 data cut August 31, 2020 (~24h cohort)

<sup>§</sup> Identified as optimal dose

<sup>\*\*</sup> For cycle 1 and for all treatment cycles

<sup>#</sup> Cycle not characterized

<sup>‡</sup> Hart et al. ASCO 2019 (Slide 9) – G1 Therapeutics; pivotal clinical trial in SCLC patients receiving topotecan

<sup>\*</sup> Excludes any RBC transfusions administered in the first 5 weeks

<sup>†</sup> Febrile neutropenia reported for 29 patients



# Chemoprotection Led to Fewer Dose Reductions Of Chemotherapy

Topotecan dose reductions in SCLC patients:

- Without Chemoprotection: 29% ^ to 32%\* of patients
- With Chemoprotection:
  - with Trilaciclib#: 19% of patients
  - with ALRN-6924§: 14% of patients

# Hart et al., Adv Ther 2020; topotecan + *trilaciclib*-treated patients (G1-Therapeutics' pivotal clinical trial in SCLC patients receiving topotecan)

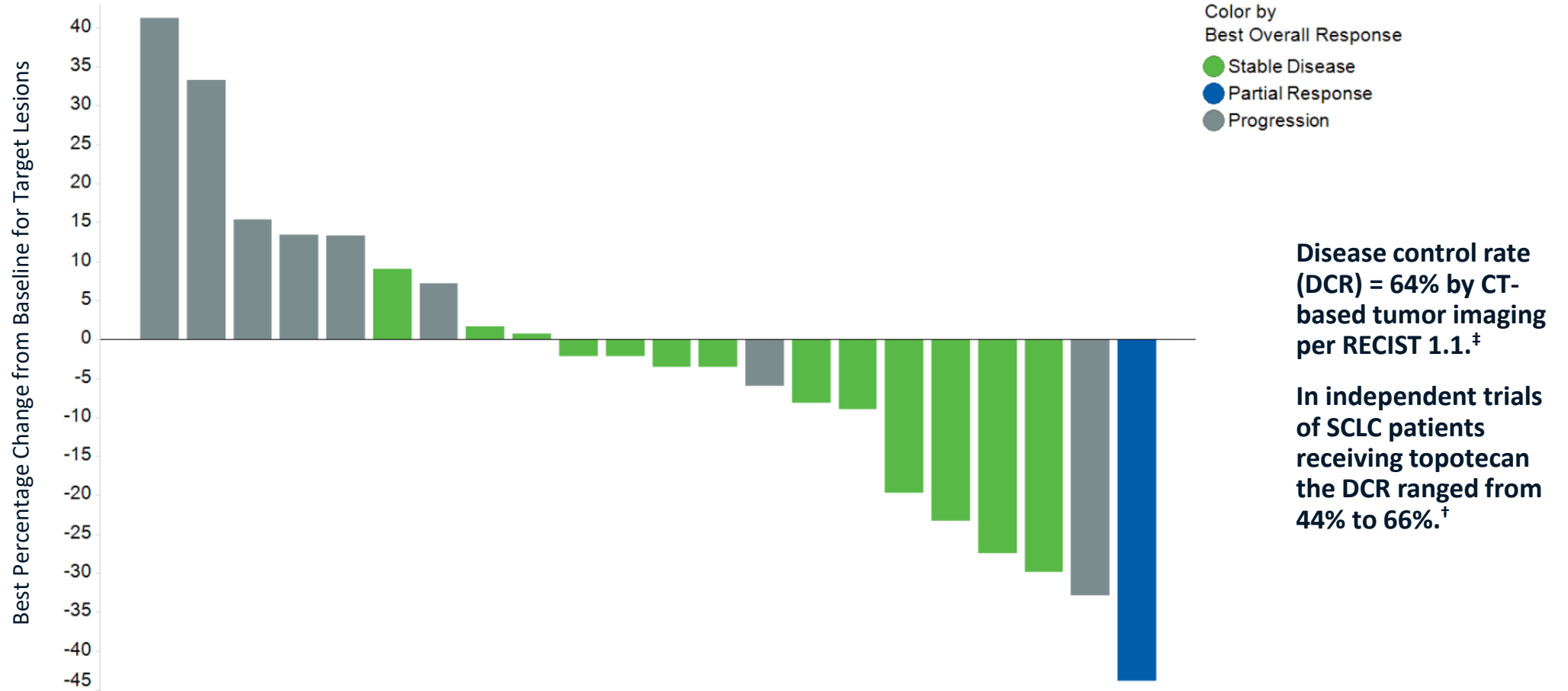
\* Hart et al., Adv Ther 2020; topotecan + *placebo*-treated patients (G1-Therapeutics' pivotal clinical trial in SCLC patients receiving topotecan)

^ U.S. Prescribing Information for topotecan (2019)

§ Andric et al, ENA 2020; patients receiving topotecan + ALRN-6924 (0.3 mg/kg, N=14)

Vision: Chemoprotection → fewer dose reductions → better outcomes

## Preservation Of Chemotherapy's Anticancer Effects During Treatment With ALRN-6924 And Topotecan As Reflected By Disease Control Rate



\*4/26 enrolled patients discontinued prior to radiological evaluation. † Pawel J. et al, J. Clinical Oncol. 32(35): 4012-4019, 2014. Eckhardt J.R. et al. J. Clin. Oncol. 25(15): 2086-2092, 2007. Jotte R. et al, J. Clin. Oncol. 29(3): 287-293, 2011. Inoue A. et al, J. Clin. Oncol. 26(33): 5401-5406, 2008.

