

SLFN11 and EZH2 Protein Expression and Localization in Circulating Tumor Cells to Predict Response or Resistance to DNA Damaging Therapies in Small Cell Lung Cancer



Lauren Averett Byers¹, C. Allison Stewart¹, Carl Gay¹, John Heymach¹, Luisa Fernandez², David Lu², Robin Richardson², Lincy Chu², Yipeng Wang², Ryan Dittamore²

¹Department of Thoracic Head & Neck Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX ● mdanderson.org;

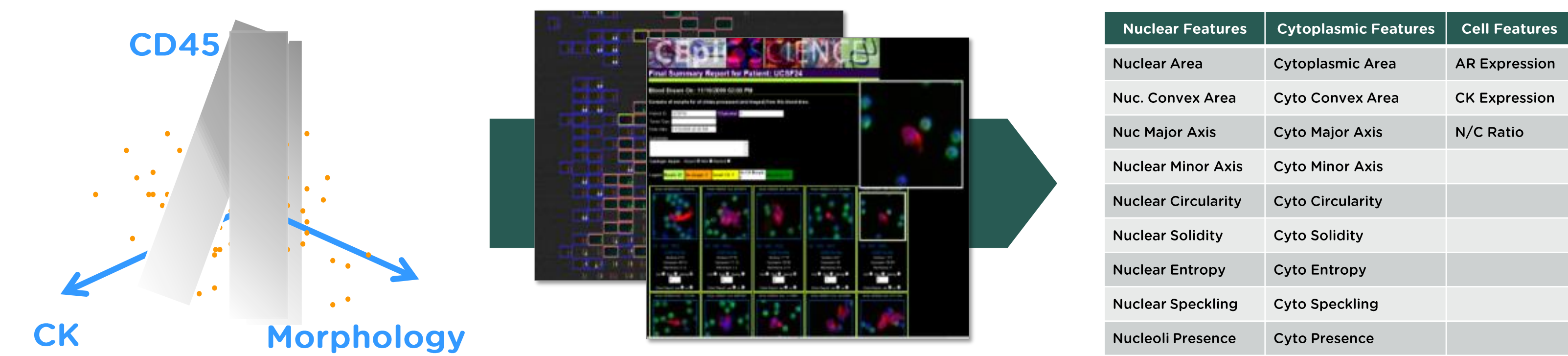
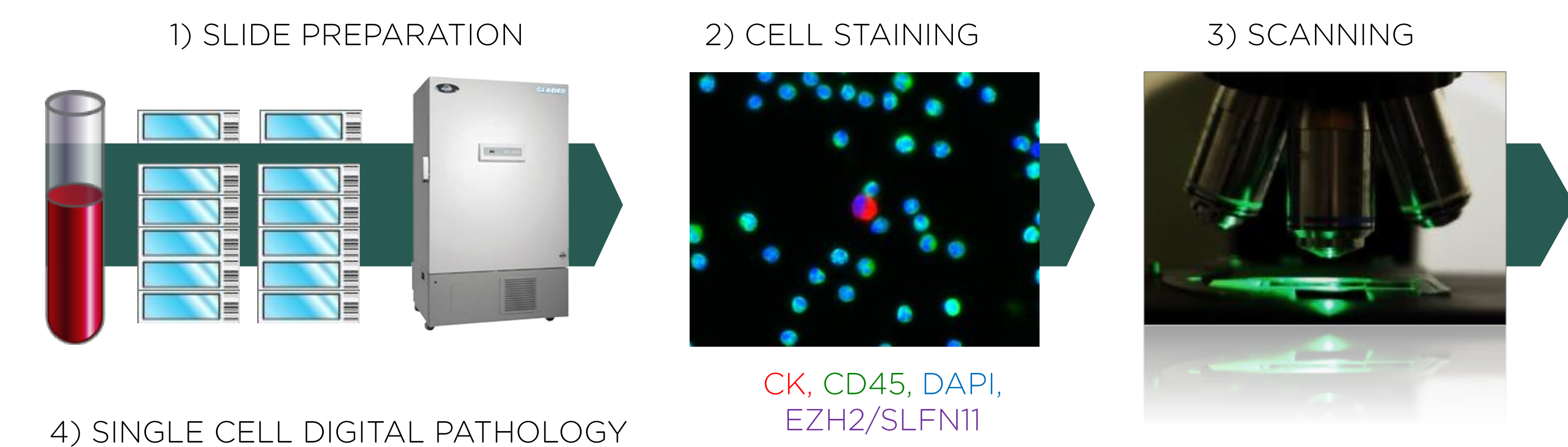
²Epic Sciences, San Diego, CA ● epicsciences.com

