ALRN-6924 Phase 1b NSCLC Trial Interim Data and Next Steps for ALRN-6924 Phase 1b Breast Cancer Trial

June 29, 2022

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Developing ALRN-6924 as a Selective Cell Cycle Arresting Agent to Protect Patients with p53-Mutant Cancers from Multiple Chemotherapy-Induced Side Effects

Nonclinical Proof of Mechanism

In vitro (mouse & human)

Bone marrow stem cells

Carvajal et al., EORTC 2019

In vivo (mouse)

Epithelial gut mucosa cells

Annis et al., ASH 2021

Ex vivo (human)

Hair follicles and their stem cells

Gherardini et al., SID 2022

Clinical Development

Proof of Mechanism in Healthy Volunteers

CCA in BM stem cells after single and repeated doses of ALRN-6924

Voors-Pette et al., ESMO 2021

CCA in hair follicle cells after single dose of ALRN-6924

To be presented 2H 2022

Proof of Concept in Phase 1

Reduced multilineage BM toxicity in topotecan-treated, p53-mutant SCLC

Andric et al., ESMO 2021

Path to Approval: Randomized Clinical Trials

Ongoing clinical trial in carboplatin/ pemetrexed-treated, p53-mutant NSCLC

- Planned interim (n=20 pts): 2Q22
- Planned topline (n=60 pts): 4Q22

Ongoing clinical trial in doxorubicin/ cyclophosphamide + docetaxel-treated, p53-mutant BC

- Planned interim: 4Q22
- Up to 30 pts

Phase 3 trial(s)

Ultimate Goal

Chemoprotection for all patients with p53-mutated cancer

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NSCLC Trial: Overview & Protocol Highlights

- **Carboplatin/Pemetrexed:** Historically not associated with high frequency of Grade 3/4 hematologic toxicities; no single standout hematologic toxicity
- **Exploratory composite primary endpoint:** Proportion of treatment cycles free of severe neutropenia, thrombocytopenia and anemia, blood transfusions, and the use of growth factors, as well as dose reductions or dose delays in the first 4 cycles
- **Measures to maximize detection of hematologic toxicities:** Hematologic AEs coded using lab values; frequent blood testing; carboplatin dose = AUC6
- **ALRN-6924 was dosed at 0.3 mg/kg:** Based on successful SCLC/topotecan chemoprotection trial (Andric, ESMO 2021)
- **None of the 20 patients in the interim analysis received checkpoint inhibitors:** Standard of care with checkpoint inhibitors = 4 cycles; Standard of care without checkpoint inhibitors = 6 cycles