-24h cohort, data cut August 31, 2020

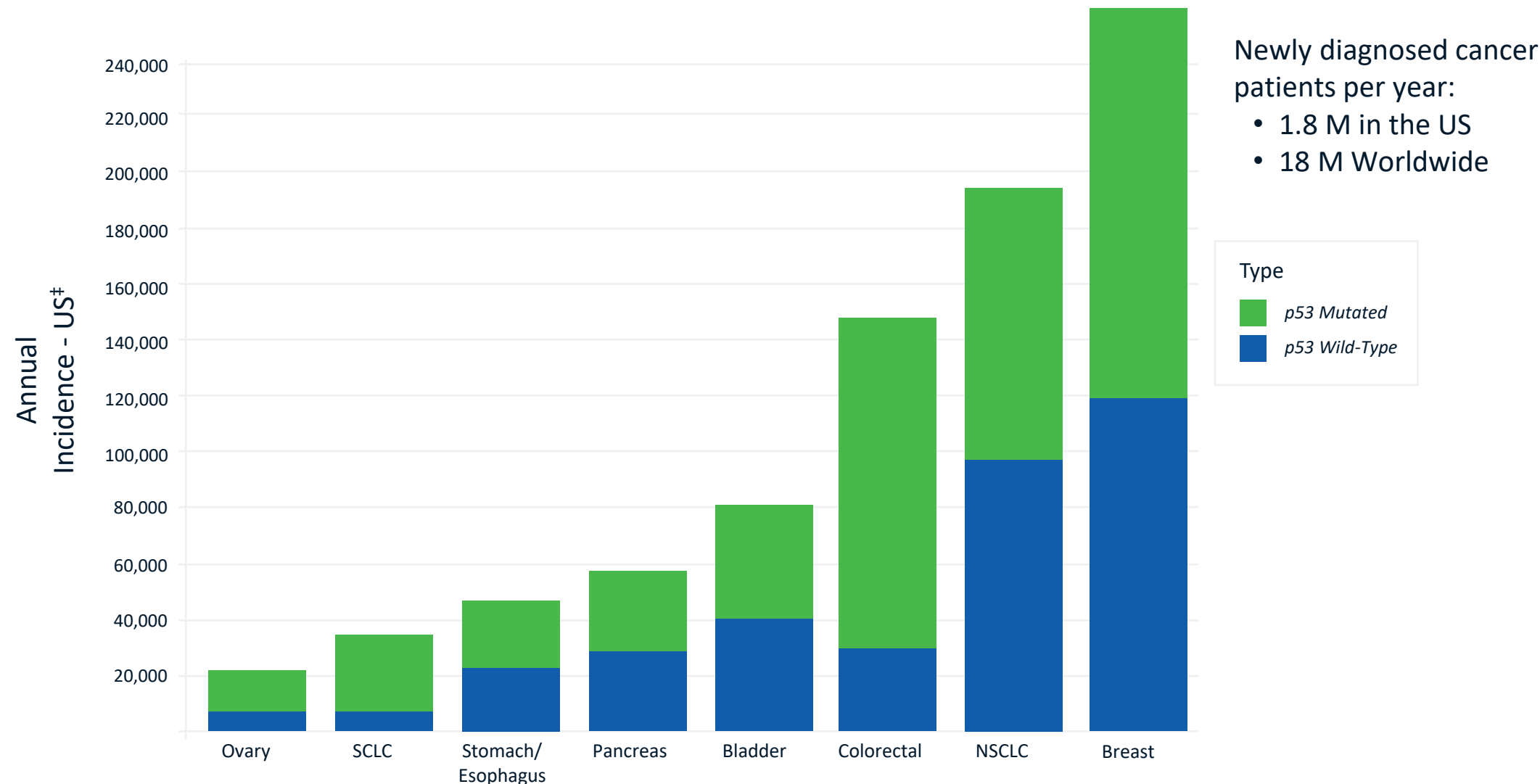
NON-CONFIDENTIAL AILERON THERAPEUTICS 2021

A green-tinted photograph of a laboratory or clinical setting. The image shows various pieces of medical equipment, including monitors, carts, and specialized machines. Several people in white lab coats are visible, working or moving through the space. The ceiling has exposed structural elements and large pendant lights. The floor is a light-colored tile.

# ALRN-6924 Opportunity and Clinical Development Strategy



# Large Market Opportunities In p53-mutated Cancers Across Most Cancer Types

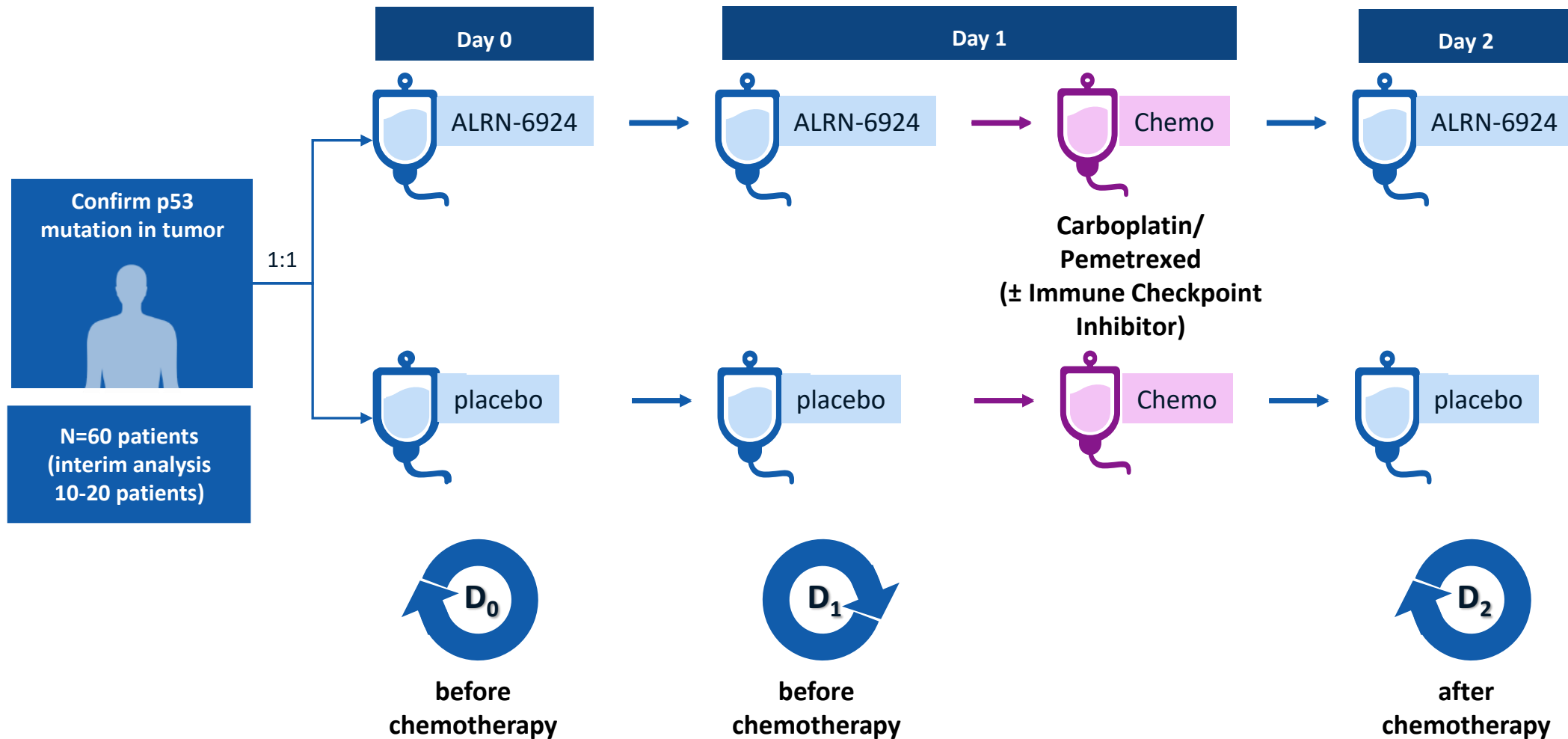


‡ Siegel et al, “Cancer statistics, 2020” American Cancer Society journal CA: A Cancer Journal for Clinicians. Genetic alterations from Foundation “Insights” Database 18-May-2020 (297,209 sample set).

