

ALRN-6924 and Palbociclib in Patients with MDM2 Amplified or MDM2/CDK4 Co-amplified Tumors: Interim Analysis

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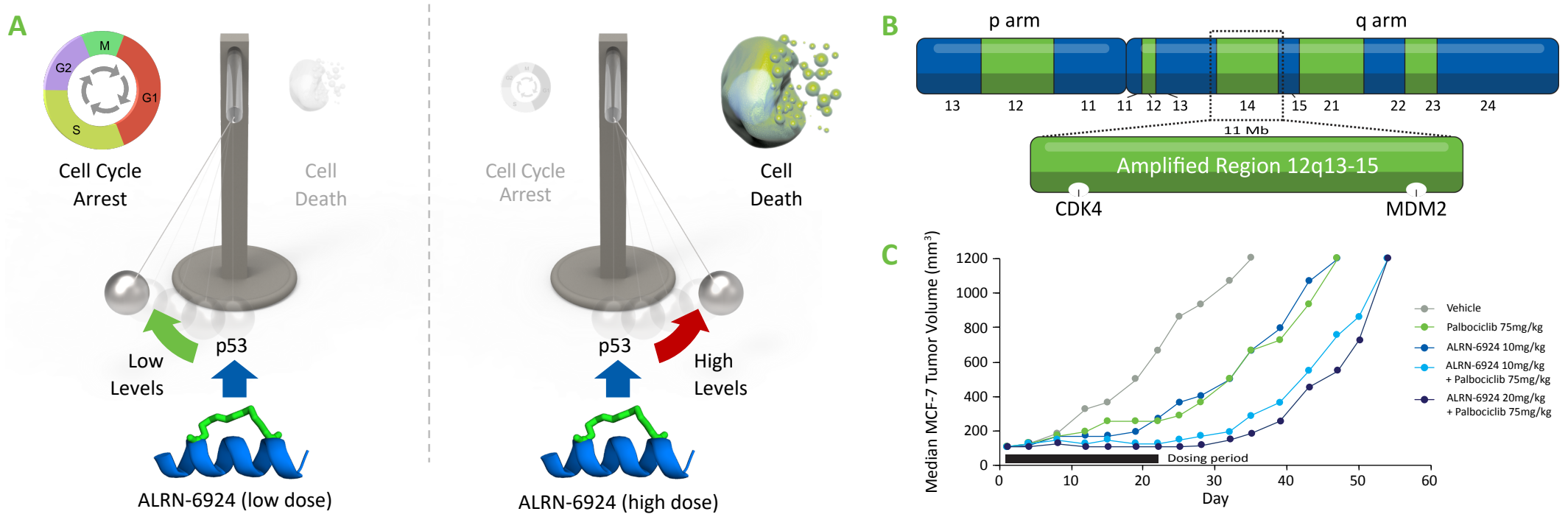


Background

ALRN-6924 is a stabilized, cell-permeating alpha-helical peptide that mimics the p53 tumor suppressor protein to disrupt p53's interactions with its endogenous inhibitors, MDM2 and MDMX (Figure 1A). ALRN-6924 has been evaluated in >175 cancer patients and demonstrated single-agent activity and a well-tolerated single-agent safety profile.¹⁻³

MDM2 amplification is an oncogenic event found in up to 4% of all cancers. Co-amplification of MDM2 and cyclin-dependent kinase 4 (CDK4), which are co-located on chromosome 12q13 (Figure 1B), provides the rationale for combined use of the MDM2-inhibitor ALRN-6924 and the CDK4/6 inhibitor palbociclib in this population, and is further supported by enhanced combination activity in preclinical models (Figure 1C).

