A FIRST-IN-HUMAN STUDY OF CDK9 INHIBITOR KB-0742 DEMONSTRATES PRELIMINARY EVIDENCE OF CLINICAL ACTIVITY IN TRANSCRIPTIONALLY ADDICTED SARCOMAS

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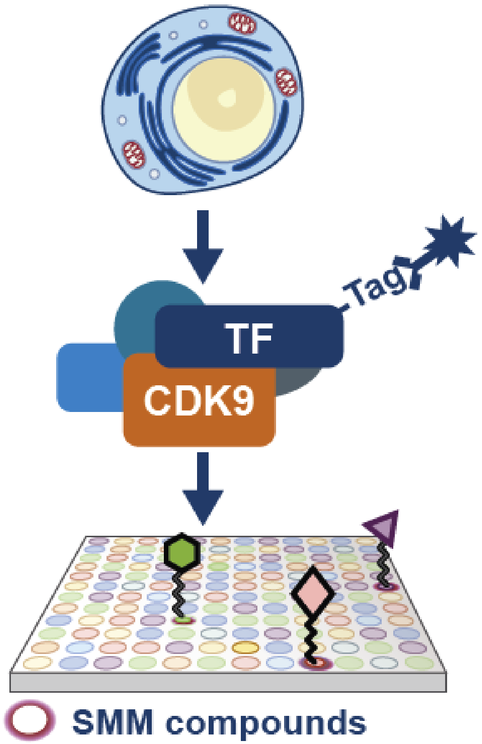
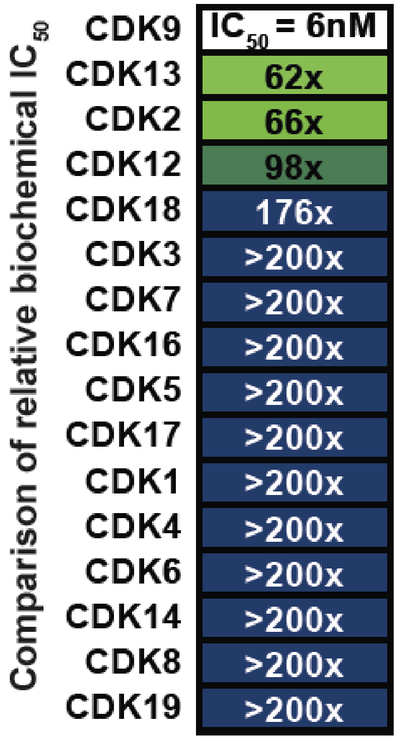
KB-0742 is a highly selective, orally bioavailable inhibitor of CDK9, a critical regulator of oncogene transcription

KB-0742 emerged from a small molecule microarray (SMM) screen against an oncogenic variant of the androgen receptor TF





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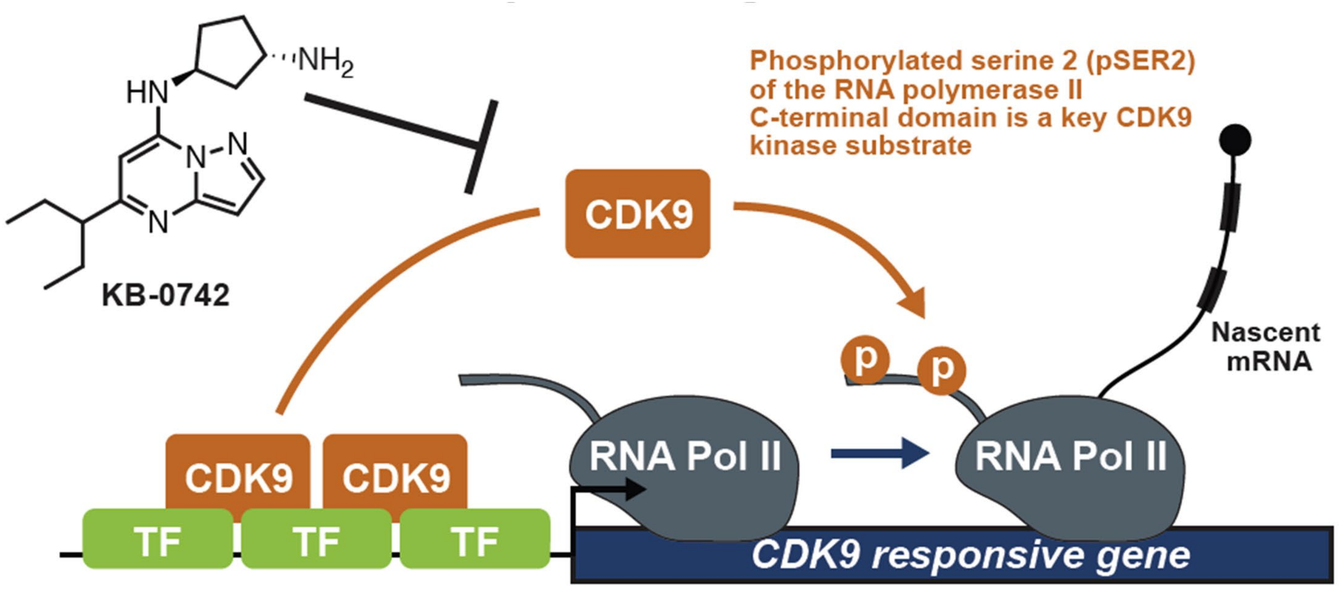
Reference: Richters et al., 2020, Cell Chemical Biology