# Advanced NSCLC patients treated in 1<sup>st</sup> line with carboplatin/pemetrexed (± Immune Checkpoint Inhibitor) and ALRN-6924 or placebo

Randomized, double-blind, placebo-controlled Phase 1b clinical trial starting 2Q 2021; final data mid-2022

Evaluations: proportion of treatment cycles free of severe toxicities, transfusions and use of growth factors, as well as impact on quality of life



## Strong Intellectual Property Portfolio

- Aileron owns or has exclusive license to over 200 U.S. and foreign patents, with another 100+ applications in prosecution.
- These patents and applications include ALRN-6924 methods of manufacture, methods of use, drug product formulations, and compositions of matter.
- Composition of matter patent expiration in 2033 (+ up to 5 additional years subject to patent term extensions).
- Of note, Aileron maintains global exclusive rights to its technology and ALRN-6924 worldwide.



## Key Financial Highlights

Cash, Cash Equivalents and Investments (as of Dec. 31, 2020 )	\$13.8M
Cash Raised in 1 <sup>st</sup> Quarter 2021	\$55.7M

Expected to Support Operations Into	2 <sup>nd</sup> Half 2023
-------------------------------------	---------------------------

Common Shares Outstanding (March 2021)	90M
--	-----

Analyst Coverage by William Blair, Canaccord, H.C. Wainwright and Jones Trading

# Our Belief: Chemoprotection Will Transform Chemotherapy Like Anesthesia Transformed Surgery

## Validated Core Differentiator

Selective chemoprotection without protecting cancer cells

## Achieved Proof-of-Concept

Reduction of multiple hematological toxicities and blood transfusions

## Stepwise Clinical Development Strategy

Phase 1b Trial in NSCLC: planned start in Q2 2021

Seek NSCLC indication 1st, then seek other large cancer indications

Ultimately pursue tumor-agnostic indication

## OUR VISION

Chemoprotection for patients with p53-mutated cancers across all cancer types and chemotherapies

**50%**

of cancer patients have p53-mutated cancer

# Supplementary Information

## Representative Demographics And Key Baseline Characteristics

			0.3 mg/kg N (%) N=14	0.6 mg/kg N (%) N=5	1.2 mg/kg N (%) N=6	Total N (%) N=25
	<b>AGE</b>	Median	68.5	67	58	67
	<b>GENDER</b>	Male	14 (100)	2 (40)	4 (67)	20 (80)
	<b>ECOG PS</b>	0	10 (71)	2 (40)	3 (50)	15 (60)
		1	4 (29)	3 (60)	3 (50)	10 (40)
	<b>BASELINE LDH</b>	≥ULN	5 (36)	3 (60)	2 (33)	10 (40)
	<b>TIME SINCE PREVIOUS THERAPY</b>	<60 days	7 (50)	1 (20)	5 (83)	13 (52)
	<b>STAGE AT INITIAL TUMOR DIAGNOSIS</b>	Extensive Disease	6 (100)	5 (100)	6 (100)	25 (100)
	<b>P53 MUTATION STATUS</b>	Mutated	13 (93)	5 (100)	6 (100)	24 (96)

# Impact Of Chemoprotection On Topotecan-Induced Grade $\geq 3$ Nausea or Fatigue

Topotecan-treated SCLC patients (%) experiencing Grade  $\geq 3$  nausea or fatigue:

- Without Chemoprotection: Nausea: 4%\* to 8%^ , Fatigue: 6%^ to 7%\*
- With Chemoprotection:
  - with Trilaciclib#: Nausea: 0%, Fatigue: 6%
  - with ALRN-6924§: Nausea: 0%, Fatigue: 0%

# Hart et al., Adv Ther 2020; topotecan + *trilaciclib*-treated patients (G1-Therapeutics' pivotal clinical trial in SCLC patients receiving topotecan)

\* Hart et al., Adv Ther 2020; topotecan + *placebo*-treated patients (G1-Therapeutics' pivotal clinical trial in SCLC patients receiving topotecan)

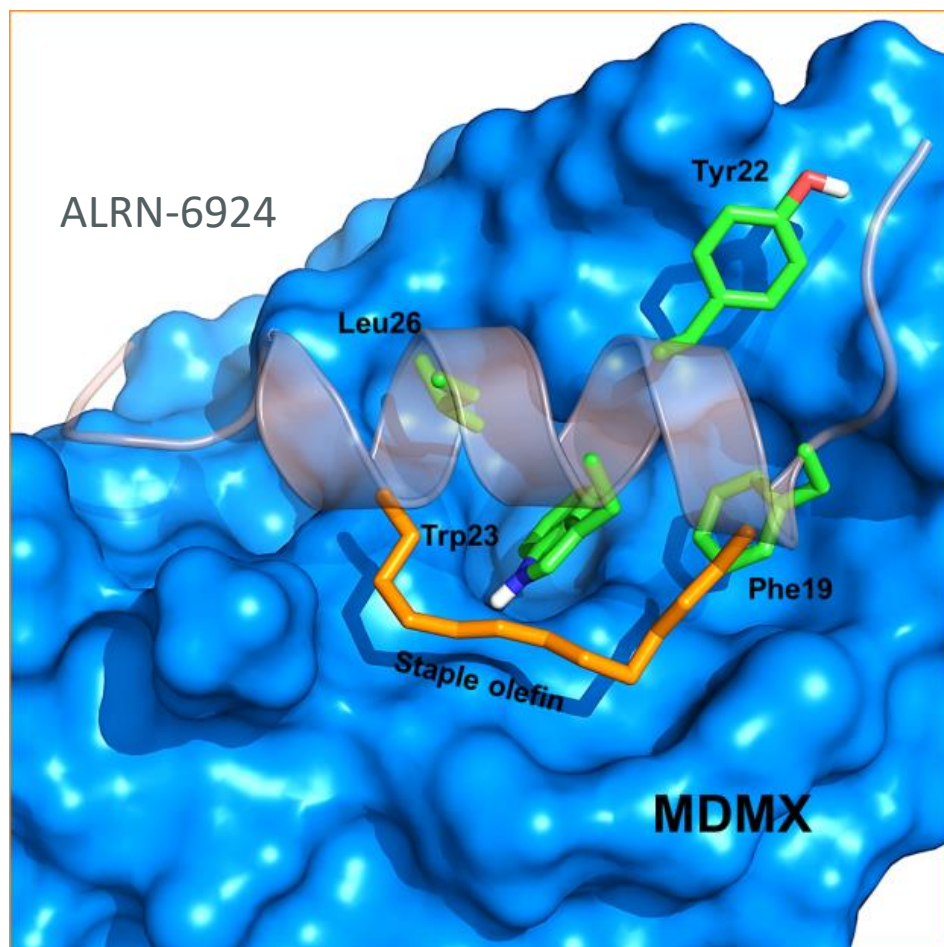
^ U.S. Prescribing Information for topotecan (2019)

§ Andric et al, ENA 2020; patients receiving topotecan + ALRN-6924 (0.3 mg/kg, N=14)



# Structure And Key Design Properties Of ALRN-6924

Structure based on the  $\alpha$ -helical domain of p53, with chemical modifications