Figure 1: The Dual MDM2/MDMX Inhibitor ALRN-6924 Activates p53 to Induce Cell Cycle Arrest and Apoptosis, and Synergizes with the CDK4/6 Inhibitor Palbociclib

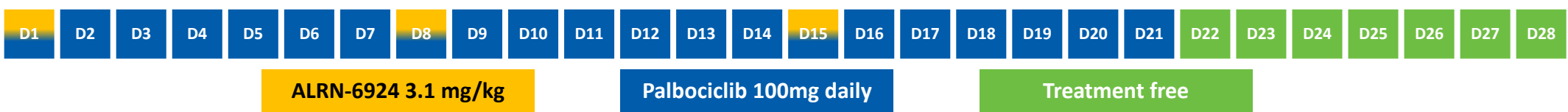


Methods

This is a multicenter, open-label, Phase 2a expansion cohort of an ongoing Phase 1 clinical trial that is enrolling MDM2 amplified or MDM2/CDK4 co-amplified cancer patients (ClinicalTrials.gov NCT02264613).

This Phase 2a trial is designed to enroll 25 patients with solid tumors harboring wild-type p53 and MDM2 amplification or MDM2/CDK4 co-amplifications. Patients have exhausted or are not eligible for other treatment options. ALRN-6924 is given at a dose of 3.1 mg/kg as IV infusion on Days 1, 8 and 15, and palbociclib is given as an oral dose of 100 mg/day on Days 1-21 of every 28-day treatment cycle. The first nine patients enrolled were evaluated for safety and tolerability after completion of one treatment cycle (safety lead-in). Anti-tumor activity is evaluated with imaging every 8 weeks.

Treatment Schedule



Primary Objectives

- Evaluation of safety and tolerability of the ALRN-6924 and palbociclib combination
- Assessment of objective tumor response rate

Secondary Objectives

- Evaluation of PK for ALRN-6924 and its metabolites, and palbociclib
- Evaluation of additional measures of efficacy, including DOR, PFS and OS

Results

Table 1: Demographic and Clinical Characteristics

Characteristic	All patients N=26 (100%)	Liposarcoma patients N=17 (100%) †
Gender		
Male	16 (62)	10 (59)
Female	10 (39)	7 (41)
Age		
Median (range)	59 (27,79)	58 (41, 75)
ECOG PS at Study Entry		
0	5 (19)	4 (24)
1	21 (81)	13 (76)
Predominant Histology		
WDLPS	-	5 (29)
DDLPS	-	8 (47)
WDLPS+DDLPS	-	3 (18)
Unknown	-	1 (6)
Metastatic Disease		
Yes		16 (94)
No		1 (6)
Number of Prior Systemic Therapy Regimens		
1	8 (31)	8 (47)
≥2	17 (65)	8 (47)
none	1 (4)	1 (6)
MDM2/CDK4 Amplification		
MDM2 amplified	4 (15)	2 (12)
MDM2/CDK4 co-amplified	17 (65)	15 (88)
Missing	5 (19)	-

†Efficacy-evaluable liposarcoma patients having ≥1 post-baseline radiological assessment, MDM2 amplification, and TP53-WT as of 02-Sep-2019 data cutoff.

Figure 2: Duration of Exposure for All Enrolled Patients (N=26)