Background

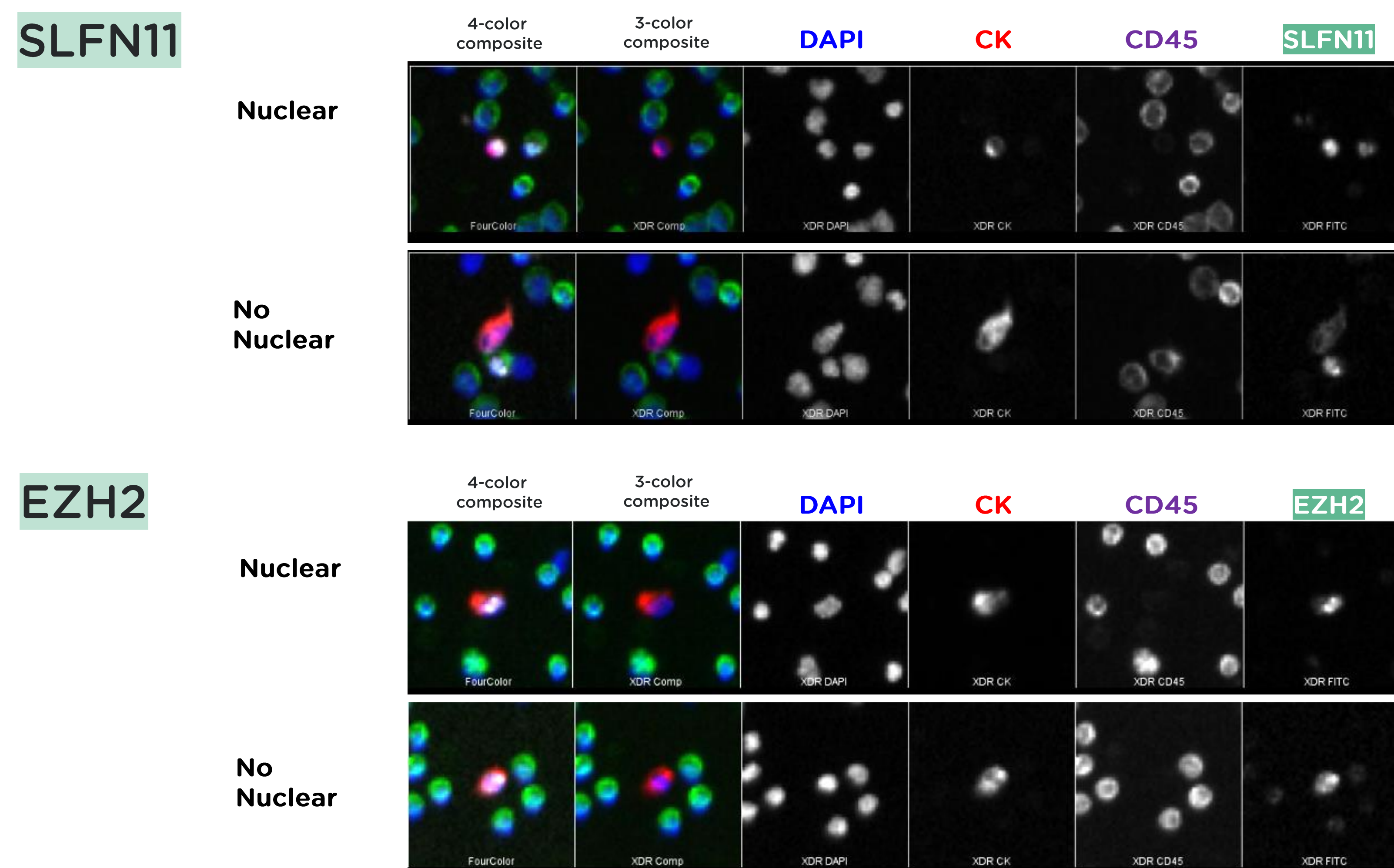
- A recent phase II trial in recurrent small cell lung cancer (SCLC) demonstrated that patients with high SLFN11 expression in tissue biopsies had improved survival when treated with PARP inhibition (PARPi)
- EZH2 is also highly expressed in SCLC tissue and is associated with chemo-resistance through epigenetic silencing of SLFN11
- Here we developed a liquid biopsy test to explore the clinical feasibility of utilizing SLFN11 and EZH2 expression on circulating tumor cells (CTCs) to aid in the prediction of drug response/resistance to DNA damaging chemotherapy or PARPi in SCLC