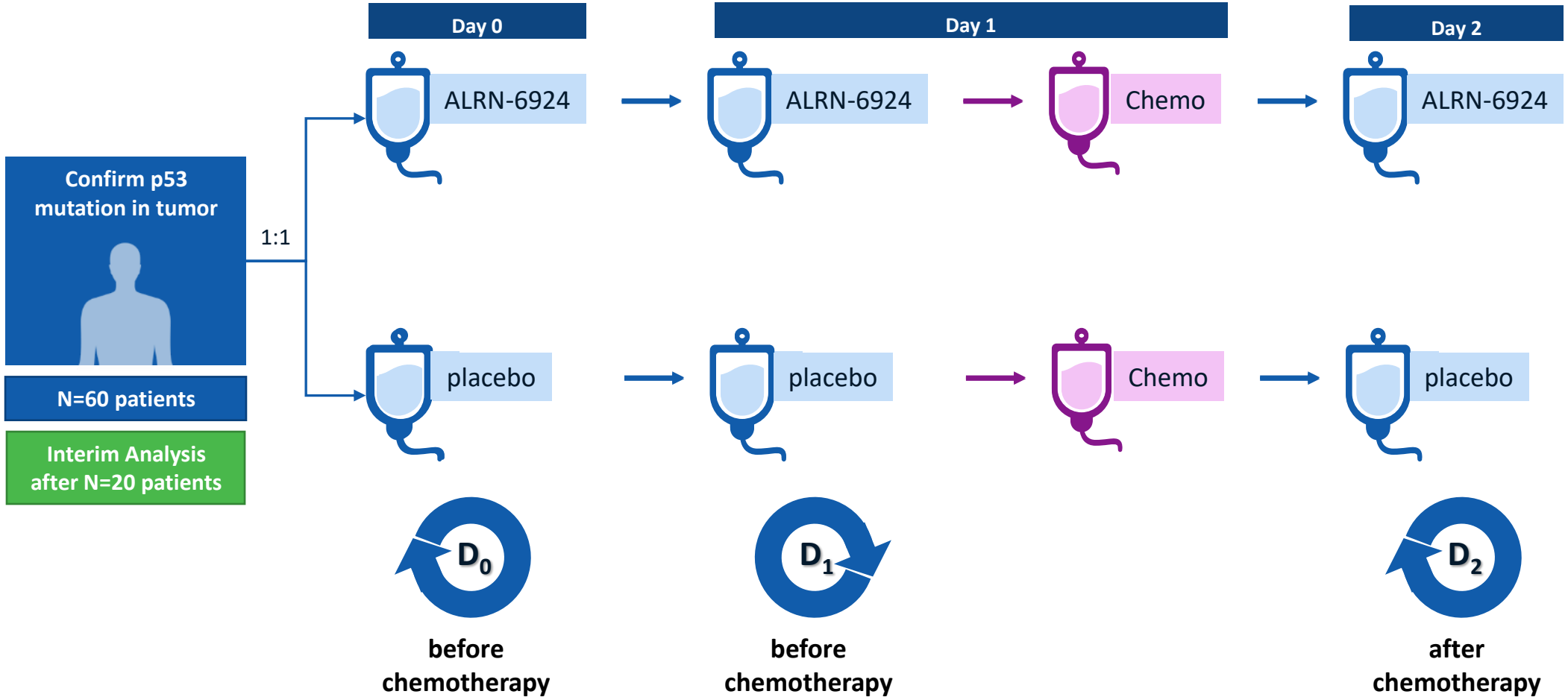
Key Highlights of Today's Announcement

- **Two inextricably-linked findings from the NSCLC trial interim analysis:**
  1. Patients on ALRN-6924 were able to stay on chemotherapy longer, completing 93% of the first 4 cycles of carboplatin/pemetrexed compared to 78% on placebo.
     a) Imbalances increased to 79% on ALRN-6924 versus 57% on placebo evaluating cycles 1-6
  2. Composite primary endpoint: ALRN-6924 treated patients demonstrated 56% of cycles free from Grade 3/4 hematologic toxicities and related events compared to 50% placebo*
- **Hematologic toxicities observed reflect historical AE reporting**
- **Will stop further enrollment in the NSCLC trial**

Will apply key learnings from the NSCLC data to strengthen the Phase 1b breast cancer trial in accordance with clinical and regulatory precedents

* As evaluated in cycles 1 through 4

Phase 1b Trial of ALRN-6924 in Advanced p53-Mutated NSCLC Patients Treated in First Line with Carboplatin/Pemetrexed ± Immune Checkpoint Inhibitor† and ALRN-6924 or Placebo



† None of first 20 patient for interim analysis received immunotherapy
‡ As of the interim analysis data cut-off of June 16, 2022, 3 patients remained on treatment on each arm.