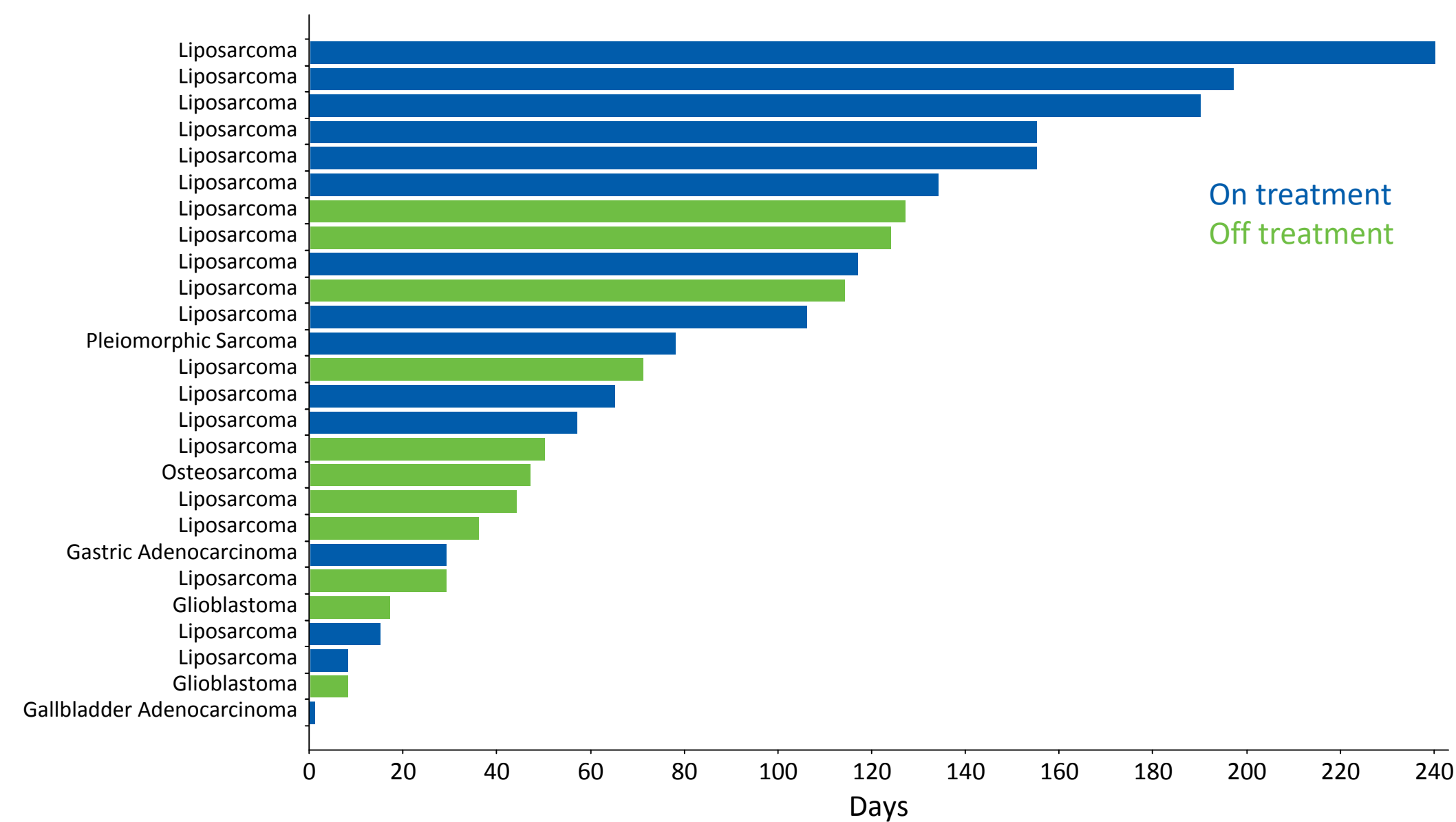
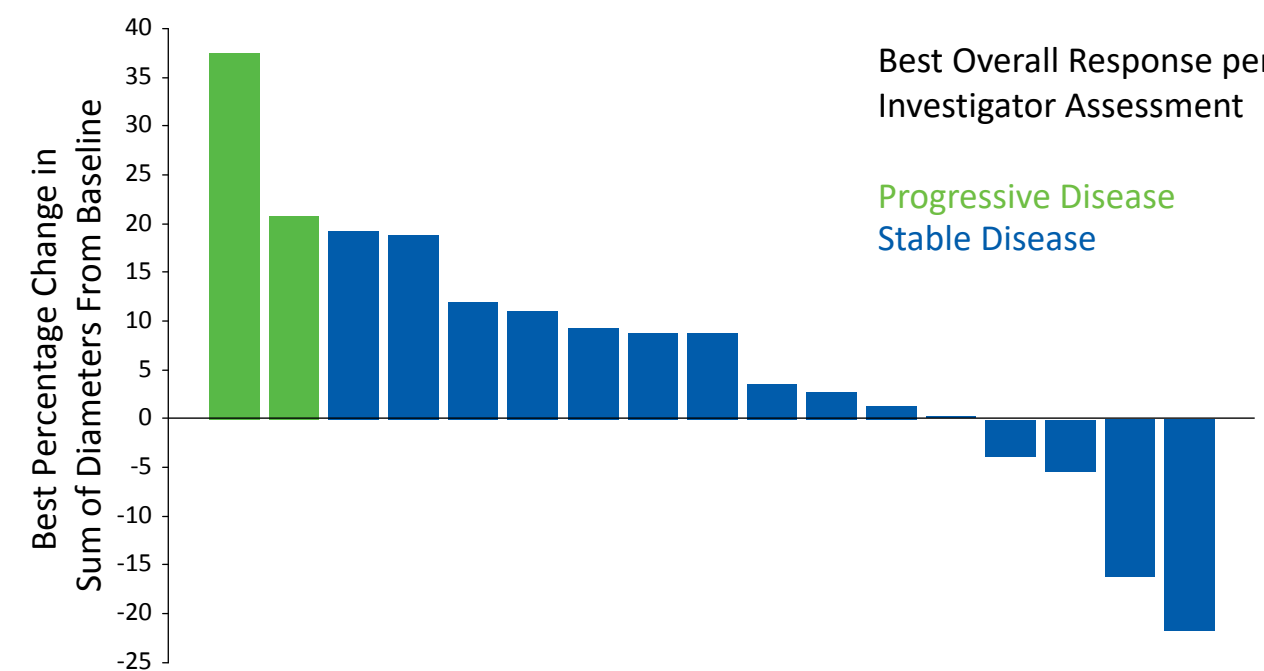