KB-0742 modulates CDK9, a kinase that is recruited to DNA by TFs (Transcription Factors) and drives transcription elongation



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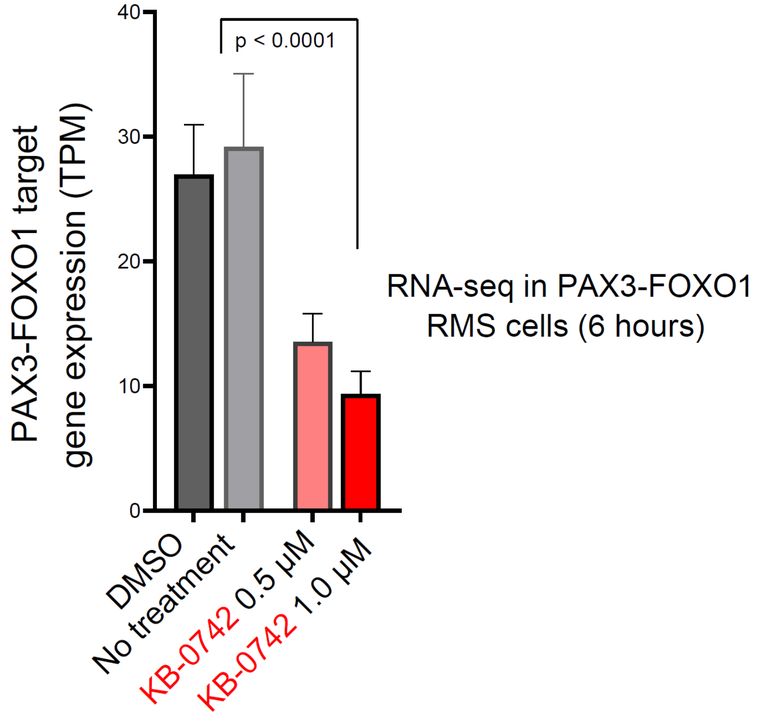
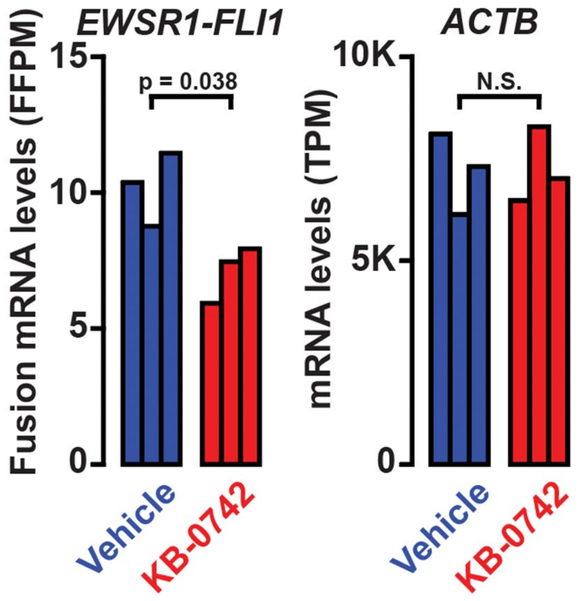
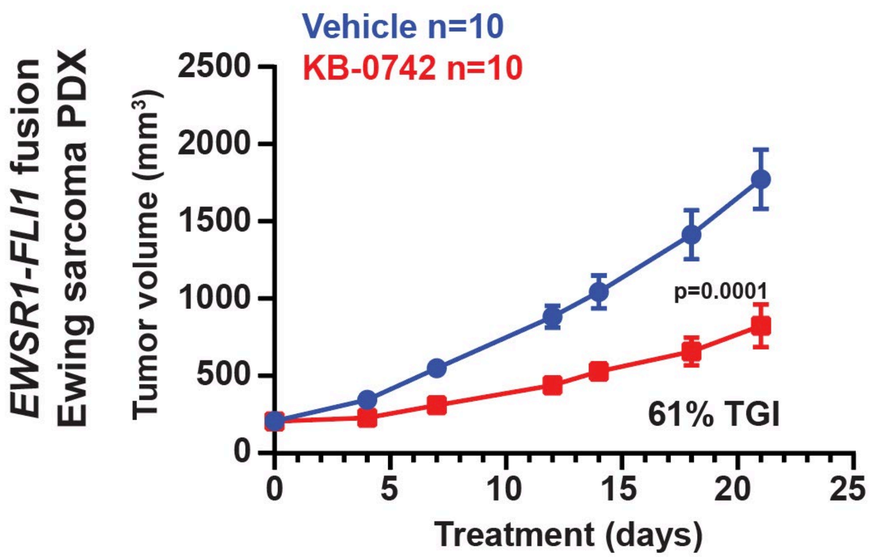
Reference: Richters et al., 2020, Cell Chemical Biology

