AZD0466, a dual BCL-2/XL targeting nanomedicine, is active in small cell lung cancer models

Courtney L. Andersen[1], Giulia Fabbri[1], David Jenkins[1], Zumla Cader[2], Shring Sharma[3], Areya Tabatabai[1], Srividya Balachander[1], Jordan Roebuck[4], Melanie Galvin[4], Kathryn Simpson[4], Caroline Dive[4], Jordi Rodon Ahnert[5], Jamal Saeh[1]

[1]Oncology R&D, AstraZeneca, Waltham, MA; [2]Oncology R&D, AstraZeneca, Cambridge, ENG, United Kingdom; [3]Oncology R&D AstraZeneca, South San Francisco, CA; [4]Cancer Research UK Cancer Biomarker Centre, University of Manchester, Manchester, ENG, United Kingdom; [5]MD Anderson Cancer Center, Houston, TX

Small cell lung cancer (SCLC)

- Small cell lung cancer is an aggressive, heterogenous malignancy
  - Accounts for ~15% of all lung cancer cases in the US[1]
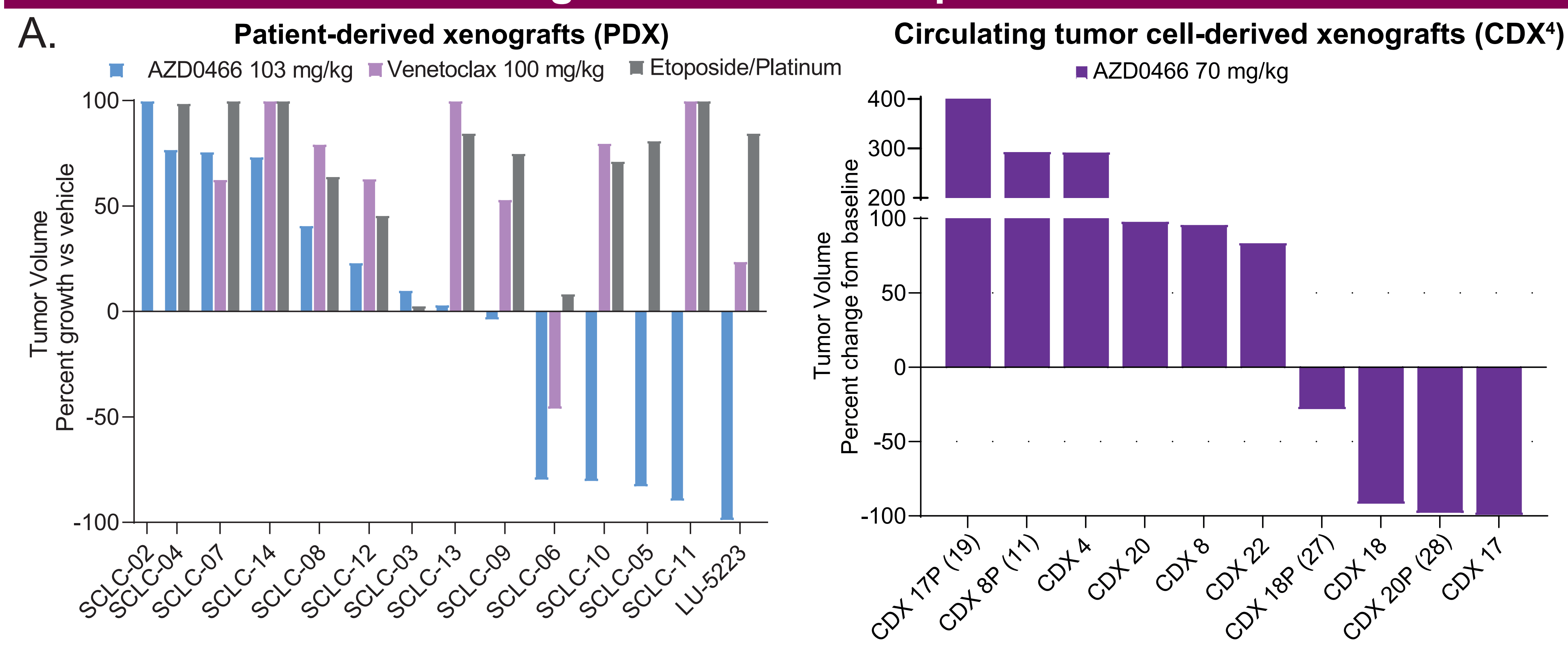 - Five (5)-year survival is <7%[1]

