2021 ASCO ANNUAL MEETING

FIRST-IN-HUMAN PHASE I/II STUDY OF CYT-0851, A FIRST-IN-CLASS INHIBITOR OF RAD51-MEDIATED HOMOLOGOUS RECOMBINATION IN PATIENTS WITH ADVANCED SOLID AND HEMATOLOGIC CANCERS

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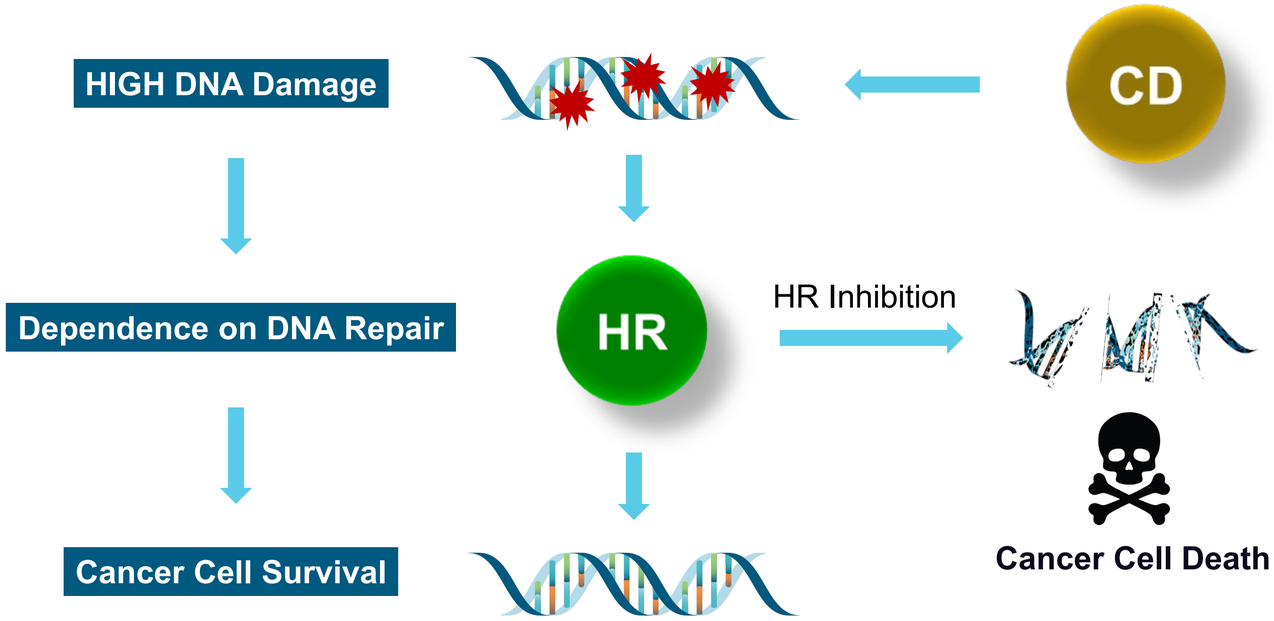
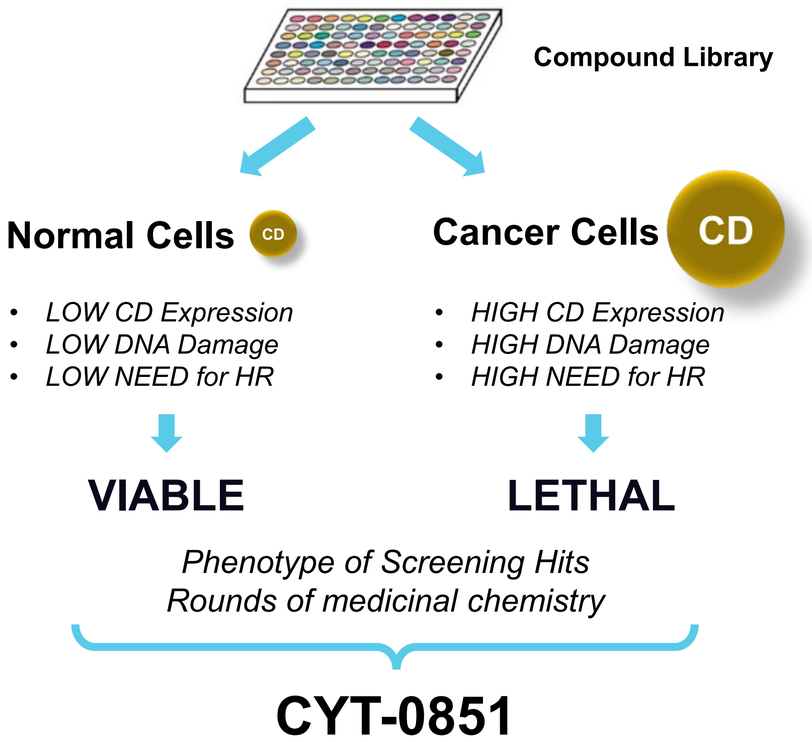
CYT-0851: Exploiting a Novel Gain-of-Function Synthetic Lethality