KB-0742 reduces the expression of key oncogenic TFs in sarcoma models*



RNA-seq in PAX3-FOXO1 RMS cells (6 hours)





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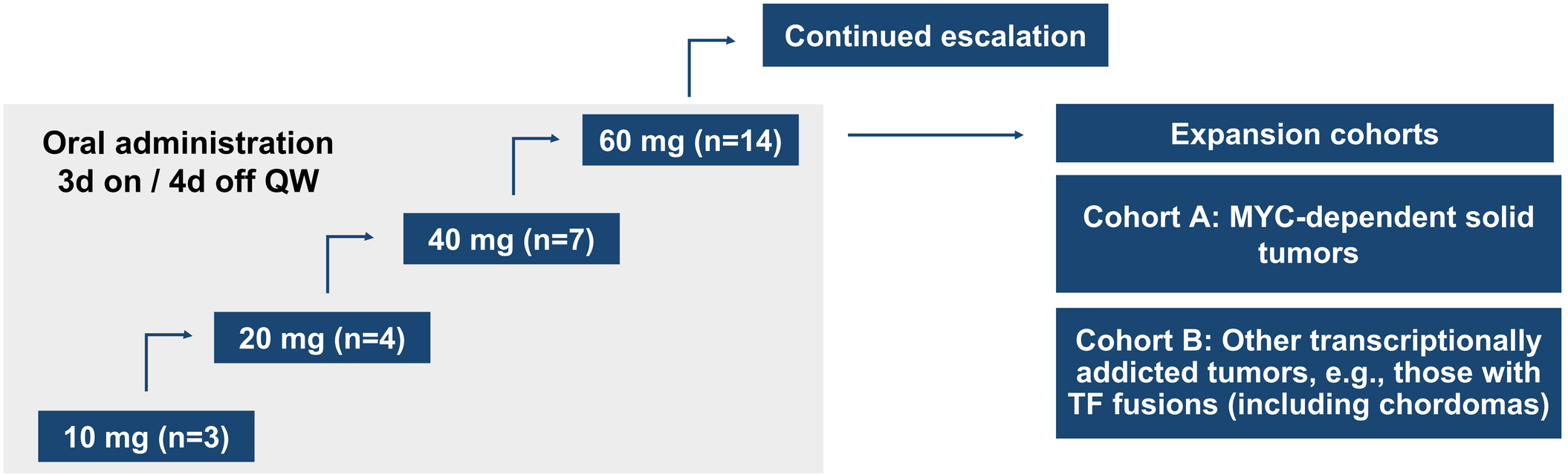
*With Berkley Gryder, CWRU

KB-0742 Phase I Dose Escalation Trial Design

This is an ongoing Phase 1, first-in-human, open-label, modified CRM dose escalation (N = 28) and expansion study of KB-0742 in patients with relapsed or refractory solid tumors or NHL



- Relapsed/refractory solid tumors and NHL (no enrichment for transcriptionally addicted tumors)
- MTD not yet defined; continuing to dose escalate in parallel with expansions at 60 mg

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Patient characteristics

	10 mg (N=3)	20 mg (N=4)	40 mg (N=7)	60 mg (N=14)	Total (N=28)
Median age, years (range)	60.0 (51 - 60)	48.5 (29 - 70)	62.0 (34 - 83)	58.5 (41 - 84)	59.5 (29 - 84)
Female, N (%)	2 (67)	2 (50)	4 (57)	9 (64)	17 (61)
Ethnicity, N (%)					
Asian	0	1 (25)	1 (14)	0	2 (7)
Black or African American	1 (33)	0	1 (14)	0	2 (7)
White	2 (67)	3 (75)	5 (71)	14 (100)	24 (86)
Other	0	0	0	0	0
Median prior systemic anticancer regimens, N (range)	2.0 (0 - 3)	6.5 (5 - 11)	4.0 (0 - 8)	3.0 (0 - 6)	3.5 (0 - 11)