- Currently all patients receive same upfront chemotherapy (platinum/etoposide)

- SCLC is comprised of distinct transcriptional subtypes requiring unique targeted therapeutic approaches[2,3]
 - ASCL1 (A), POU2F3 (P), NEUROD1 (N), and YAP (Y)

- BCL-2 is highly expressed in A- and P- subtypes
  - Subtypes represent ~51% (A) and ~7% (P) of SCLC patients[2]

- We evaluated the potential of AZD0466, a dual BCL-2/XL inhibitor, in SCLC models

AZD0466: a dual BCL-2/XL inhibitor

AZD0466 is a novel drug-dendrimer conjugate, where the active moiety, AZD4320, is chemically conjugated to Starpharma's clinically validated DEP® dendrimer platform

AZD0466 dosed intermittently to deliver efficacy while maximizing therapeutic index

AZD4320 is active in SCLC cell lines

A- and P-subtype SCLC cell lines have higher BCL-2 and are more sensitive to AZD4320

AZD0466 drives regressions in SCLC patient-derived models

A.

-Response in 12 / 24 models (PDX + CDX)
-Regression in 8 / 24
-Dual BCL-2/XL inhibition more active than selective BCL-2 inhibition with venetoclax
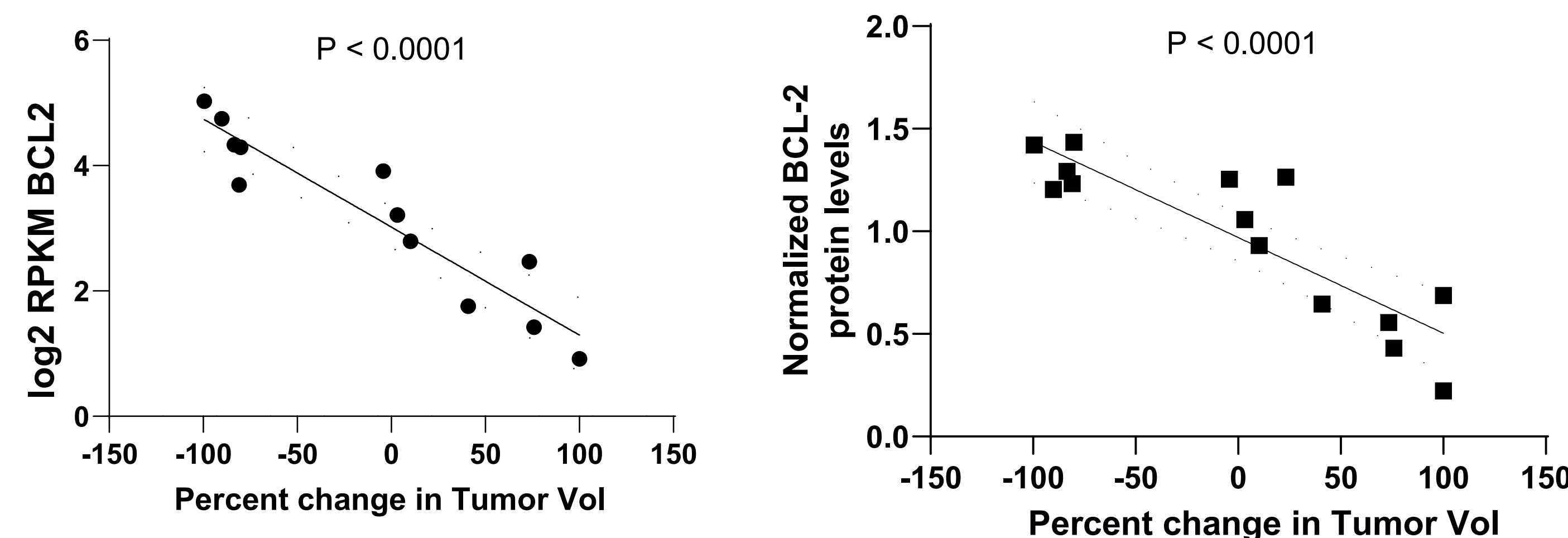-AZD0466 active in models resistant to Platnium/Etoposide (SOC)

B.