Methods

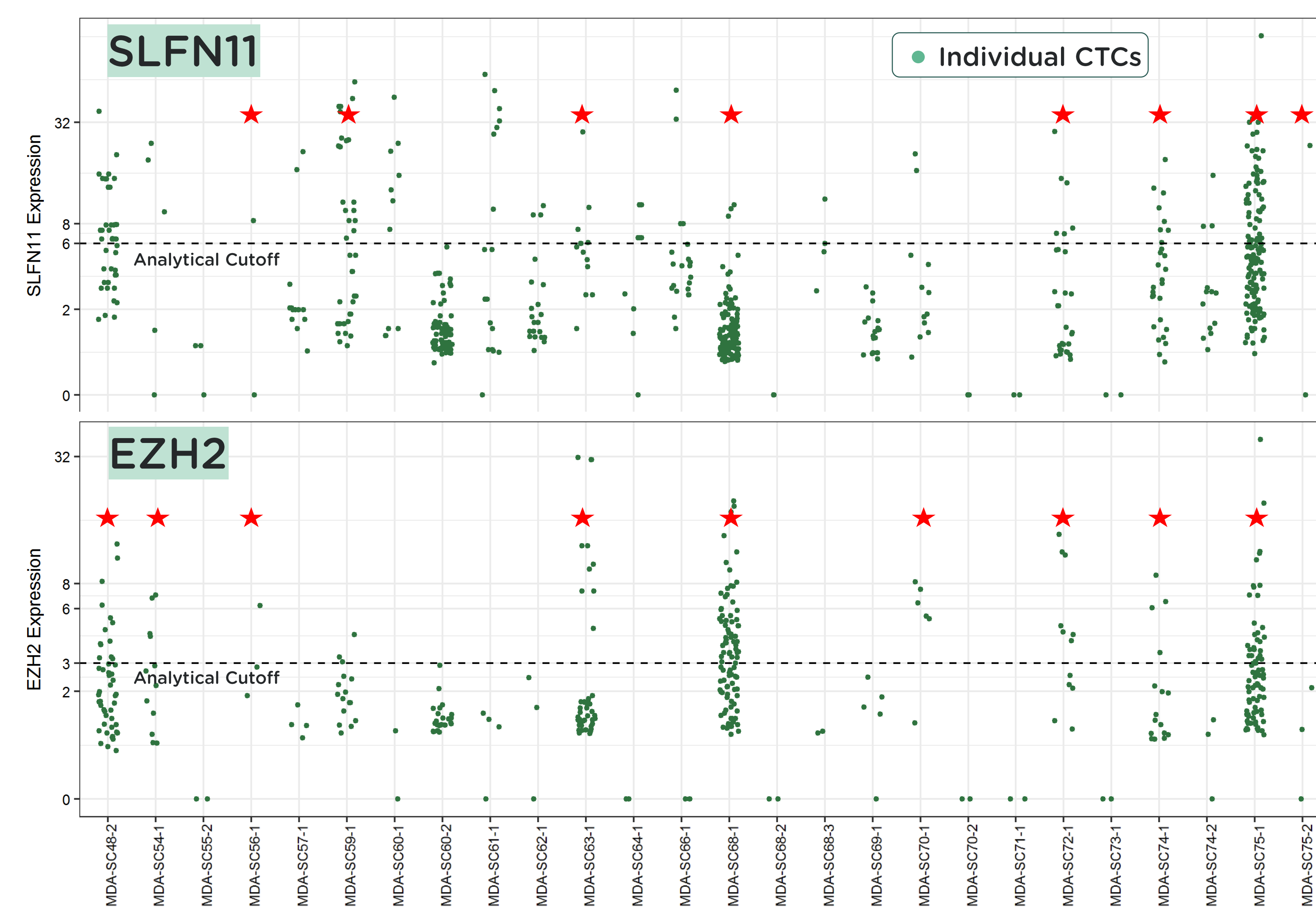
26 Blood samples were drawn from 20 SCLC pts, including 11 treatment naïve, 7 on-Tx, 8 relapse samples (5 pts had multiple draws). Samples were sent to Epic Sciences for analysis utilizing Epic Sciences' EZH2 and SLFN11 immunofluorescence assays.