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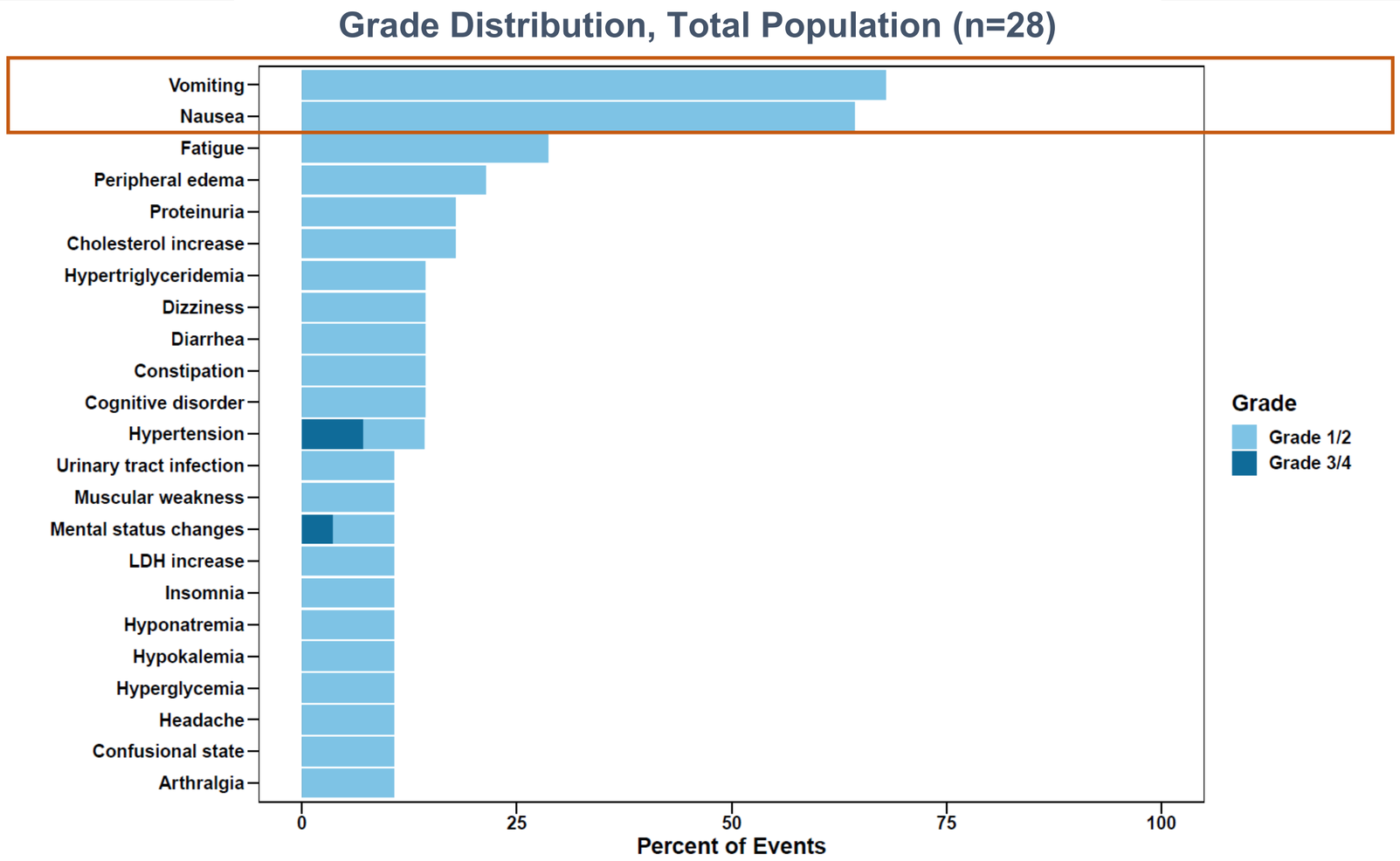
Safety & tolerability: most common TEAEs (in ≥ 10% of patients)

- All 28 patients experienced at least one TEAE, with more than half (61%) of these events being grade 1 or 2*



*AEs occurring in < 10% of patients include two patients who experienced a single episode of seizures. While there is no known mechanistic link between CDK9 inhibition and CNS toxicity, these events are being closely monitored