High levels of DNA damage in cancer cells enables **Synthetic Lethality** with selective inhibition of DNA repair

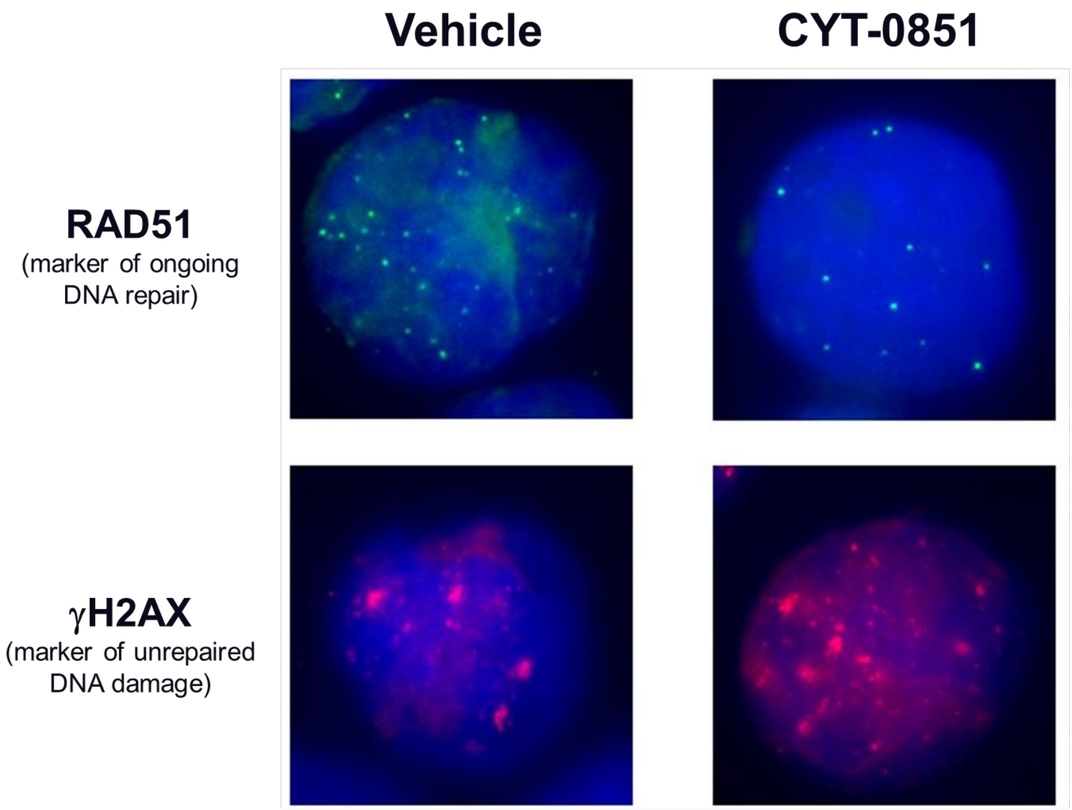
Cytidine Deaminase (CD) Overexpression Creates Dependence on DNA Repair by Homologous Recombination (HR)