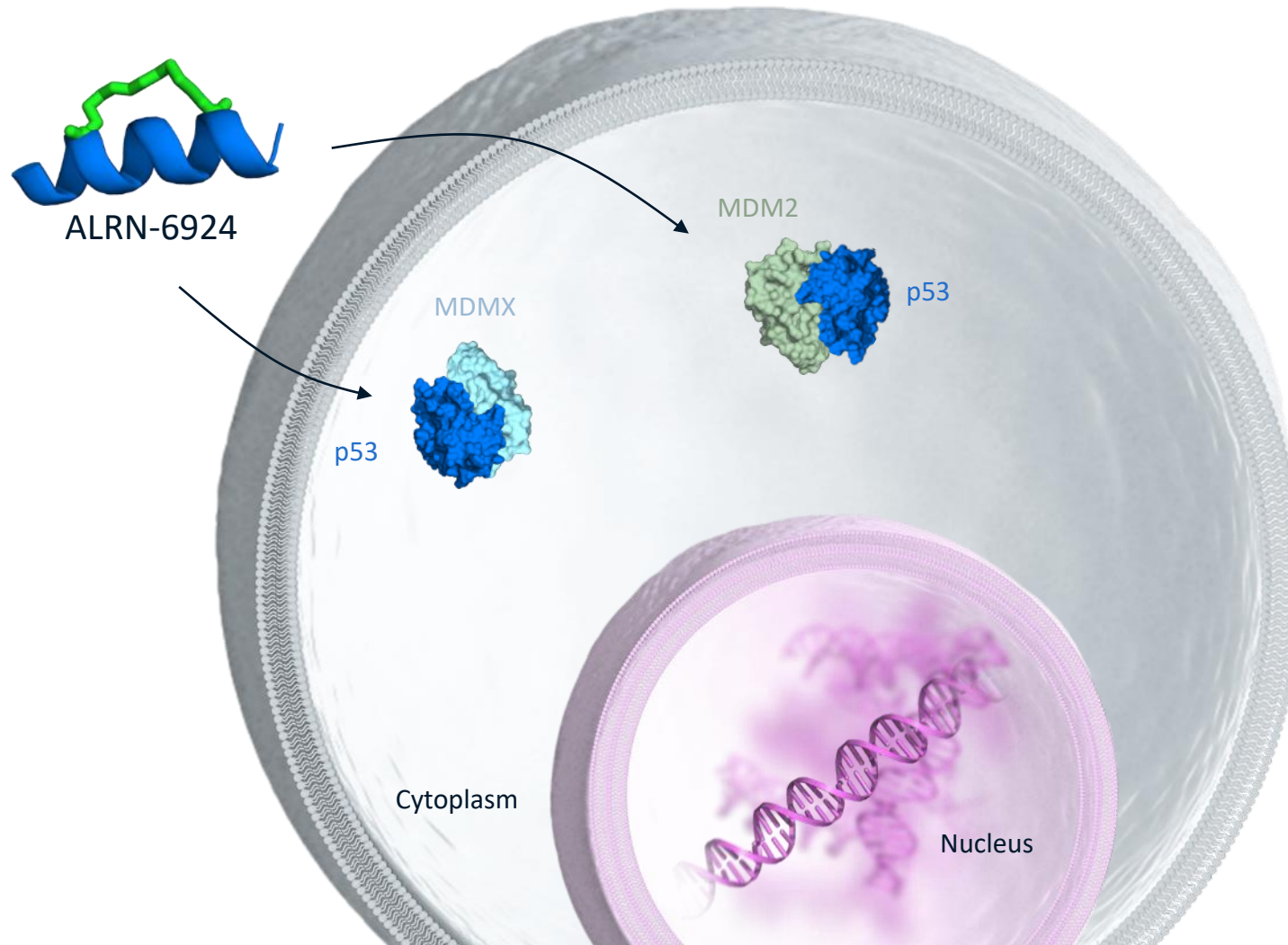


ALRN-6924-MDMX co-crystal structure

The hydrocarbon staple and other modifications ensure:

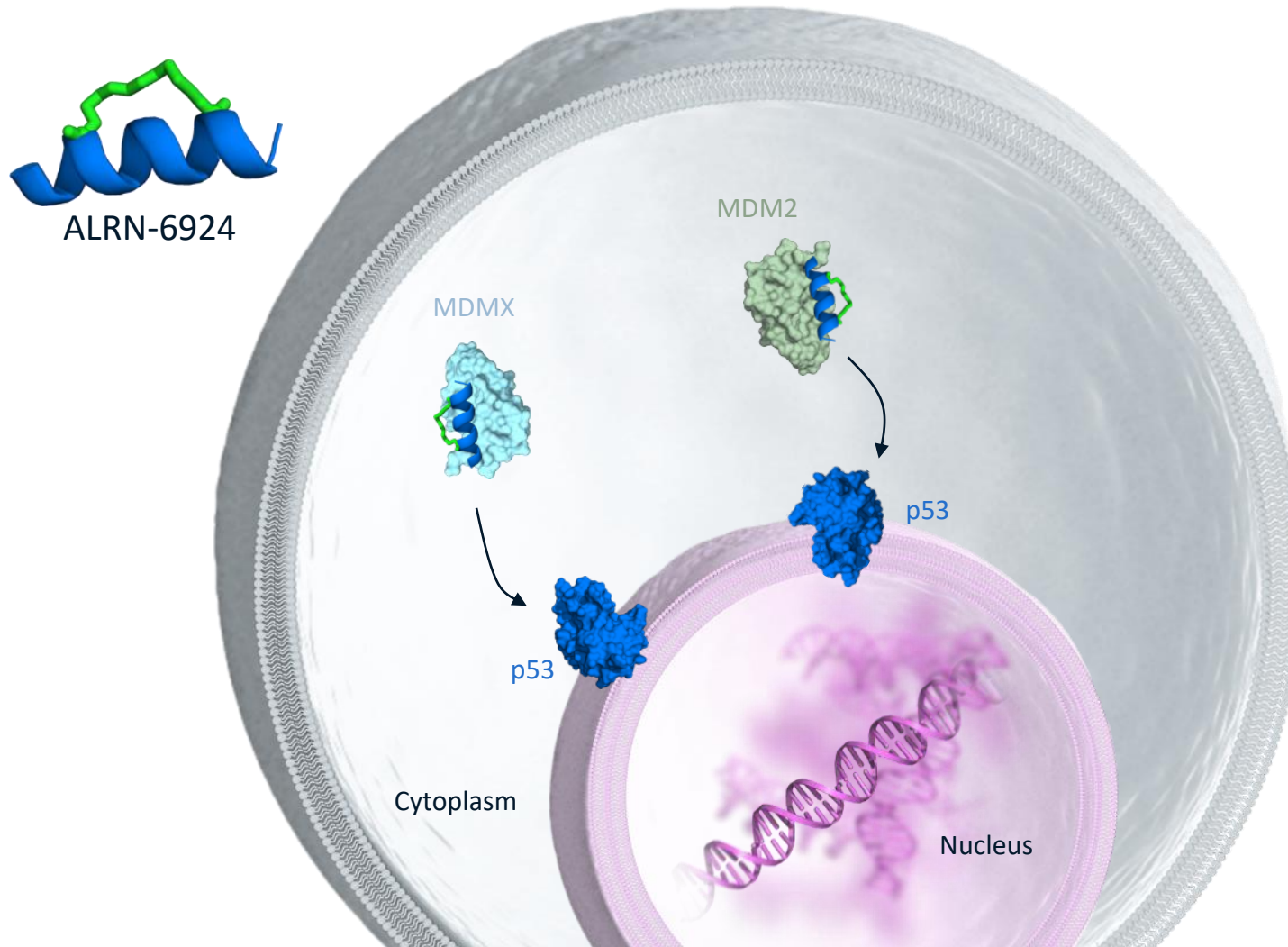
- I. Protection from proteolytic cleavage
- II. Permeation of cell membranes and cell entry
- III. High affinity binding to its targets
- IV. Preclinical and clinical on-target, on-mechanism effects