Demographics and Baseline Characteristics

	ALRN-6924 (n=11)†	Placebo (n=9)	Overall (n=20)
Age, mean (range)	66.3 (54, 74)	70.0 (62, 78)	68.0 (54, 78)
Gender (n, % male)	9 (88.1)	4 (44.4)	13 (65.0)
Race (%)			
Caucasian	11 (100)	9 (100)	20 (100)
Ethnicity (n, %)			
Hispanic or Latino	0	1 (11)	1 (5)
Not Hispanic or Latino	11 (100)	8 (89)	19 (95)
Baseline ECOG, n (%)			
0	8 (72.7)	7 (77.8)	15 (75.0)
1	3 (27.3)	2 (22.2)	5 (25.0)
2+	0	0	0

† One patient was randomized to the placebo arm, but treatment was initiated with ALRN-6924 due to a dispensing error, and the decision was made to maintain that patient on ALRN-6924.

Max Grade of Neutropenia, Thrombocytopenia, or Anemia per Patient per Cycle

		Neutropenia						Thrombocytopenia						Anemia					
Treatment	**Patient**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**	**1**	**2**	**3**	**4**	**5**	**6**
ALRN-6924 (n=11)	1	1	2	0	1	1	0	1	0	0	0	0	0	0	0	0	0	0	0
	2	1	1	0	0	0	1	1	3	1	1	1	3	0	1	1	1	1	2
	3	2	3	3	2			1	1	2	1			1	1	2	1		
	4*	3	4	3	3	4	3	0	3	3	4	4	4	1	2	3	3	3	3
	5	1	2					1	3					2	2				
	6	0	1	1	1	1	1	0	1	0	0	0	0	0	1	2	2	2	2
	7	0	1	1				0	1	0				1	1	2			
	8	1	2	3	3	3	2	1	2	2	2	1	1	1	1	1	1	1	1
	9	0	1	3	0	0		1	1	3	1	0		0	1	2	2	2	
	10	3	2	1	0			1	2	3	3			0	1	1	1		
	11	0	1	0	0			0	0	0	0			1	1	1	1		
Placebo (n=9)	12	0						0						1					
	13	1	1	2	2	1	1	2	1	2	3	2	3	1	1	1	2	1	2
	14	0	1	0	3			0	0	0	4			2	2	3	3		
	15	1	0					1	0					2	2				
	16	0	0	0	1			2	0	1	4			0	0	0	1		
	17	0						1						3					
	18	1	0	2	0	0		1	1	1	0	1		0	1	2	2	2	
	19	1	2	2	2			0	1	0	1			0	0	0	1		
	20	1	1	2	3			1	2	2	3			1	1	1	2		

Completed 6 cycles

- Of 83 cycles administered, Grade ≥3 toxicities were observed in 25 (30%). Only 3 were in Cycle 1 (12%)
- Grade 4 toxicities were infrequent, occurring in one pt on ALRN-6924 and two pts on placebo
- 5/11 (45%) on ALRN-6924 completed 6 cycles, vs. 1/9 (11%) on placebo
- 18 cycles showed 28 Grade ≥3 toxicities on ALRN-6924; 7 cycles with 10 instances on placebo
- One pt (#4) on ALRN-6924 accounted for 15 of 28 Grade ≥3 instances (53%)*

* Despite 15 instances Grade ≥3 heme toxicities, patient completed 6 cycles, achieved partial response, investigator reported patient “felt great”

Results by Treatment Group

Average cycles completed by patients: 4.7 on ALRN-6924, 3.4 on Placebo

	Treatment (n of pts)	Primary composite endpoint: Cycles without Grade ≥3 cytopenia or DD, DR, transfusion, growth factor	Pts with grade ≥3 neutropenia n (%)	Pts with grade ≥3 thrombo-cytopenia n (%)	Pts with grade ≥3 anemia n (%)	Total cycles completed†
Cycles 1-4	ALRN-6924 (n=11)	23 / 41 (56%)	5 (45%)	5 (45%)	1 (9%)	41 / 44 possible (93%)
	Placebo (n=9)	14 / 28 (50%)	2 (22%)	4 (44%)	2 (22%)	28 / 36 possible (78%)
Cycles 1-6	ALRN-6924 (n=11)	29 / 52 (56%)	5 (45%)	5 (45%)	1 (9%)	52 / 66 possible (79%)
	Placebo (n=9)	16 / 31 (52%)	2 (22%)	4 (44%)	2 (22%)	31 / 54 possible (57%)