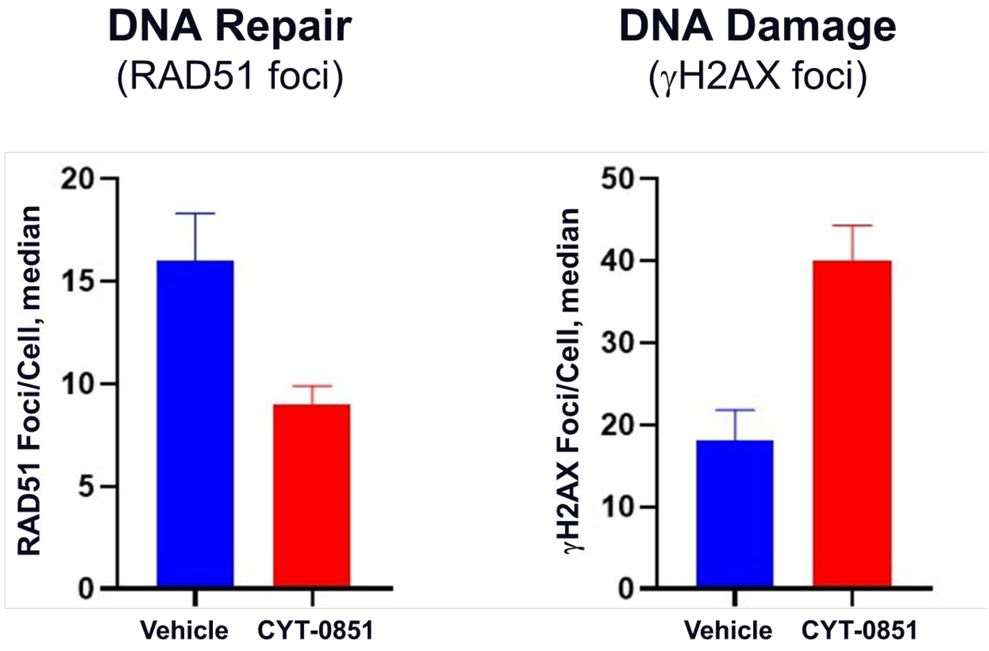


Phenotypic Synthetic Lethality Screen



CYT-0851 Treatment Reduces RAD51 Foci and Increases DNA Damage Measured by γH2AX





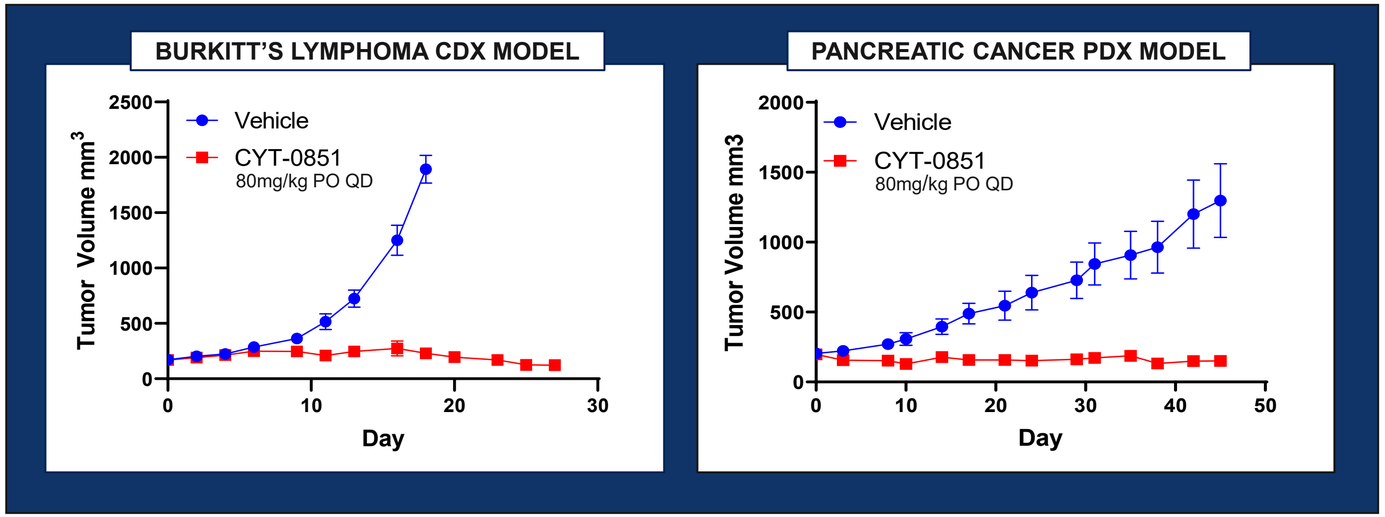
AID+ U698 B-cell Lymphoma Cell Line
1.25 μM CYT-0851, 4-day treatment

CYT-0851 Preclinical Characterization

IN VITRO BIOCHEMICAL AND CELLULAR ACTIVITY

CYT-0851 Property	Value
Cellular Potency Daudi (Burkitt's B Cell Lymphoma) screening cell line EC_{50}	200nM
Cellular Selectivity MEC1 CLL cell line (EC_{50} AID^+ vs AID knockout)	>30-fold
Kinase Selectivity Hits with >50% inhibition at 10μM (371 kinase panel)	0
Secondary Pharmacodynamic Selectivity Hits with >50% inhibition at 10μM (38 human Panlabs panel)	0
Bone Marrow Progenitors Selectivity IC_{50} for human erythroid, myeloid & megakaryocyte progenitor inhibition	>10μM (erythroid) 8.3μM (myeloid) 4.0μM (megakaryocyte)
hERG Ion Channel Selectivity	>3μM

IN VIVO ANTI-TUMOR ACTIVITY



CYT-0851: Highly selective small-molecule inhibitor of HR with single agent activity in hematologic and solid tumor models *in vivo*

CYT-0851 Phase 1 Trial Design

(Data cut-off Apr 6, 2021)

Dosing:
- Oral, 28-day continuous dosing per cycle

Design:
- 3+3 Dose Escalation
- Pharmacodynamic backfill up to 12 total patients per dose to obtain paired biopsies