*Post-chemotherapy relapsed model
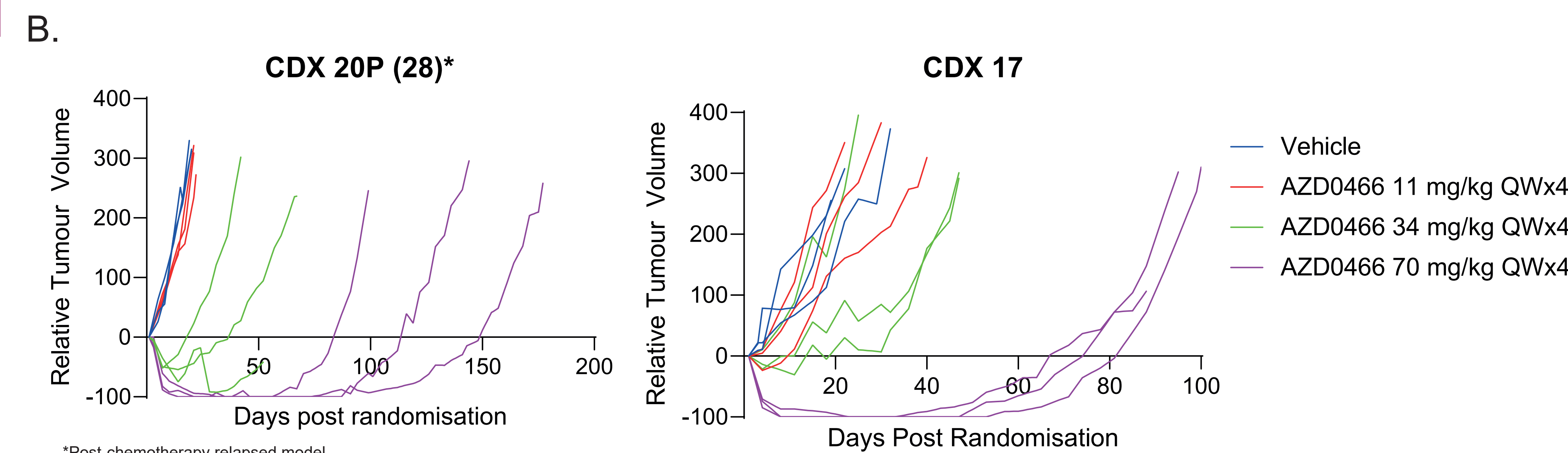
AZD0466 can produce prolonged CRs in SCLC models