DD Dose Delay, DR Dose reduction

† Completed cycles = received ≥1 dose of ALRN-6924 and chemotherapy. Average cycles completed per patient: 4.7 on ALRN-6924, 3.4 on placebo

Summary of Safety Findings

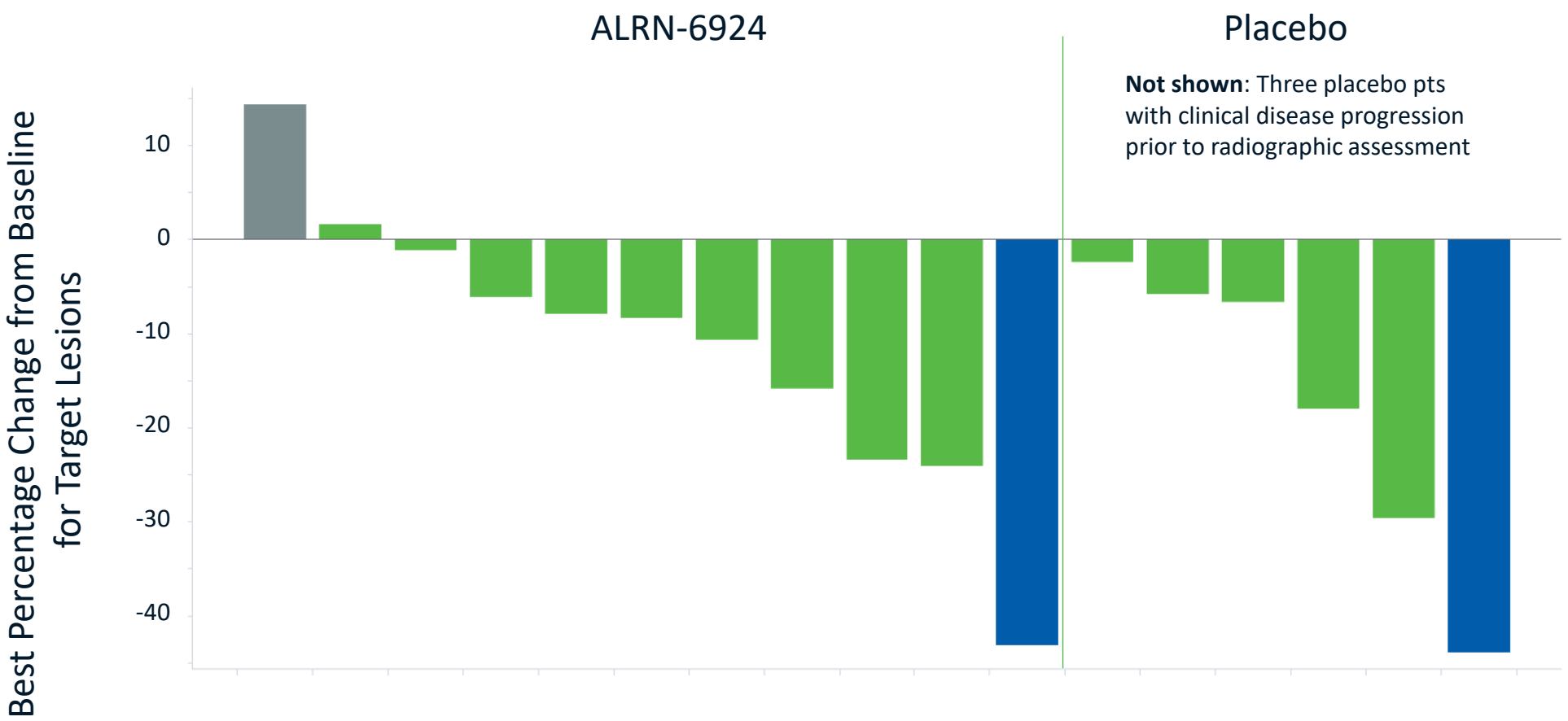
	ALRN-6924 (N=11) n (%)	Placebo (N=9) n (%)
Any TEAE	8 (72.7)	8 (88.9)
Serious TEAEs	2 (18.2)	2 (22.2)
Grade ≥3 Higher TEAEs	7 (63.6)	5 (55.6)
TEAEs Leading to Discontinuation of ALRN-6924/Placebo	0	1 (11.1)[&]
TEAEs Leading to Discontinuation of Pemetrexed	0	1 (11.1)
TEAEs Leading to Discontinuation of Carboplatin	0	1 (11.1)
TEAEs Leading to Death	1 (9.1)*	0
TEAEs Related to ALRN-6924/Placebo	0	1 (11.1)
TEAEs Related to pemetrexed	7 (63.6)	7 (77.8)
Serious TEA Related to pemetrexed	2 (18.2)	1 (11.1)
TEAEs Related to carboplatin	7 (63.6)	7 (77.8)
Serious TEA Related to carboplatin	2 (18.2)	1 (11.1)