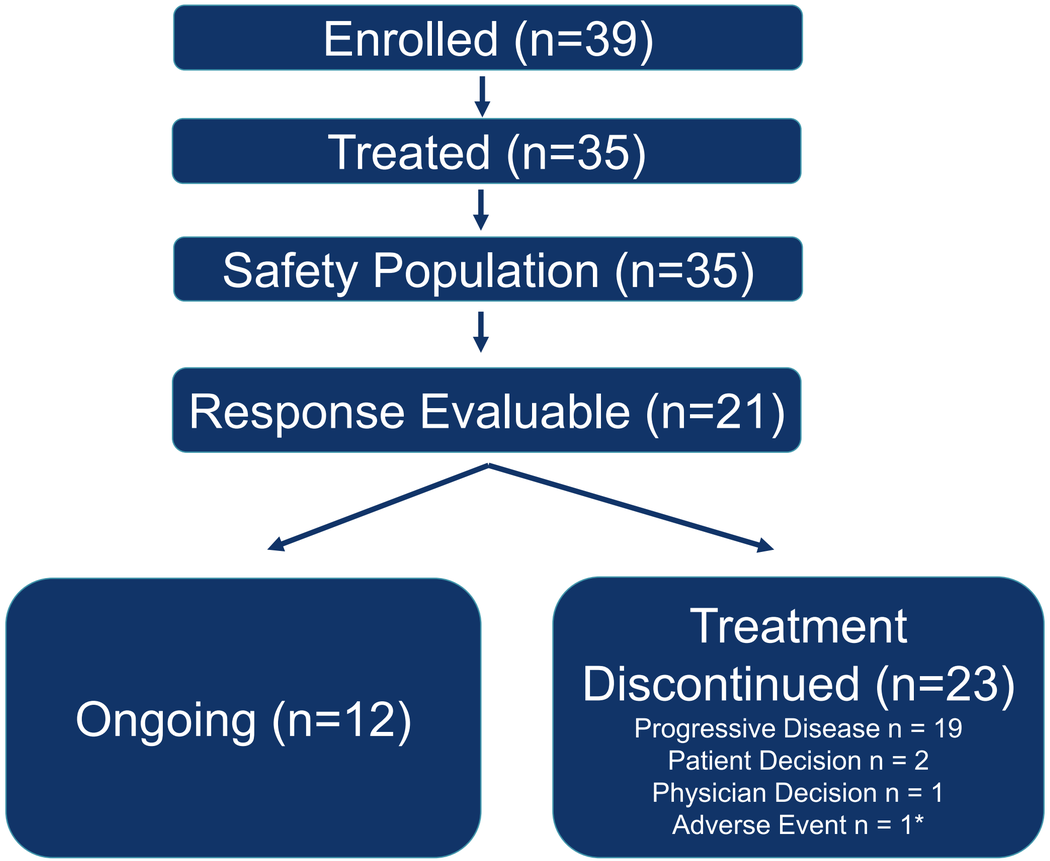
Objectives/Endpoints:
- Primary
  - MTD/RP2D
- Secondary
  - Safety
  - Pharmacokinetics
  - Anti-tumor Activity
- Exploratory
  - Pharmacodynamics
  - PK/PD relationship
  - Predictive biomarkers

Key Inclusion Criteria:
- ECOG 0-1
- Measurable disease
- Relapsed/refractory B-cell malignancies
  - NHL, CLL, Multiple myeloma
- Advanced solid tumors
  - Breast, HNSCC, ovarian, soft-tissue sarcoma, SCLC and pancreatic cancer

Key Exclusion Criteria:
- Prior allogeneic SCT
- ANC < 1.0×10^9/L
- Plt < 75×10^9/L
- Hgb < 9.0 g/dL
- CrCl < 40 mL/min
- AST/ALT > 2.0 x ULN

Patient Characteristics, Enrollment and Disposition

Characteristics	Total (n=35) n (%)
Female	19 (54)
Male	16 (46)
Median age (range)	59 (41-82)
ECOG Performance Status	
0	6 (17)
1	27 (77)
Prior Lines of Therapy	
Median (range)	4 (1-12)
1	2 (6)
2	5 (14)
≥ 3	28 (80)
Tumor Type	
Breast Cancer	5 (14)
Head and Neck Cancer	1 (3)
SCLC	1 (3)
Mucoepidermoid Cancer	1 (3)
NHL	8 (23)
Ovarian Cancer	3 (9)
Pancreatic Cancer	4 (11)
Soft-Tissue Sarcoma	12 (34)