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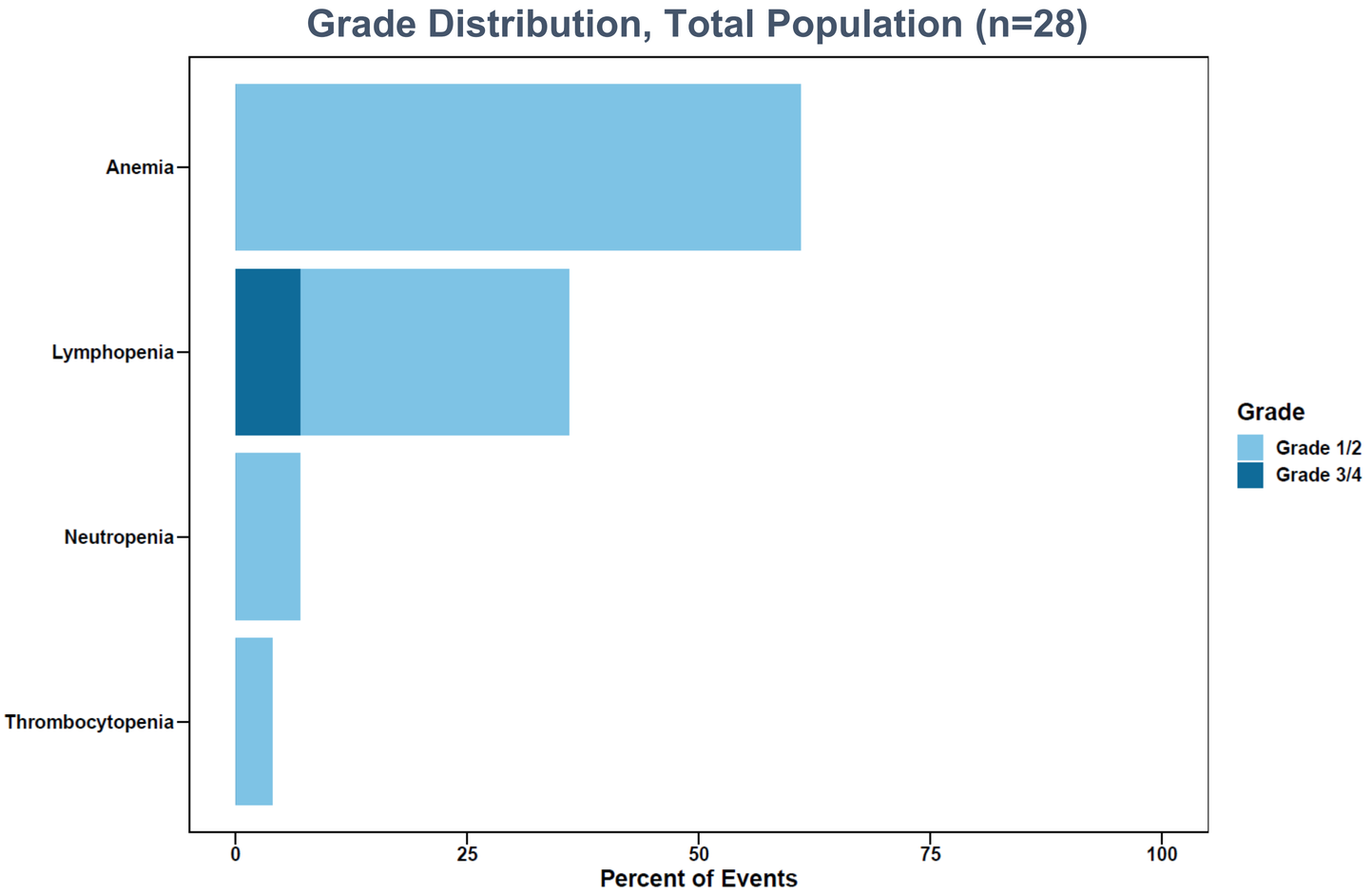
Safety & tolerability: hematologic laboratory abnormalities (based on NCI-CTCAE grading)