## ALRN-6924 Mechanism Of Action In Wild-type p53 Cells



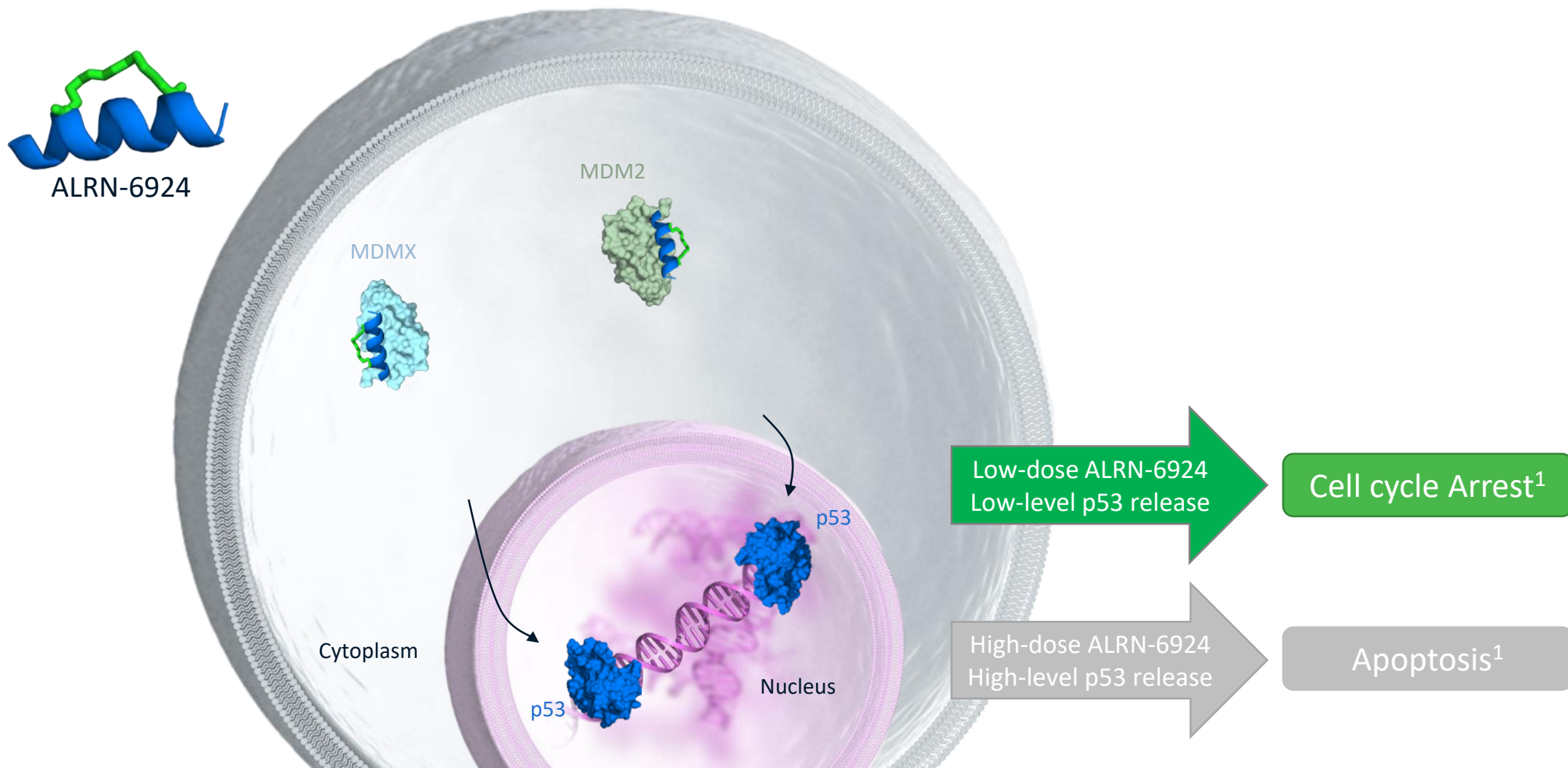
ALRN-6924 is a decoy that mimics p53 and selectively binds to MDMX + MDM2, releasing p53 to induce cell cycle arrest

## ALRN-6924 Mechanism Of Action In Wild-type p53 Cells



ALRN-6924 is a decoy that mimics p53 and selectively binds to MDMX + MDM2, releasing p53 to induce cell cycle arrest

# ALRN-6924 Mechanism Of Action In Wild-type p53 Cells



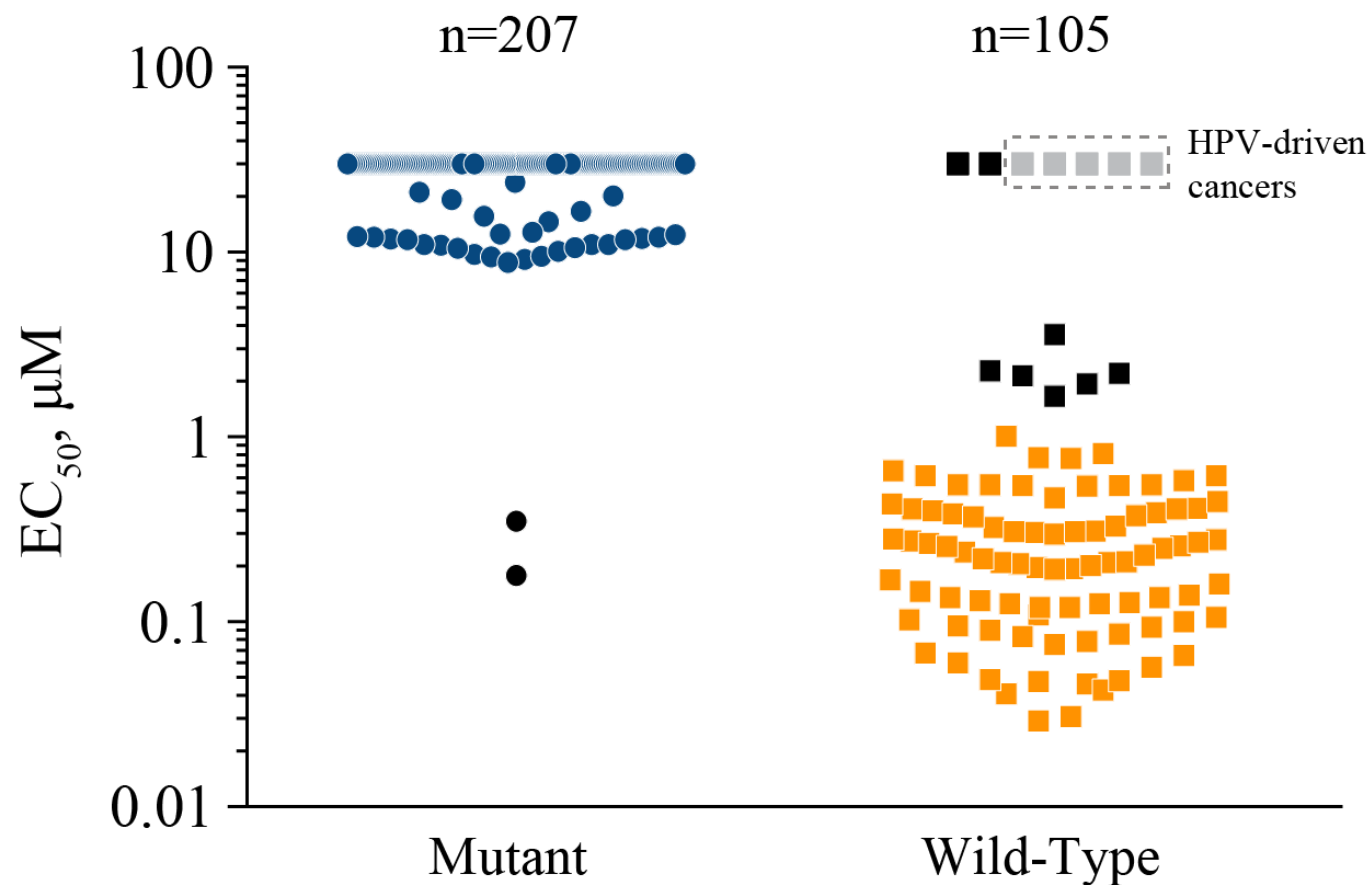
ALRN-6924 is a decoy that mimics p53 and selectively binds to MDMX + MDM2, releasing p53 to induce cell cycle arrest