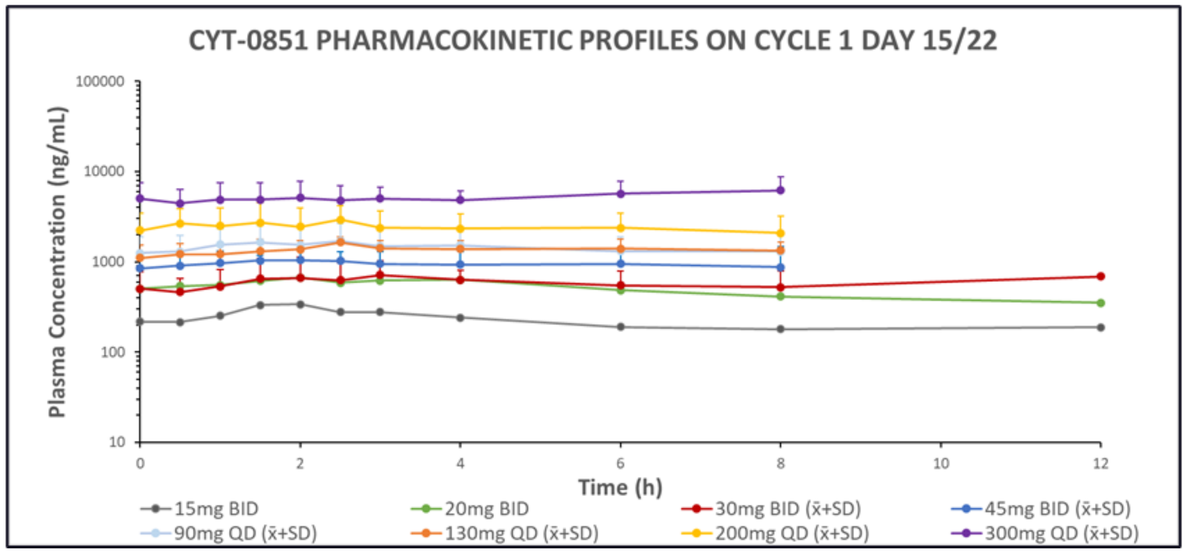
*AST/ALT increase secondary to disease

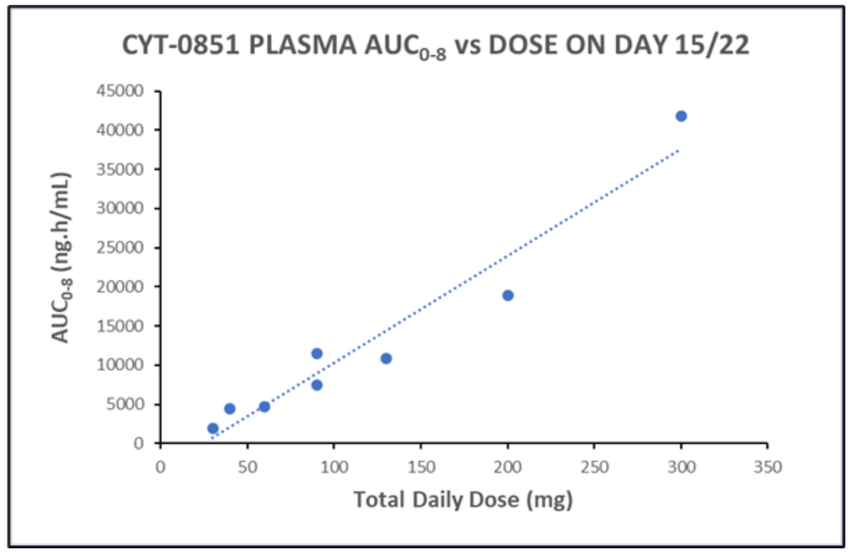
Safety Overview

Treatment-Related AEs (Occurring in > 1 pt)	Any Grade n (%)	≥ Grade 3 n (%)
Any Related Adverse Event	**13 (37.1)**	**3 (8.6)**
Blood alk phos increased	3 (8.6)	0
Fatigue	3 (8.6)	1 (2.9)
Nausea	3 (8.6)	0
Anemia	2 (5.7)	0
AST increased	2 (5.7)	0
Constipation	2 (5.7)	0
Eosinophilia	2 (5.7)	0
Hyperuricemia	2 (5.7)	0
Lymphocyte count decreased	2 (5.7)	0
Platelet count decreased	2 (5.7)	0

- No DLTs
- No treatment-related SAEs
- No clinically significant myelosuppression
- No treatment-related discontinuation
- No grade 4/5 TRAEs

CYT-0851 Pharmacokinetic Profile





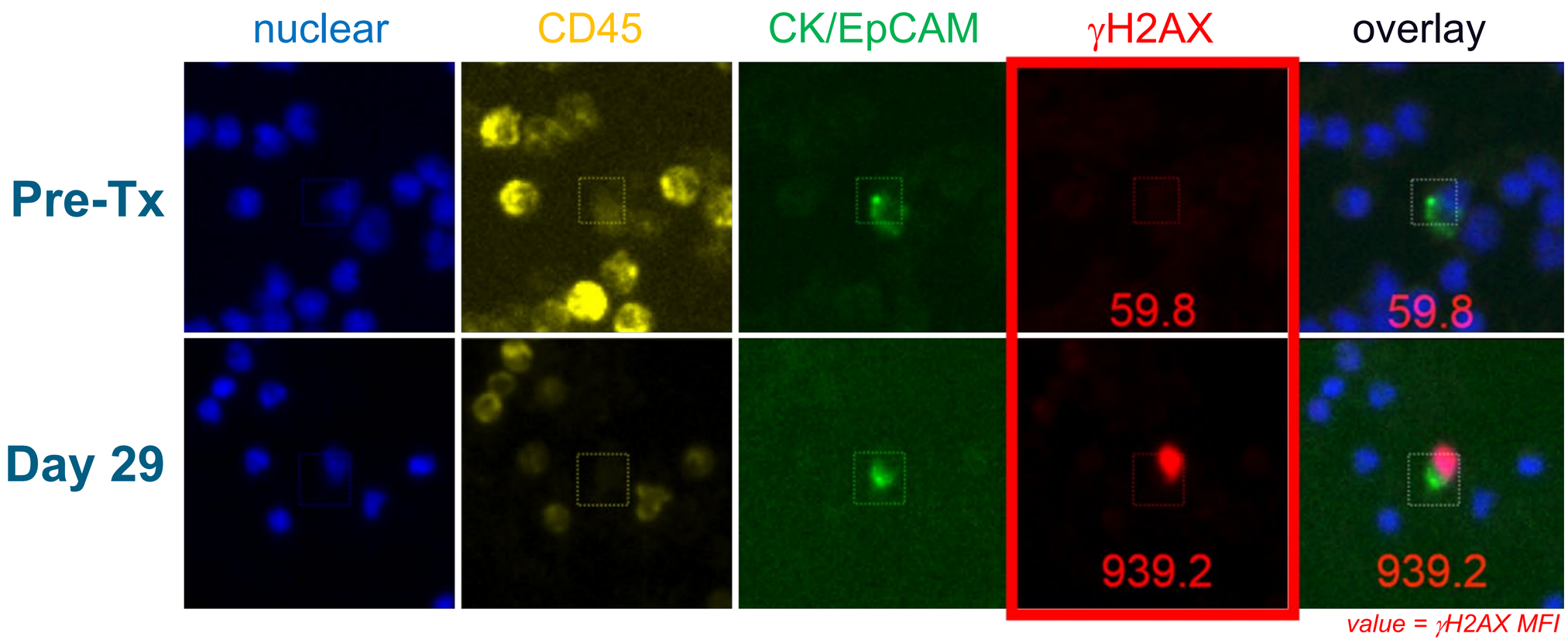
CYT-0851 Human Pharmacokinetics Summary for C1D15/22