- **Anemia (any grade): 4/11 (36%) on ALRN-6924 vs. 6/9 (67%) on placebo**
- **Fatigue (any grade): 2/11 (18%) on ALRN-6924 vs. 5/9 (56%) on placebo**

TEAE Treatment-emergent Adverse Event
* Death due to disease progression after completing 2 cycles of chemotherapy
[&] TEAE deterioration of general health

No evidence that ALRN-6924 Protected p53-mutant Tumors

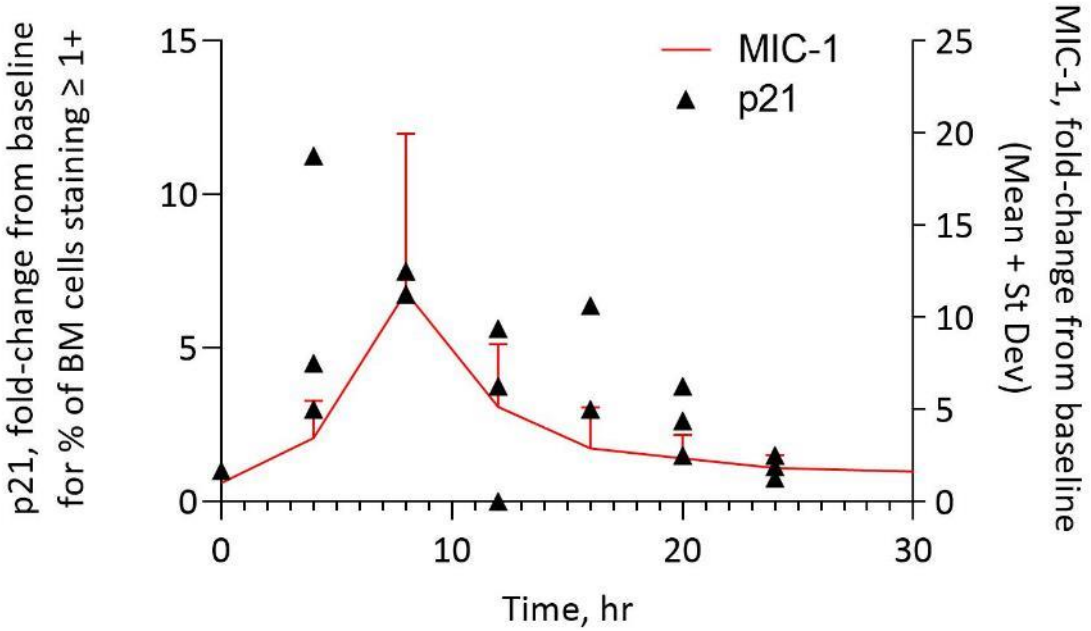
Median progression-free survival: 4.6 months ALRN-6924, 3.2 months placebo