<sup>1</sup> Chen; Cold Spring Harb Perspect Med. 2016 Mar 1



# ALRN-6924 Does Not Work In Cells With Mutant p53

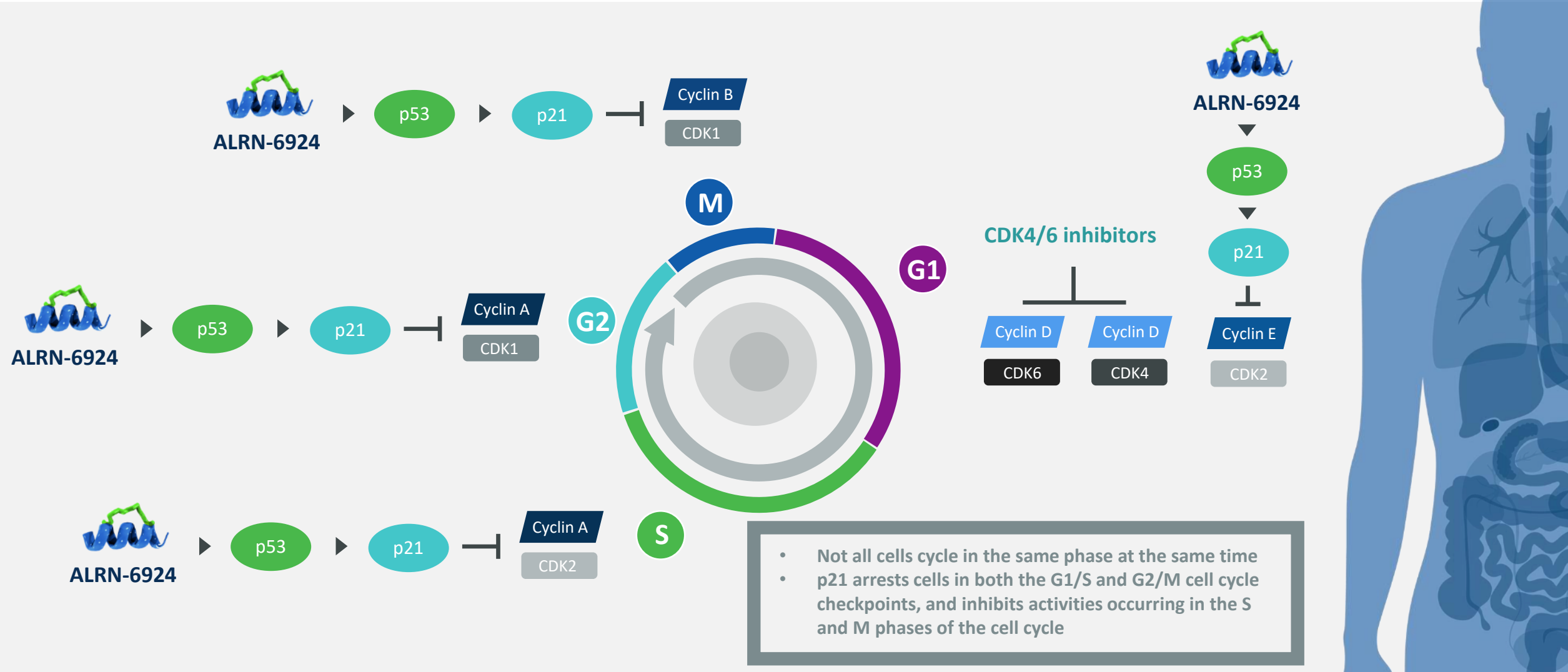
ALRN-6924 Studies in >300 Cell Lines Show Potent, On-mechanism Cellular Activity



$EC_{50}$  = Drug conc. at which 50% of tumor cells are killed  
 $EC_{50}$  values  $\geq 30 \mu M$  are shown as 30  $\mu M$