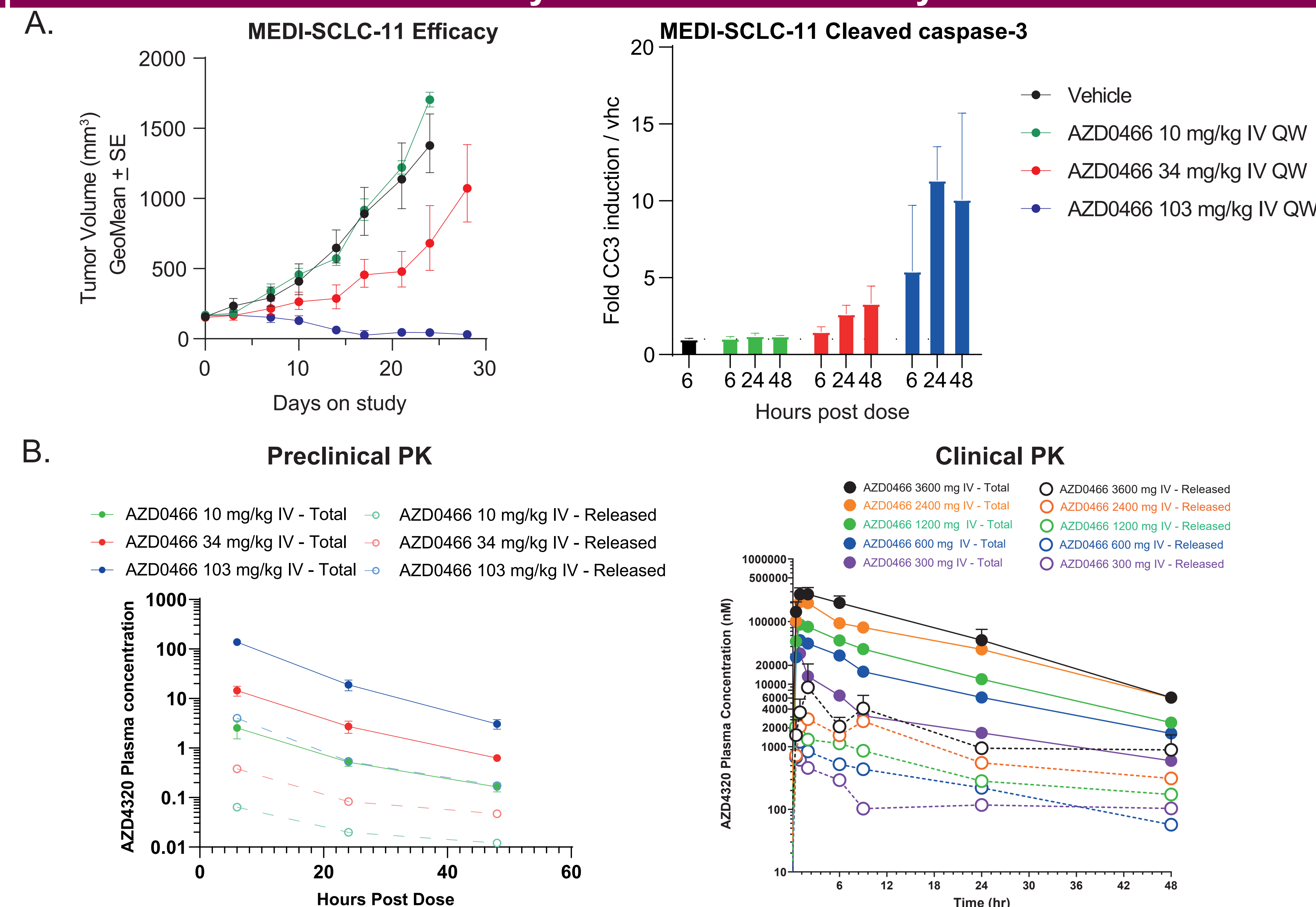## AZD0466 efficacy is enriched in subtype-A patient-derived models

Tumor volume reduction correlates with BCL2 mRNA and protein expression

N/D: no data on subtype
*CDX22 and CDX4 also have high YAP1 expression
**ATOH1 represents recently reported subtype*

Preclinical SCLC efficacy observed at clinically achievable doses

A.

B.

AZD0466 is under clinical investigation

	Advanced solid tumors[a]	Advanced hematologic malignancies[b,5]
Number of patients treated	9 patients	24 patients
Doses administered (range)	50 mg to 200 mg	300 mg to 3600 mg
Disease indication (number of patients)	Adrenal carcinoma (1), anal cancer (1), bile duct cancer (1), bladder/urethral cancer (1), colorectal cancer (1), lung cancer (1), pancreatic cancer (1), sarcoma (2)	AML (20), ALL (4), MDS (0)
Mean treatment duration	3.4 months	4.4 months
Adverse events ≥ Grade 3 related to AZD0466* (number of patients)	Aspartate aminotransferase increased (2), alanine aminotransferase increased (1)	Febrile neutropenia (3), thrombocytopenia (1), diarrhea (1), gamma-glutamyl transferase increased (1), platelet count decreased (1)

AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndrome
* Reasonable possibility adverse event was caused by AZD0466, as assessed by the investigator. Graded per CTCAE v5.
a. A study of AZD0466 in patients with advanced hematologic or solid tumors (NCT04214093). Data as of 20-Dec-2021.
b. A study of AZD0466 monotherapy or combination in patients with advanced hematologic malignancies (NCT04865419)[5]. Patient treatment is ongoing and only data up to 24-Jan-2023 are captured.