SCLC SLFN11+/EZH2+ CTC Cell Image Examples



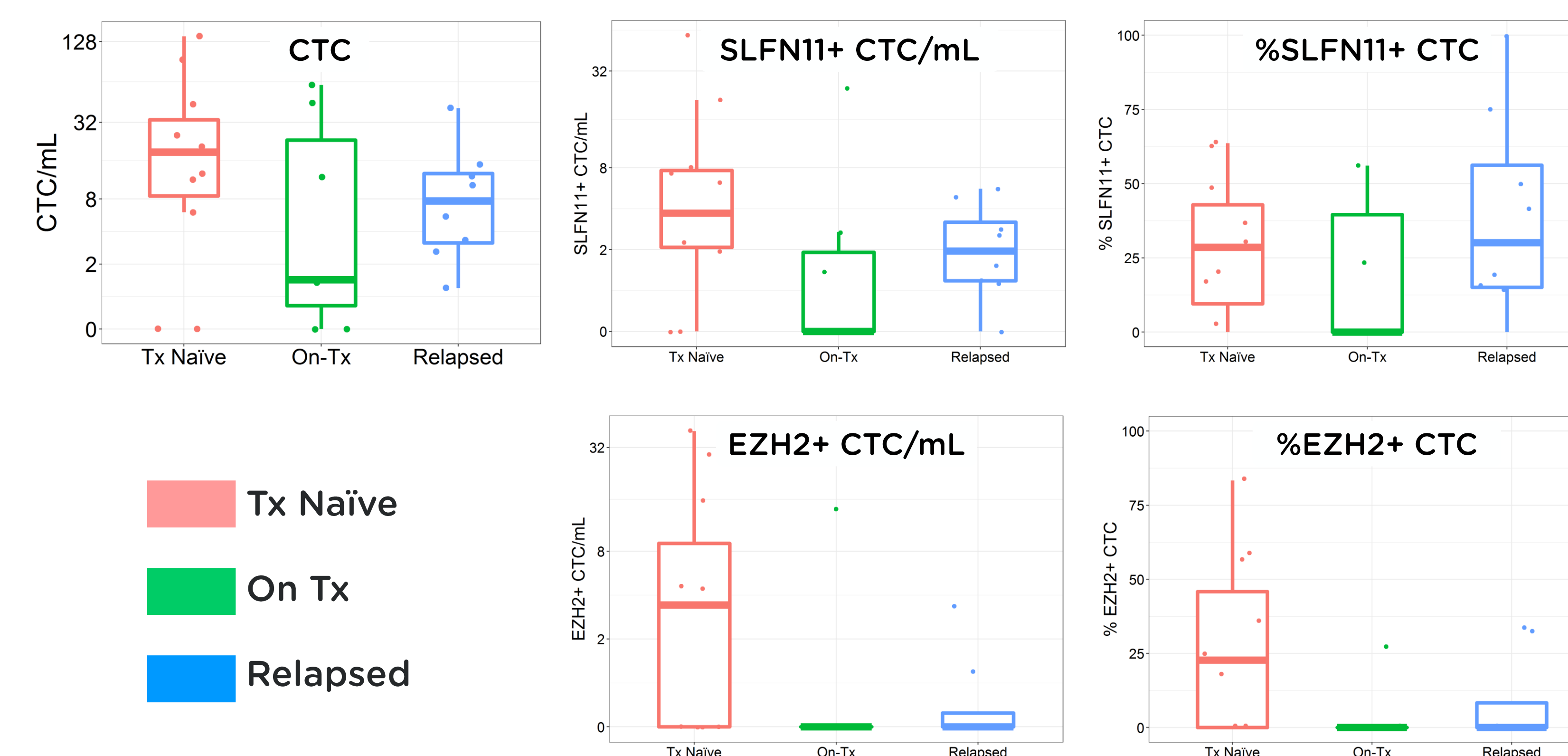
Heterogeneous SLFN11/EZH2 Expression in SCLC