Pharmacokinetic Parameter	Dose (mg)							
	15 BID (n=1)	20 BID (n=1)	30 BID (n=3)	45 BID (n=6)	90 QD (n=3)	130 QD (n=6)	200 QD (n= 4)	300 QD (n= 3)
T_{max} (h)	2.0	2.0	4 (2, 4)	2.25 (1.5, 6)[a]	2.5 (1, 2.5)[a]	2.5(1.5, 3)[a]	4.0 (1.5, 6)[a]	6.0 (6, 8)[a]
C_{max} (ng/mL)	338	670	770 ± 390	1170 ± 375[b]	1740 ± 930[b]	1700 ± 298[b]	2980 ± 1690[b]	6490 ± 2560[b]
AUC_{0-8} (ng.h/mL)	1890	4410	4710 ± 2140	7450 ± 3030[b,c]	11500 ± 5570[b]	10800 ± 2510[b]	18900 ± 9490[b]	41800± 16200[b]

[a]: median (min, max) [b]: mean ± standard deviation (SD) [c]: n=5

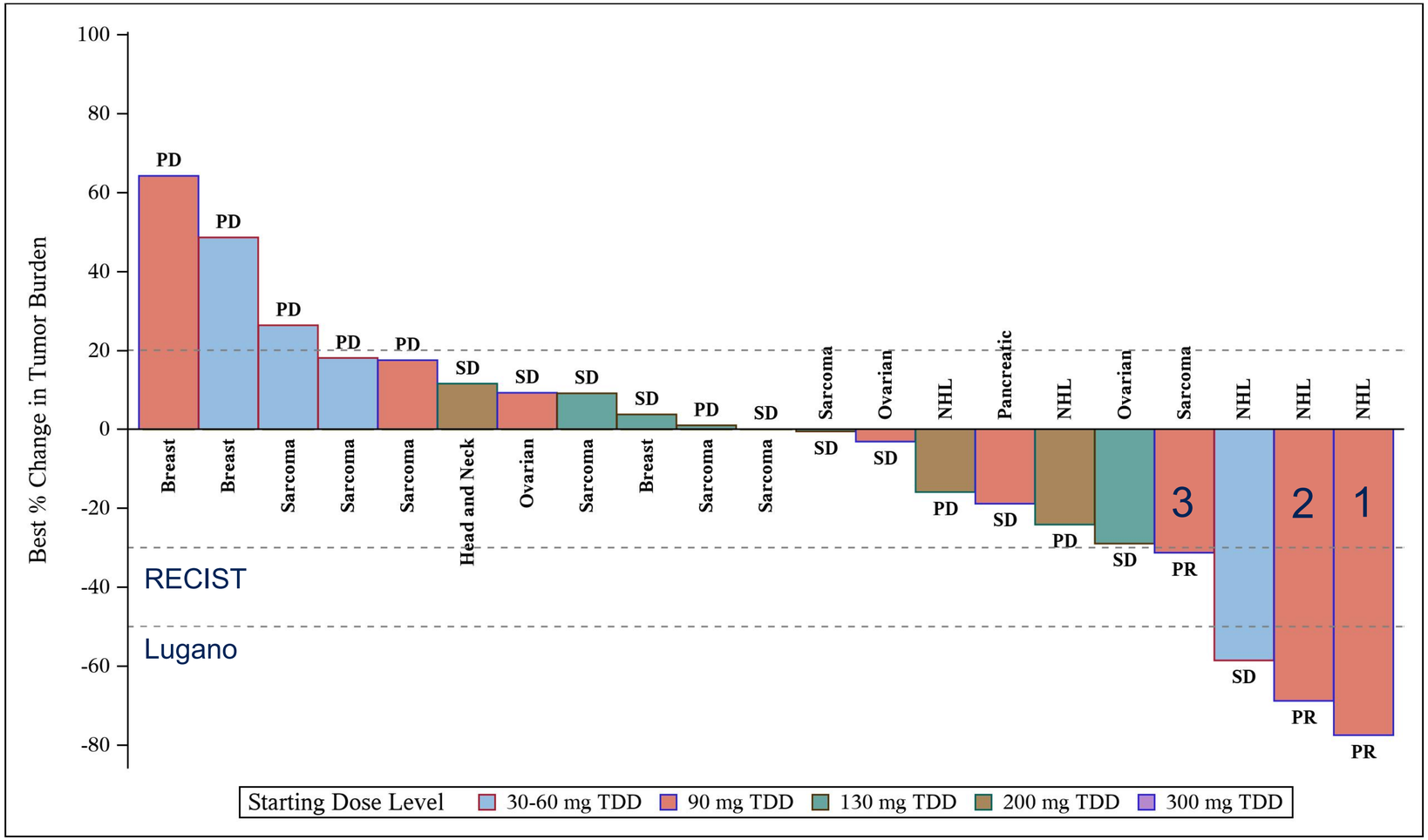
CYT-0851 PK exhibits a long effective half-life (~3 days) with dose proportional exposure