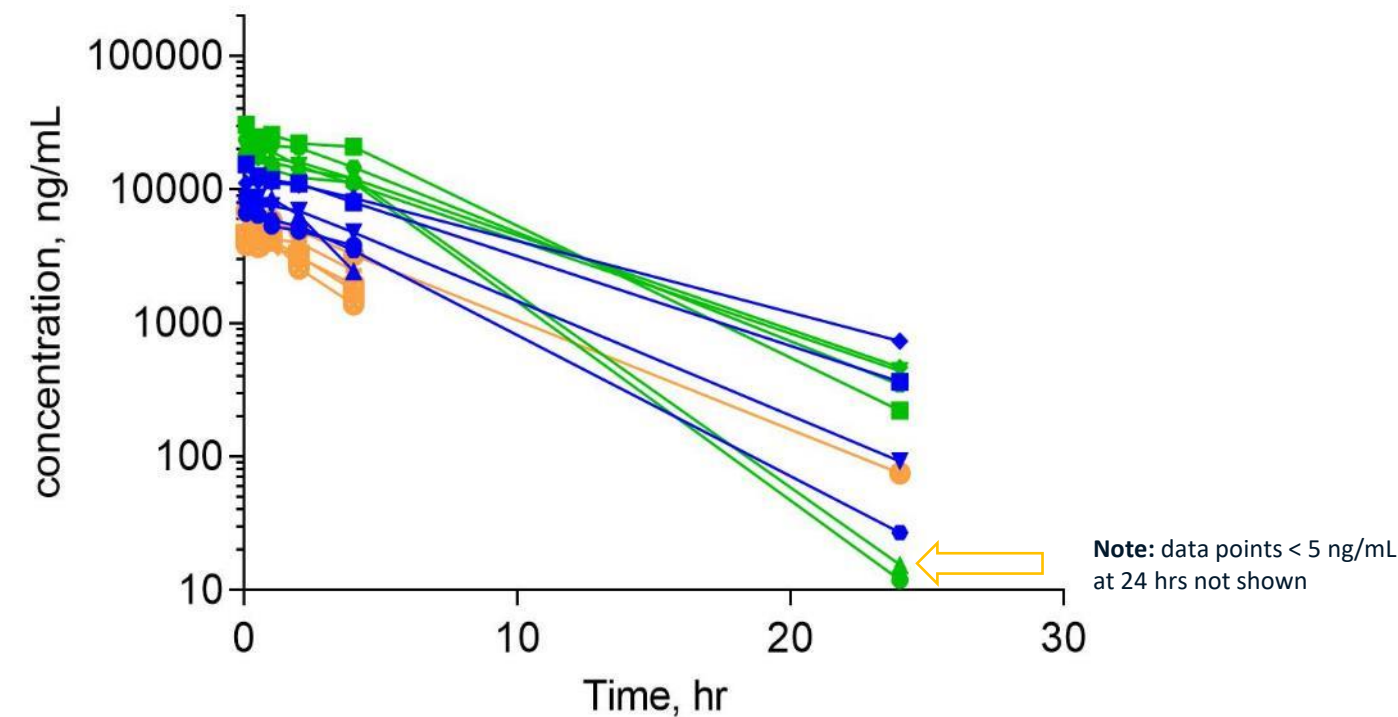


# ALRN-6924 Best-in-class Potential In Chemoprotection: Effects On All Phases Of Cell Cycle



# ALRN-6924 Shows Dose-dependent PK Profile In SCLC Patients

ALRN-6924 Plasma PK For Patients Dosed 0.3, 0.6, 1.2 mg/kg



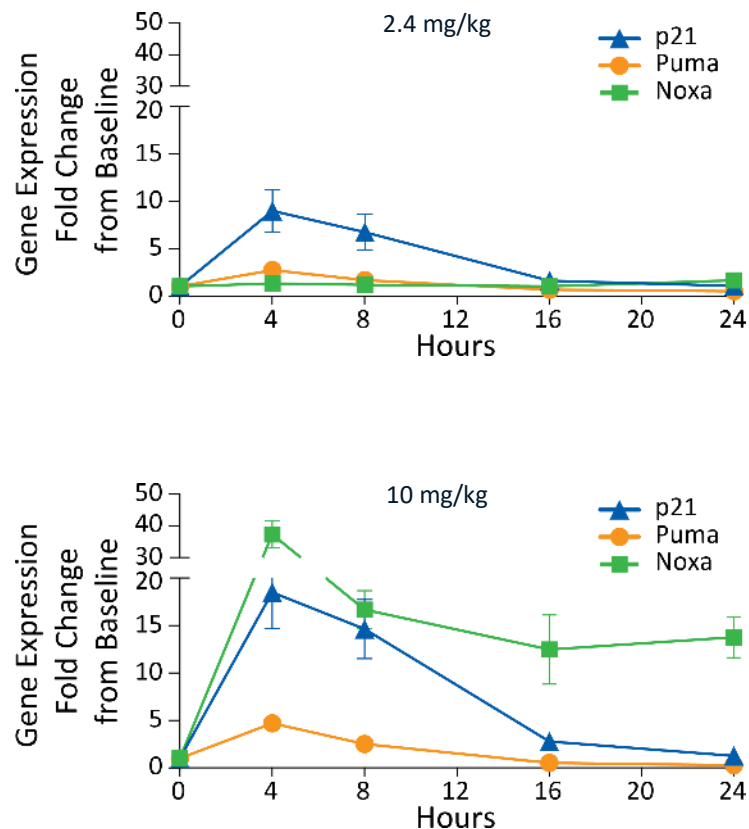
Parameter (average)	0.3 mg/kg	0.6 mg/kg	1.2 mg/kg
$C_{max}$ $\mu\text{g/mL}$	5.0	9.9	21.9
$AUC_{0-24\text{hr}}$ $\text{ng}\cdot\text{hr/mL}$	35,862	83,030	250,519
$t_{1/2}$ hr	3.4	4.5	7.1

- Monophasic clearance, low patient-to-patient variability
- Slightly less than dose-proportional exposure
- 3.4 to 7.1 hr half-life yields no accumulation on repeated dosing