- CTCs were detected in 85% (22/26) samples
- SLFN11+ CTCs was detected in 73% (19/26) samples
- Nuclear localized SLFN11+ CTCs was detected in 31% (8/26) samples
- EZH2+ CTCs was detected in 38% (10/26) samples
- Nuclear localized EZH2+ CTCs was detected in 35% (9/26) samples
- 6 samples had both SLFN11 and EZH2 nuclear localized CTCs

Dynamic Changes in Biomarker Expression by CTCs Collected Over Time

	Sample Size	CTC/mL	SLFN11+ CTC/mL	% SLFN11+ CTC	EZH2+ CTC/mL	% EZH2 CTC
Tx Naïve	11	19 (0-140)	4 (0-52)	29% (0-63%)	4 (0-40)	23% (0-83%)
On-Tx	7	1.3 (0-61)	0 (0-25)	0% (0-100%)	0 (0-14)	0% (0-27%)
Relapsed	8	8 (1-41)	2 (0-5.8)	30% (0-100%)	0 (0-3.5)	0% (0-33%)
Total	26	12 (0-140)	2.5 (0-52)	22% (0-100%)	0 (0-40)	0% (0-83%)



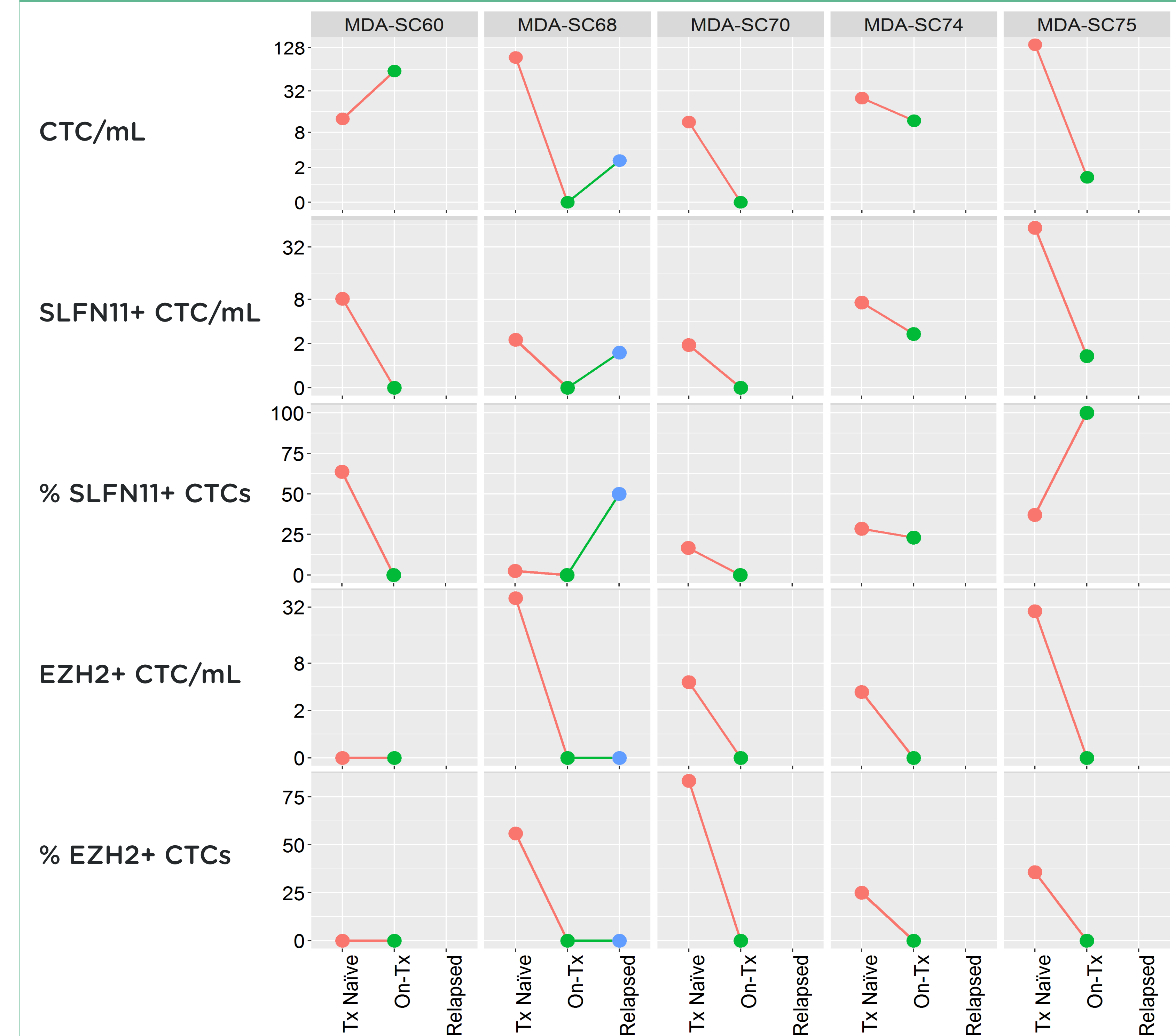
Tx Naïve Pts are More Likely to Express SLFN11 in the Nucleus of CTCs

Bio-Marker	CTC	SLFN11	EZH2		
Feature	% Pts With CTC	% Pts Marker+	% Pts with Nuclear Localization ¹	% Pts Marker+	% Pts with Nuclear Localization ²
Tx Naïve	82% (9/11)	82% (9/11)	55% (6/11)	64% (7/11)	55% (6/11)
On-Tx	71% (5/7)	43% (3/7)	14% (1/7)	14% (1/7)	14% (1/7)
Relapsed	100% (8/8)	88% (7/8)	13% (1/8)	25% (2/8)	25% (2/8)

¹Fisher Exact Test: p=0.0299

²Fisher Exact Test: p=0.0478

Longitudinal CTC and SLFN11+ CTC Changes Supporting Platinum Resistant Mechanism in SCLC



- 5 patients had multiple samples analyzed
- MDA-SC60 had longitudinally increased CTC count and decreased SLFN11 suggesting the resistant mechanism

Conclusions

- Inter- and intra-sample heterogeneous SLFN11 and EZH2 protein expression was observed in CTCs from SCLC patients
- SLFN11+ and EZH2+ CTCs, especially nuclear localized biomarker+, significantly decreased in On-Tx and relapsed samples suggesting the Tx resistant mechanism
- Use of these assays is underway in SCLC patient samples to assess correlation with PARPi and platinum agent response