PD Effects: Selective Increase in DNA damage (γH2AX) observed in CTCs (Patient 015) at 45 mg BID



Increased γH2AX observed in CTCs from 3 of 6 biomarker-evaluable patients with epithelial cancers consistent with proposed mechanism of action

CYT-0851 Efficacy: Change in Tumor Burden



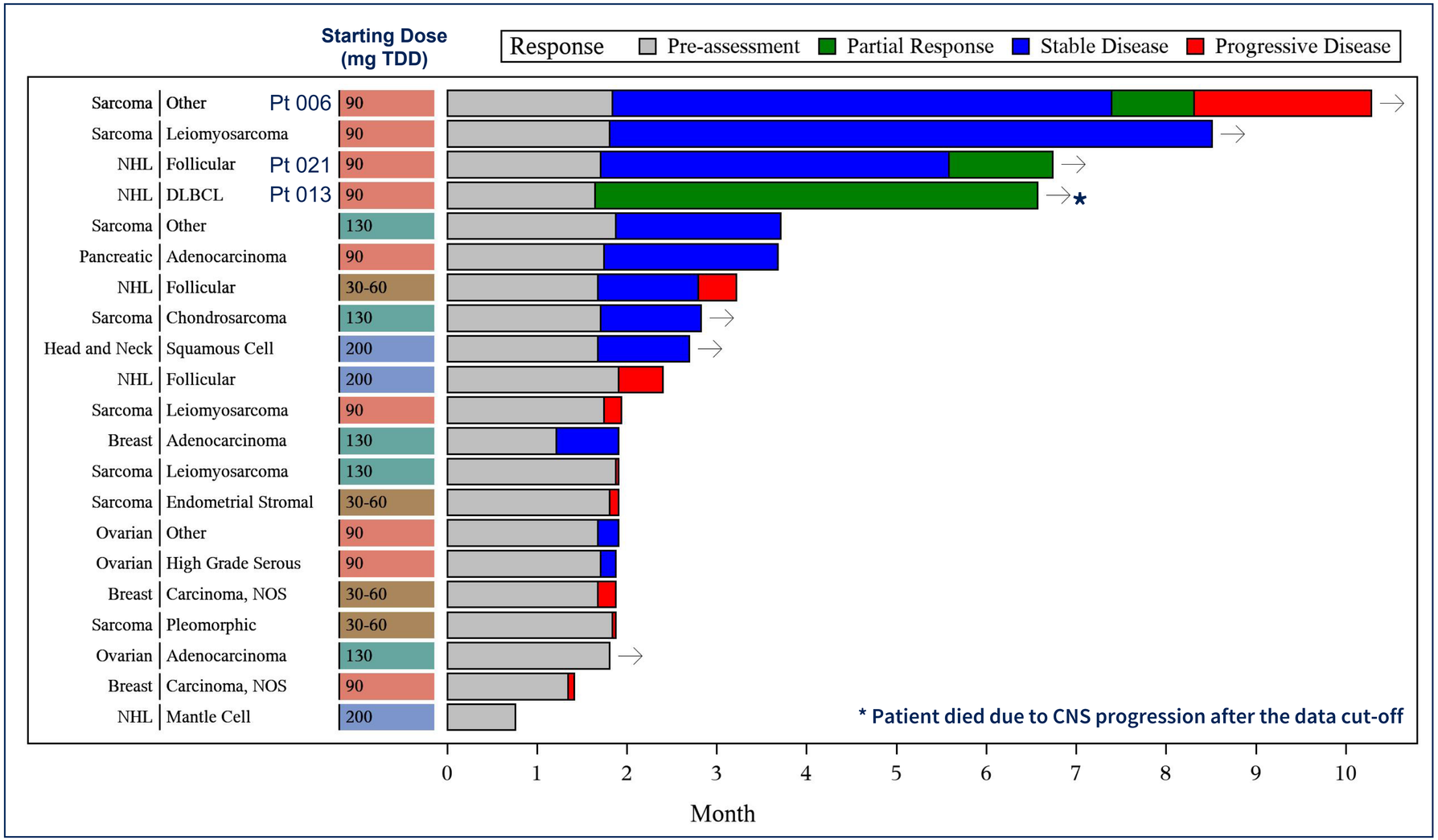
TDD = Total Daily Dose

21 patients were response-evaluable