- **No grade 3/4 neutropenia was observed with KB-0742 treatment**

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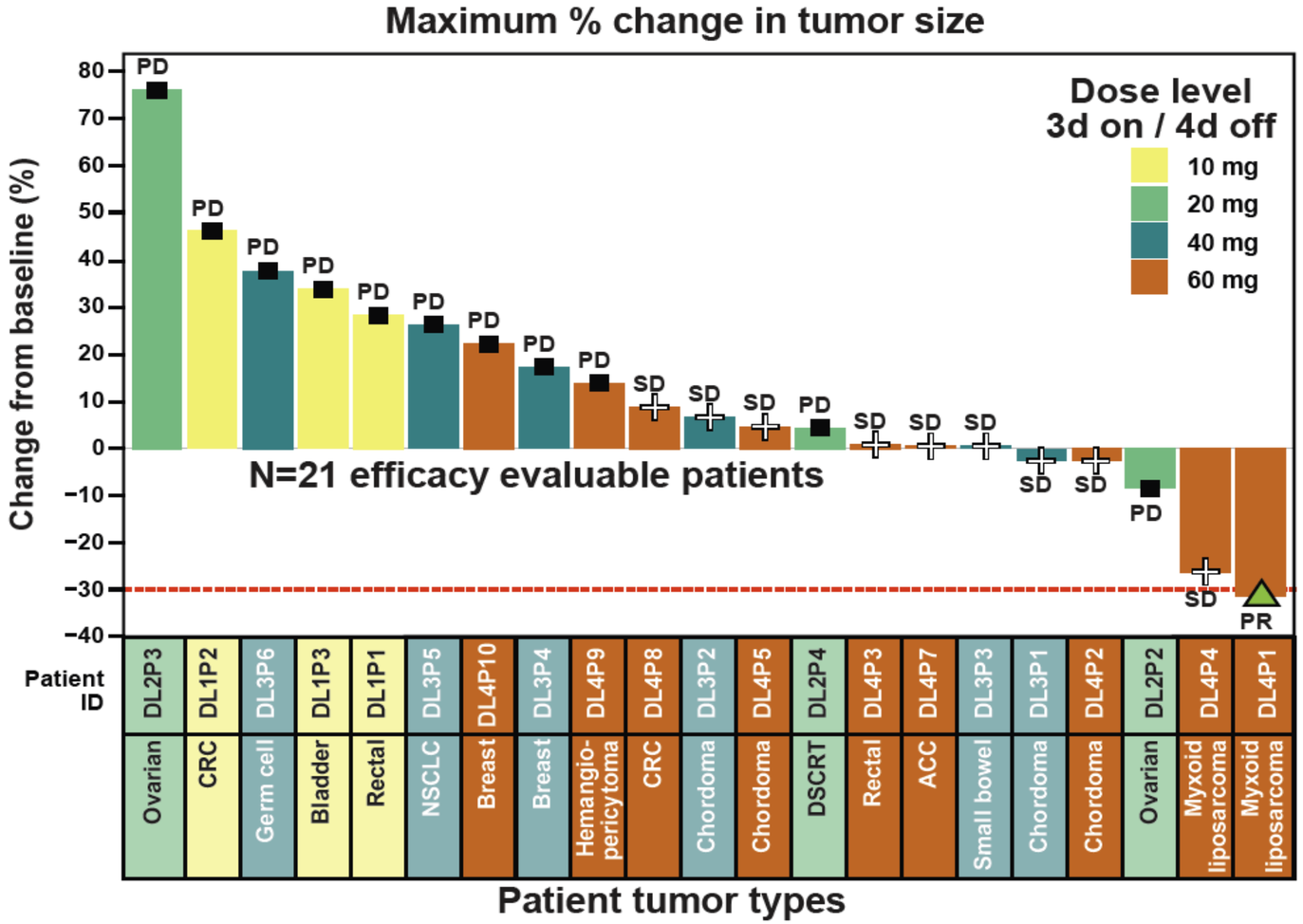
KB-0742 anti-tumor activity: objective regressions in 2 TF fusion-driven tumor patients



- One partial response lasting 113 days in a 7th line myxoid liposarcoma patient who was on treatment for 398 days. Second patient achieved 26% reduction in tumor diameters
- 9 (43%) patients had stable disease (SD) as the best response
- Overall disease control rate was 47.8% - defined as a CR (Complete Response), Partial Response (PR), or Stable Disease (SD)