Table 2: Adverse Events and Serious Adverse Events

Related AE	All Grades N=26 (100%)	Grade 3-4 N=26 (100%)
Neutropenia	13 (50)	7 (27)
Nausea	12 (46)	0
Thrombocytopenia	7 (27)	1 (4)
Fatigue	6 (23)	0
Leukopenia	5 (19)	1 (4)
Vomiting	5 (19)	0
Anemia	3 (12)	0
Decreased appetite	3 (12)	0
Dysgeusia	3 (12)	0

Related SAE	Grade	N=26 (100%)
Neutropenia	4	1 (4)
Thrombocytopenia	4	1 (4)
Pulmonary embolism	4	1 (4)

Figure 3: Activity in Liposarcoma Patients (N=17)†



†Efficacy-evaluable population includes 17 liposarcoma patients having ≥1 post-baseline radiological assessment, MDM2 amplification, and TP53-WT. Excludes patients pending 1st post-baseline radiological assessment (n=4), mutant TP53 (n=2), glioblastoma (n=2, discontinued for adverse event; clinical disease progression), and osteosarcoma (n=1, objective disease progression, received new therapy before CT scan).

Figure 4: Liposarcoma Patients PFS

PFS	N=17 (%)
PFS events, N (%)	
PD	8 (47)
Death	0
Censored	9 (53)
PFS rate at 3 months, % (95% CI)	73 (42, 89)
Median PFS, months (95% CI)	4.4 (2.0, NE)