Summary

- BCL-2/XL inhibition with AZD4320 and AZD0466 is active in SCLC models

- Efficacy is enriched in models representing A and P subtypes of SCLC

- AZD0466 is currently under clinical investigation and has been well-tolerated in doses up to 3600 mg
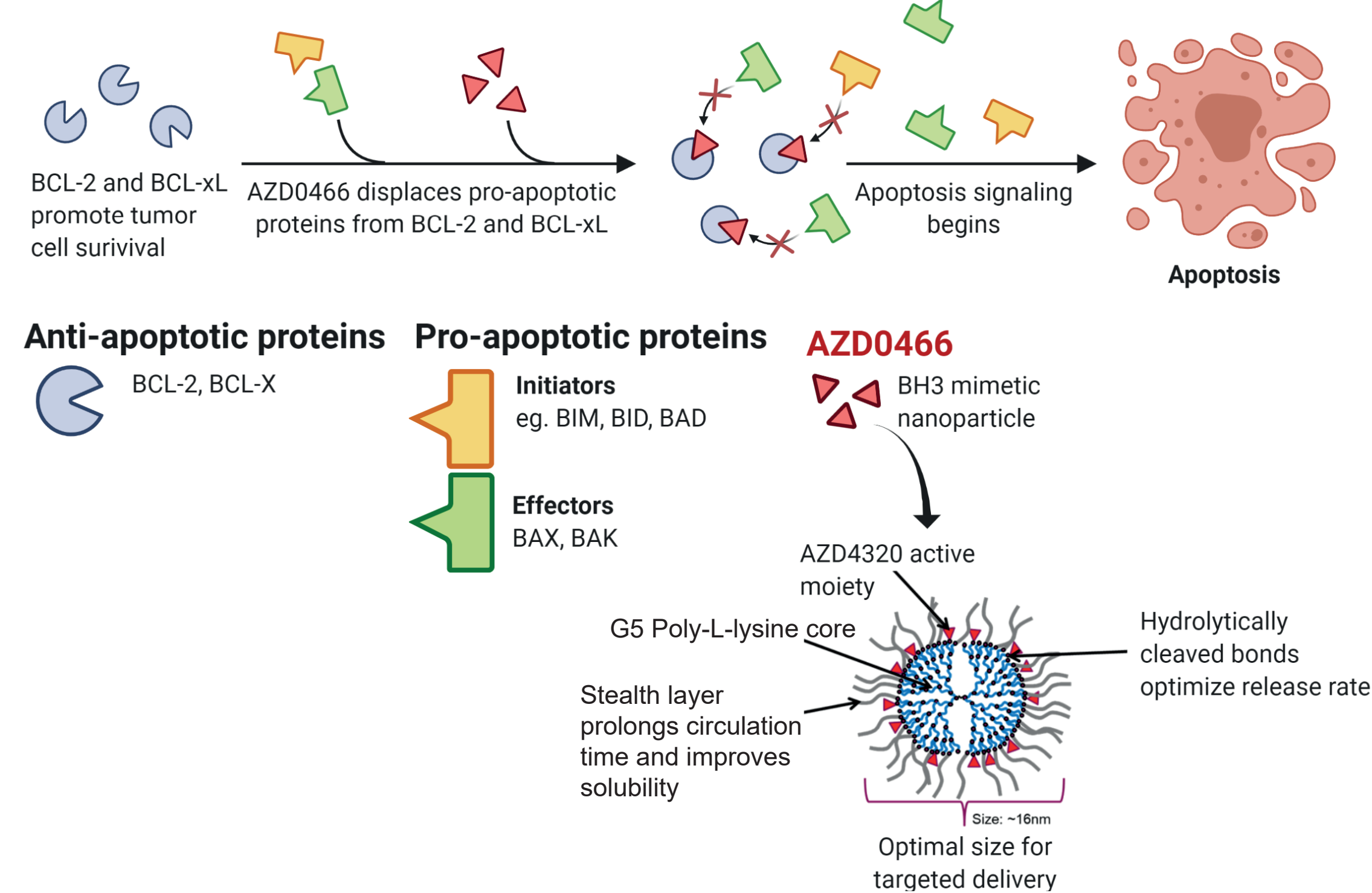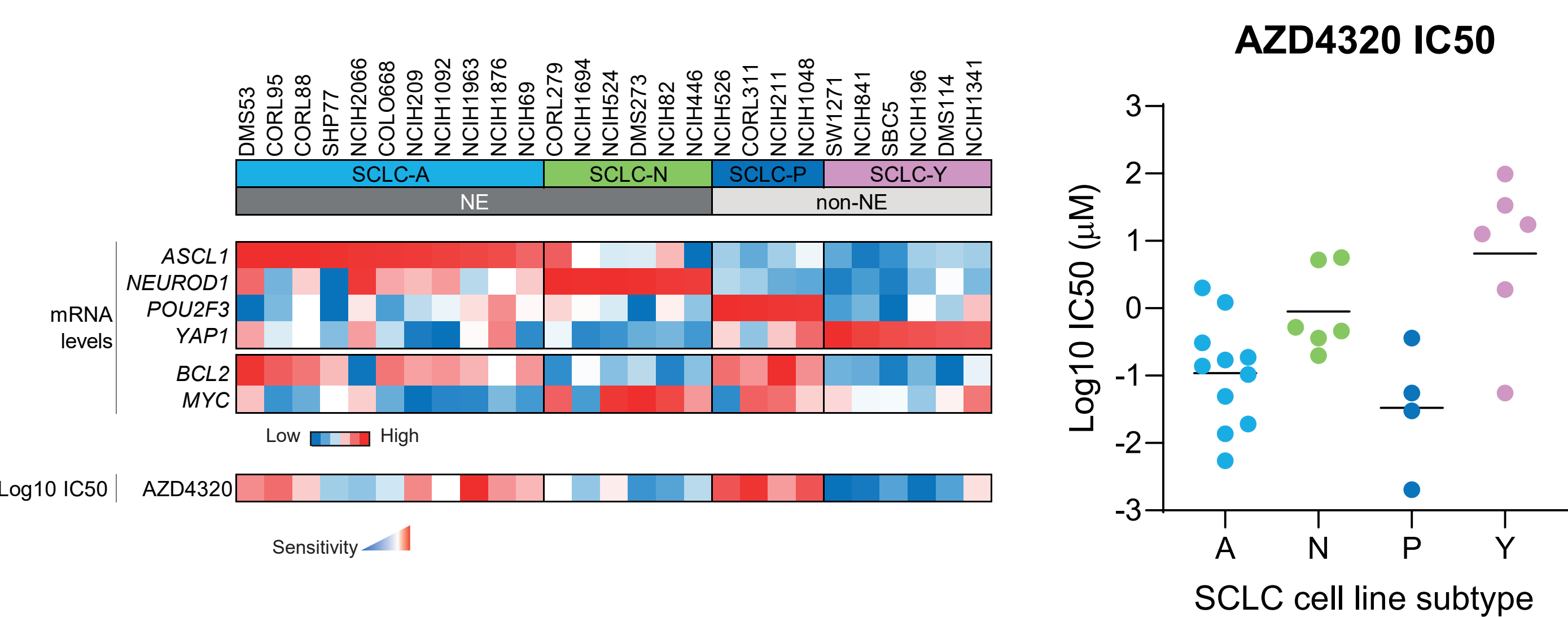
- Preclinical efficacy is observed at clinically achievable exposures