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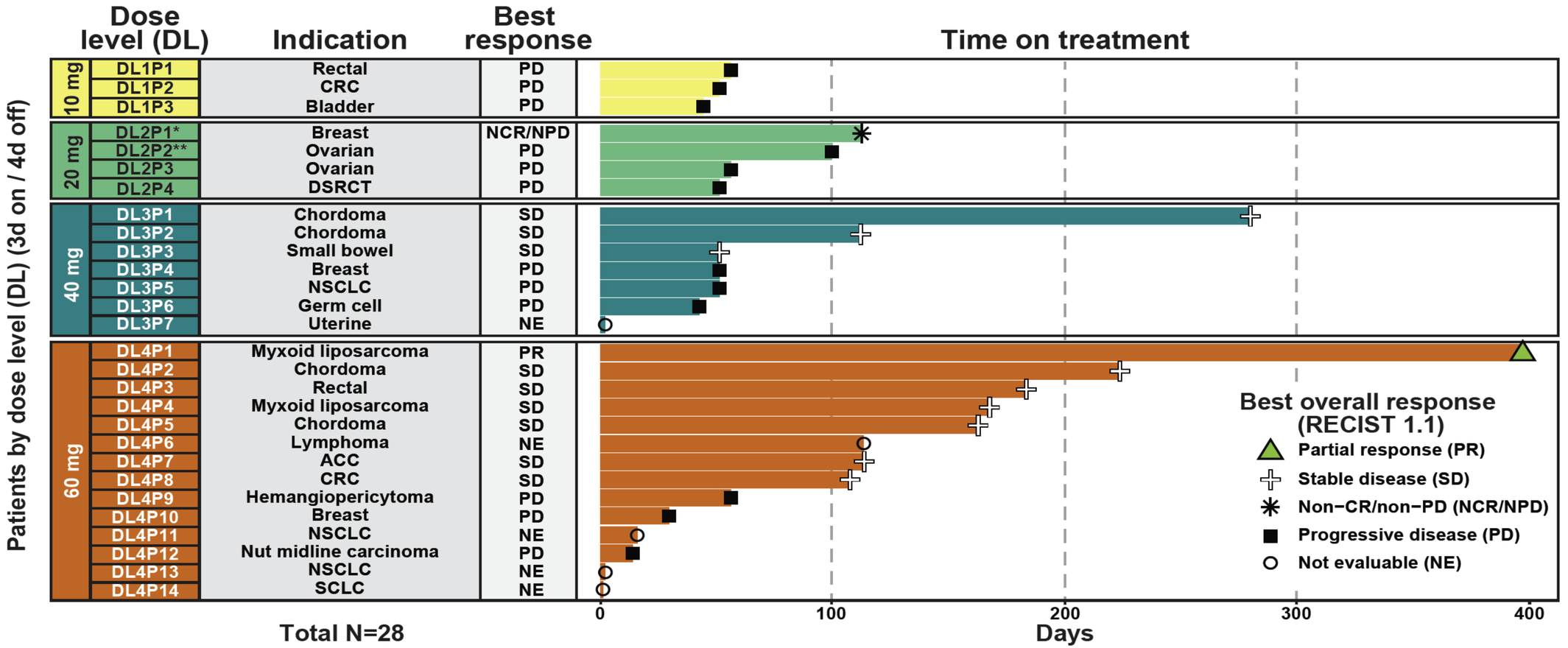
KB-0742 duration of treatment across dose levels



*Patient DL2P1 response NCR/NPD was due to the patient having evaluable but not measurable disease at baseline.

**Patient DL2P2 progressed at an earlier date and stayed on treatment post-progression.

At the 60 mg dose, median time on treatment was:

- Total population (n=14): 111 days
- Sarcoma subjects (n=3): 168 days
  - Myxoid liposarcoma subjects (n=2): 282.5 days
- Chordoma subjects (n=2): 193.5 days

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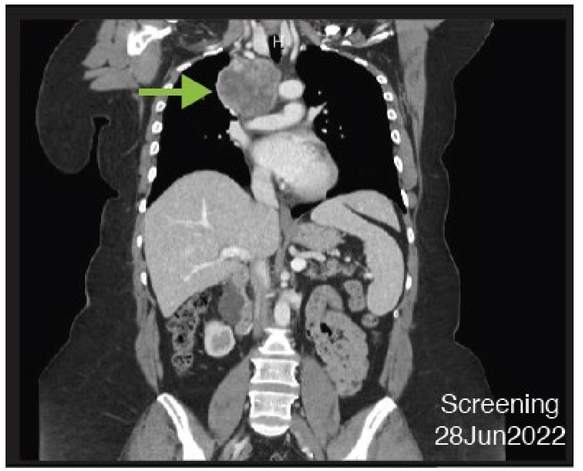
Case report: Patient DLP41 with Myxoid Liposarcoma

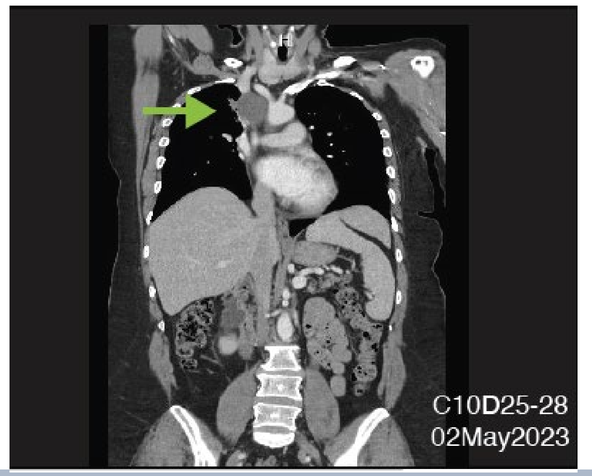
Patient characteristics and treatment history

- 50-year-old female
- Diagnosed with myxoid liposarcoma in MAY 2009
- Stage 4 at enrollment
- Six prior lines of therapy included:
  - Doxorubicin/Ifosfamide: APR-SEP 2015
  - Atezolizumab: JUL-SEP 2016
  - Trabectedin: DEC 2016-JAN 2017
  - NY-ESO-1^{C259} T: SEP 2017-JUN 2018
  - Atezolizumab: NOV 2018-JUN 2019
  - Ifosfamide: DEC 2021-JAN 2022