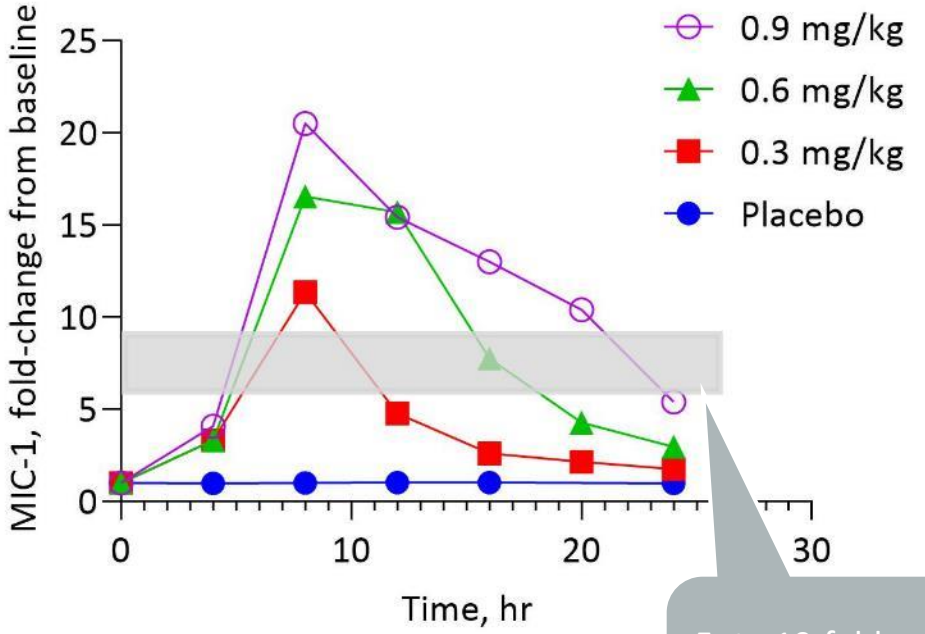
Studies in Healthy Human Volunteers Show Serum MIC-1 and Bone Marrow p21 Are Correlated and Suggest More Durable Cell Cycle Arrest at Higher ALRN-6924 Doses

A single ALRN-6924 dose yields 5- to 10-fold MIC-1 elevation (indicating sustained cell cycle arrest in BM) up to 10 hrs at 0.3 mg/kg, 18 hrs at 0.6 mg/kg, and 24 hrs at 0.9 mg/kg

0.3 mg/kg HVS Part 1†



0.3, 0.6, 0.9 mg/kg HVS Part 2



5- to 10-fold MIC-1 elevation predicts CCA

† Voors-Pette et al, "A Phase 1 Study of the Dual MDMX/MDM2 Inhibitor, ALRN 6924, in Healthy Volunteers" ESMO 2021

Summary & Next Steps

Key Learnings from NSCLC

- ALRN-6924 treated patients received more chemotherapy and stayed on treatment longer compared to placebo
- Patients on ALRN-6924 completed more planned cycles of carboplatin/pemetrexed; this may have introduced bias against ALRN-6924 on the composite primary endpoint
- Higher dose level of ALRN-6924 could provide more durable cell cycle arrest, thus more chemoprotection
- Grade 3/4 hematologic toxicities do not occur with high frequency in carboplatin/pemetrexed, even at AUC6
- Aileron plans to stop further enrollment in NSCLC trial and focus on breast cancer trial in the near term