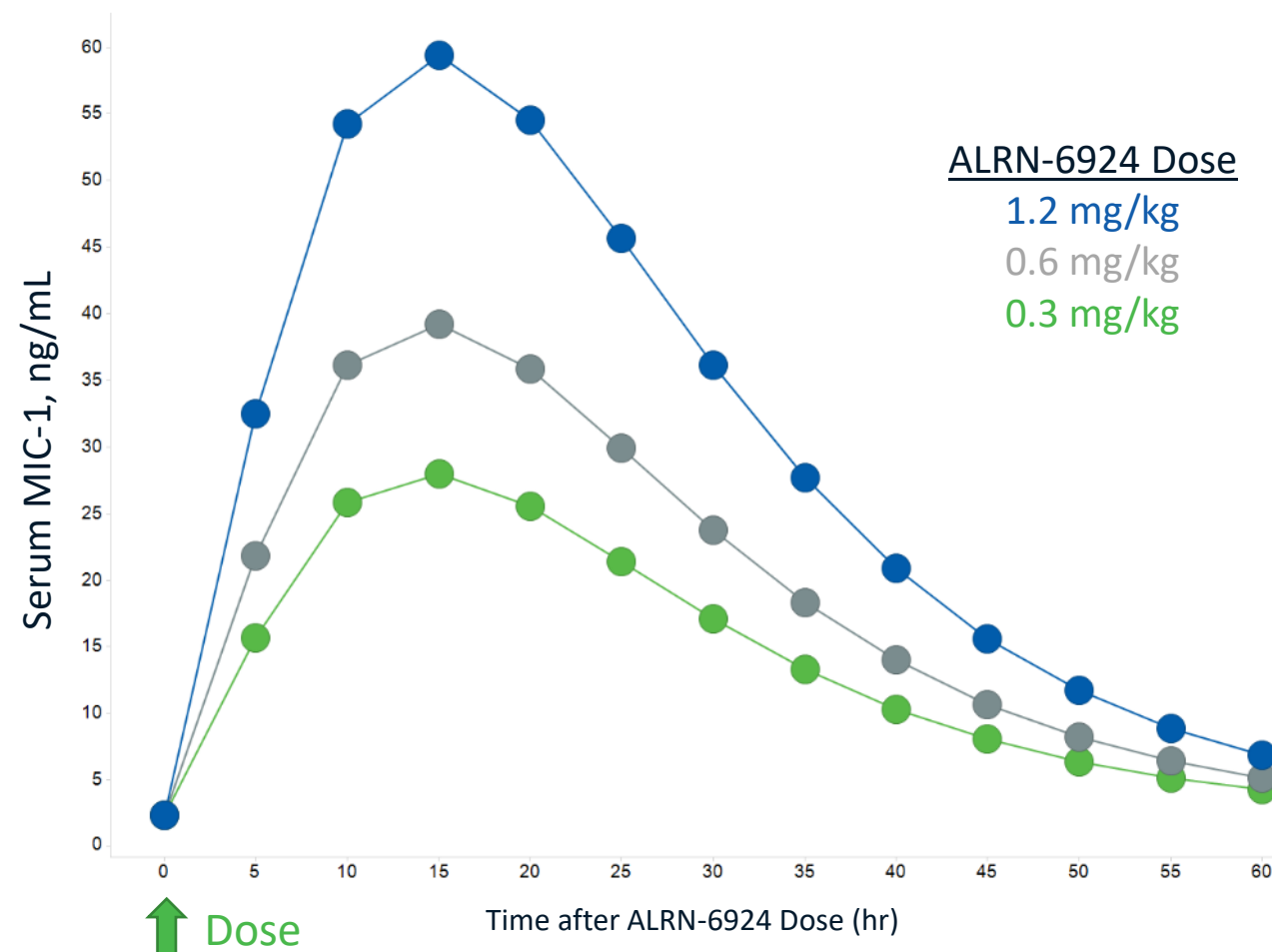
-24h cohort, data cut May 13, 2020

# Biomarkers Of Cell Cycle Arrest (p21) And Apoptosis (Puma, Noxa, And MIC-1)

Non-clinical studies<sup>†</sup>



MIC-1 levels in ongoing SCLC trial<sup>‡</sup>

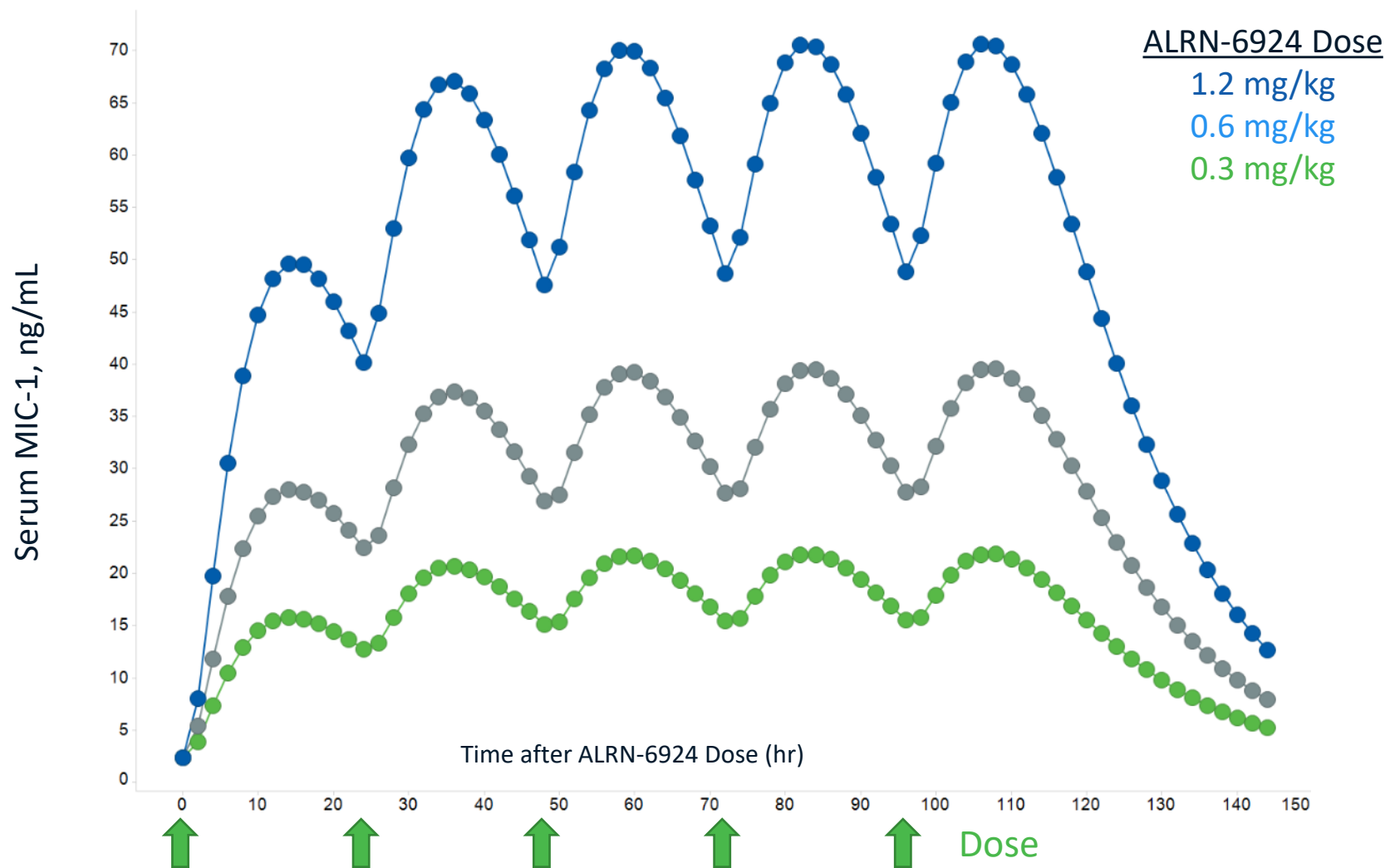


<sup>†</sup> Carvajal et al, "The Investigational Peptide Drug ALRN-6924, a Dual Inhibitor of MDMX and MDM2, is an Effective Myelopreservation Agent. AACR-NCI-EORTC Conference October 2019

<sup>‡</sup> Data modelled from this trial and other ALRN-6924 clinical studies: Meric-Bernstam F, et al Phase I trial of a novel stapled peptide ALRN-6924 disrupting MDMX and MDM2-mediated inhibition of WTP53 in patients with solid tumors and lymphomas. J. Clin. Oncol. 35(15): 2505, 2017.

# Repeat-dosing Of 6924 Leads To Sustained Activation Of P53 As Reflected By Sustained MIC-1 Levels

Data modelled from chemoprotection trial MIC-1 data plus earlier 71-patient first-in-human ALRN-6924 clinical trial results<sup>‡</sup>



NON-CONFIDENTIAL AILERON THERAPEUTICS 2021

<sup>‡</sup> Meric-Bernstam F. et al., Phase I trial of a novel stapled peptide ALRN-6924 disrupting MDMX and MDM2-mediated inhibition of WTP53 in patients with solid tumors and lymphomas, J. Clin. Oncol. 35(15):2505-2505 (2017).



AILERON

Chemoprotection May Transform Chemotherapy  
Like Anesthesia Transformed Surgery

NASDAQ: ALRN

[WWW.AILERONRX.COM](http://WWW.AILERONRX.COM)