KB-0742 treatment course

- KB-0742 treatment initiated in JUL 2022
- 60 mg for 398 days on treatment
- PR achieved at cycle 10 lasting 113 days





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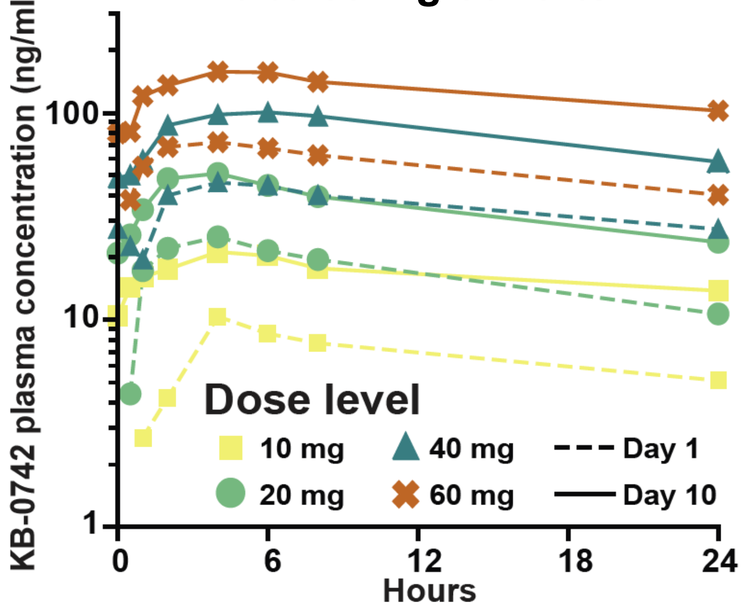
Reference: https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.3005

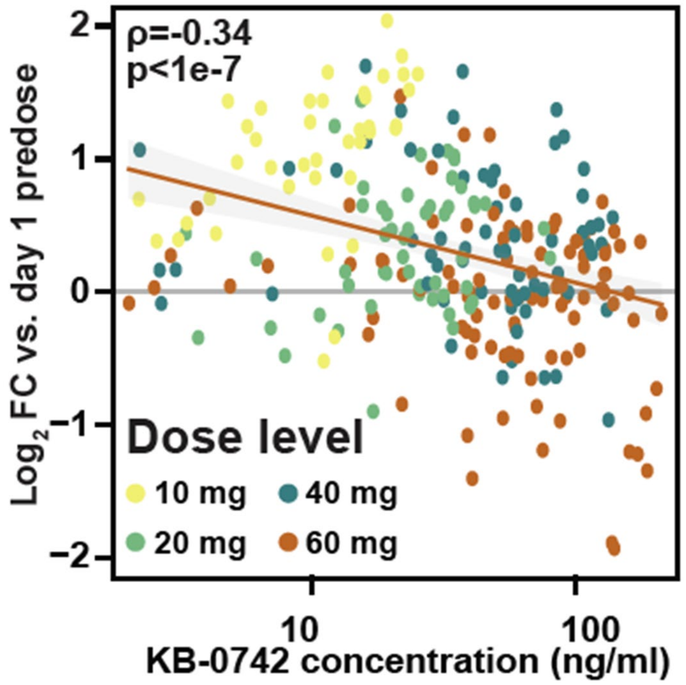
KB-0742 PK/PD profile is suitable for achieving sustained partial inhibition of CDK9 and measurable target engagement

KB-0742 plasma concentrations at day 1 and 10 of dosing across the 10 to 60 mg cohorts



- KB-0742 plasma half-life is approximately 24 hours, leading to accumulation ratios (AUC Day 10/AUC Day 1) of 2.1 to 2.5

Change in pSER2 levels vs. KB-0742 concentration



- Dose dependent CDK9 inhibition measured in peripheral blood
- Sustained, measurable reduction of RNA Pol II pSER2 observed at the 60 mg dose level

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Conclusions

- KB-0742, a selective CDK9 inhibitor, demonstrated objective single agent anti-tumor activity in heavily pre-treated patients with transcriptionally addicted tumor types
- Tumor reduction (1 PR, 1 SD with 26% reduction in tumor diameter) was observed in two patients with myxoid liposarcoma, a transcriptionally addicted tumor type characterized by a fusion TF consistent with on-mechanism activity
- KB-0742 showed dose proportional exposure and target engagement, and a 24-hour plasma half-life enabling intermittent dosing
- KB-0742 exhibited a manageable safety profile with no grade 3/4 neutropenia observed at doses ranging from 10-60 mg; dose escalation continues and MTD has not been reached
- Enrollment in the expansion phase of the study is ongoing in MYC-dependent solid tumors such as ovarian cancer, TNBC and NSCLC and in other transcriptionally addicted solid tumors such as soft tissue sarcomas with TF fusions

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