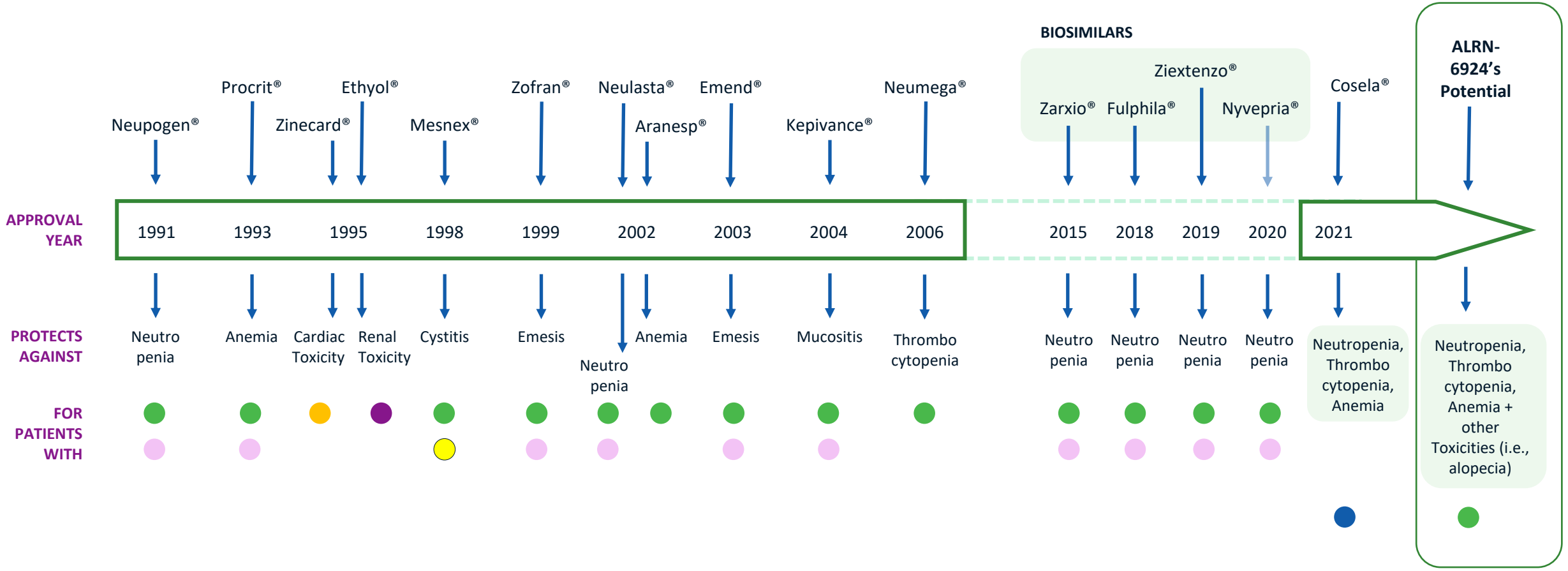
Strengthening Phase 1b Neo-/adjuvant Breast Cancer Trial

- Neo-/adjuvant chemotherapy for breast cancer is associated with frequent severe neutropenia in cycle 1
- Will leverage well-established regulatory precedent of duration of severe neutropenia in cycle 1 as primary endpoint
- Breast cancer trial allows for evaluation of protection against alopecia; occurs in >90% of patients receiving neo-/adjuvant chemotherapy
- Changing chemotherapy regimen to TAC*
- Modifying dosing strategy; will stop enrolling patients in 0.3 mg/kg and 0.6 mg/kg dose cohorts
- Evaluating additional modifications to optimize opportunity and will provide update in the near term

*doxorubicin plus cyclophosphamide and docetaxel

Cell Cycle Arresting (CCA) Agents Are Poised to Bring New Era of Innovation to Supportive Care

Historical landscape: primarily broad labels (i.e., indicated to treat all/most cancers); single toxicity drugs; innovation gap from 2006 - 2021



Our Vision:
To deliver selective chemoprotection to all patients with p53-mutated cancer regardless of type of cancer or chemotherapy