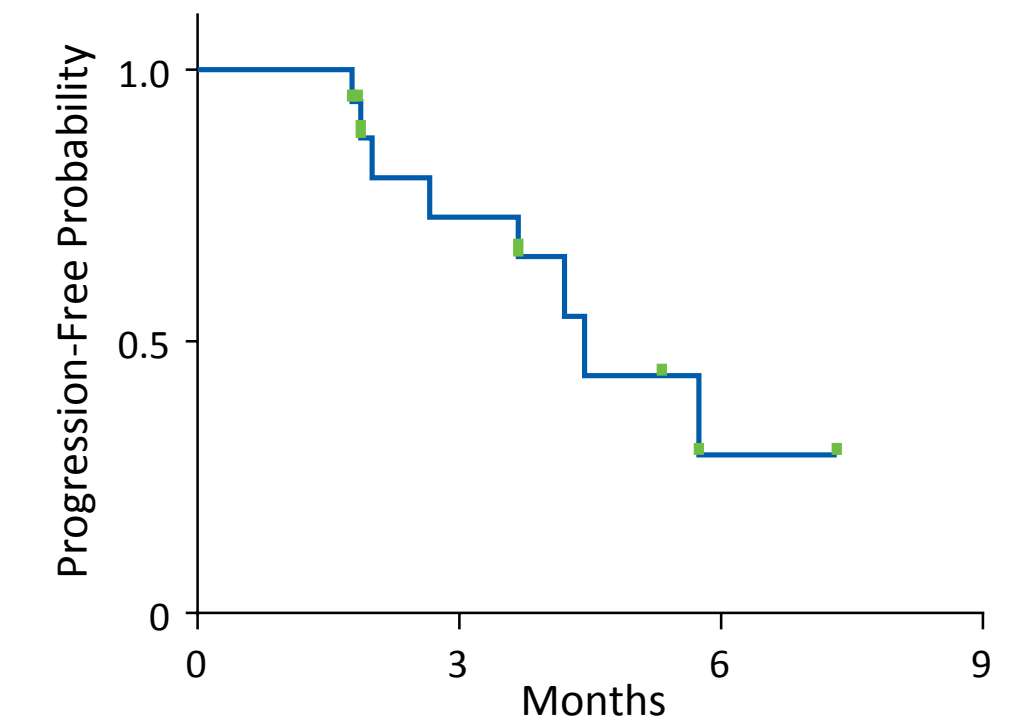
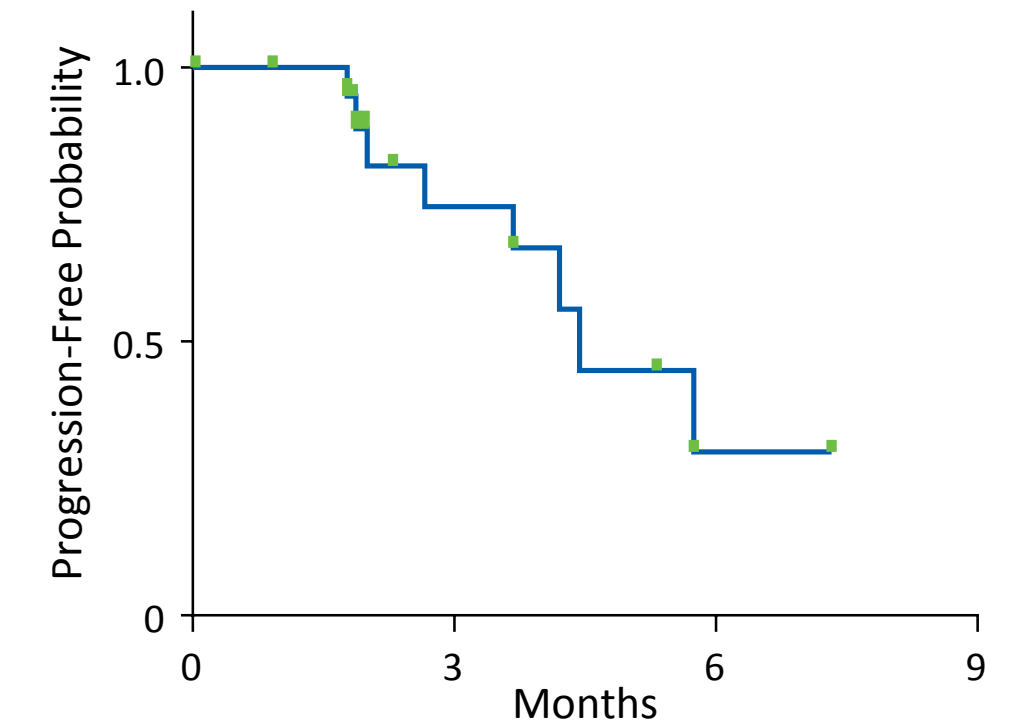


Figure 5: All Patients PFS

PFS	N=26 (%)
PFS events, N (%)	
PD	8 (31)
Death	0
Censored	18 (69)
PFS rate at 3 months, % (95% CI)	74 (43, 89)
Median PFS, months (95% CI)	4.4 (2.7, NE)



Conclusions

- This interim analysis shows the combination of ALRN-6924 and palbociclib is very well tolerated and has a good safety profile in patients with MDM2 amplified or MDM2/CDK4 co-amplified tumors
- Preliminary efficacy was observed in patients with locally advanced or metastatic liposarcomas, supporting the hypothesis that dual-targeting MDM2/CDK4 co-amplified patients with ALRN-6924 + palbociclib may result in clinical activity
- Further development of this combination in liposarcoma patients is warranted

References

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