3 partial responses
1) DLBCL (Pt 013)
2) Follicular lymphoma (Pt 021)
3) Soft-tissue sarcoma (Pt 006) (unconfirmed)

- 10 patients had stable disease

CYT-0851 Duration of Treatment

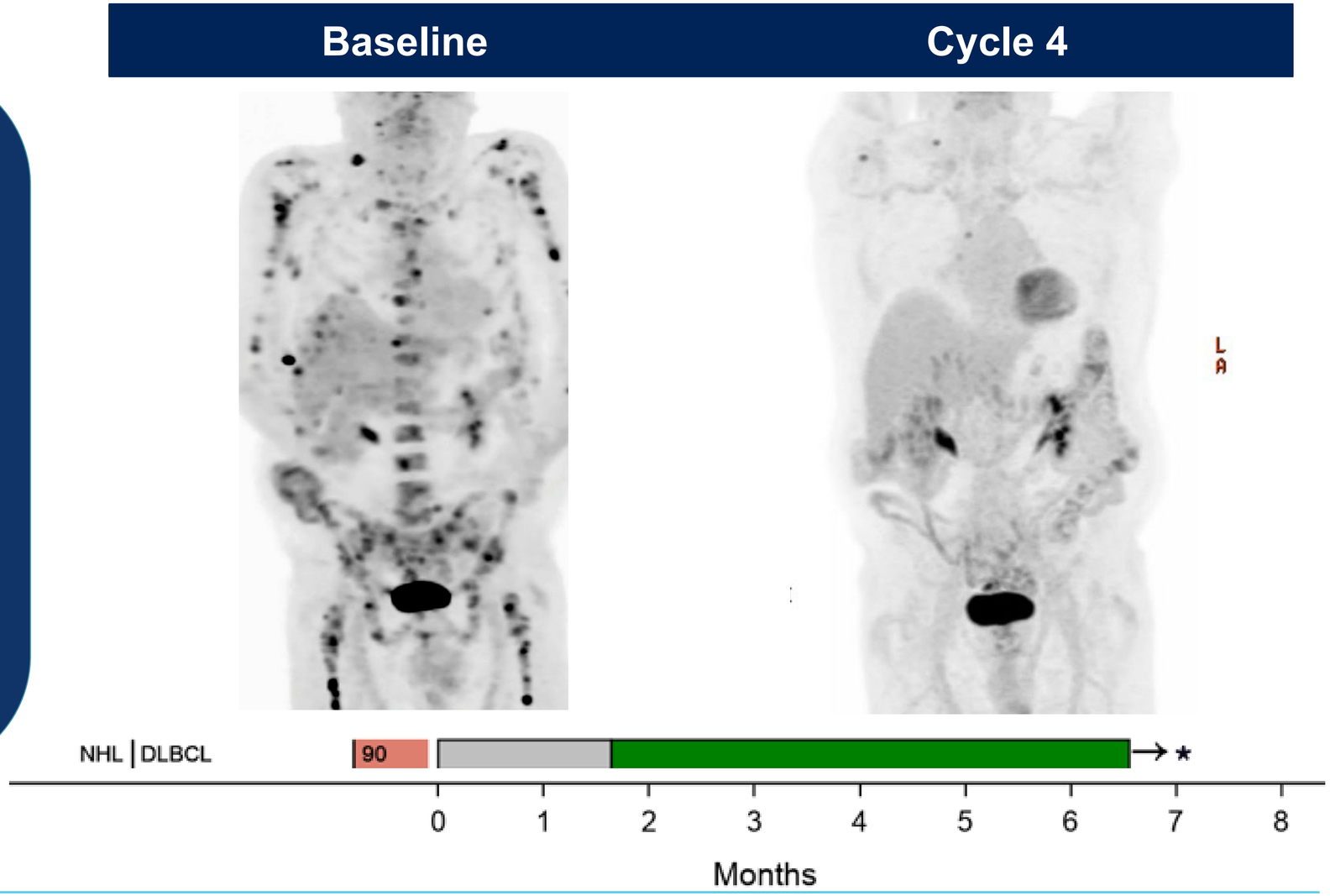


- Durable benefit has been observed in patients with clinical response
- Four patients received CYT-0851 for 6+ months with no evidence of cumulative toxicity

TDD = Total Daily Dose

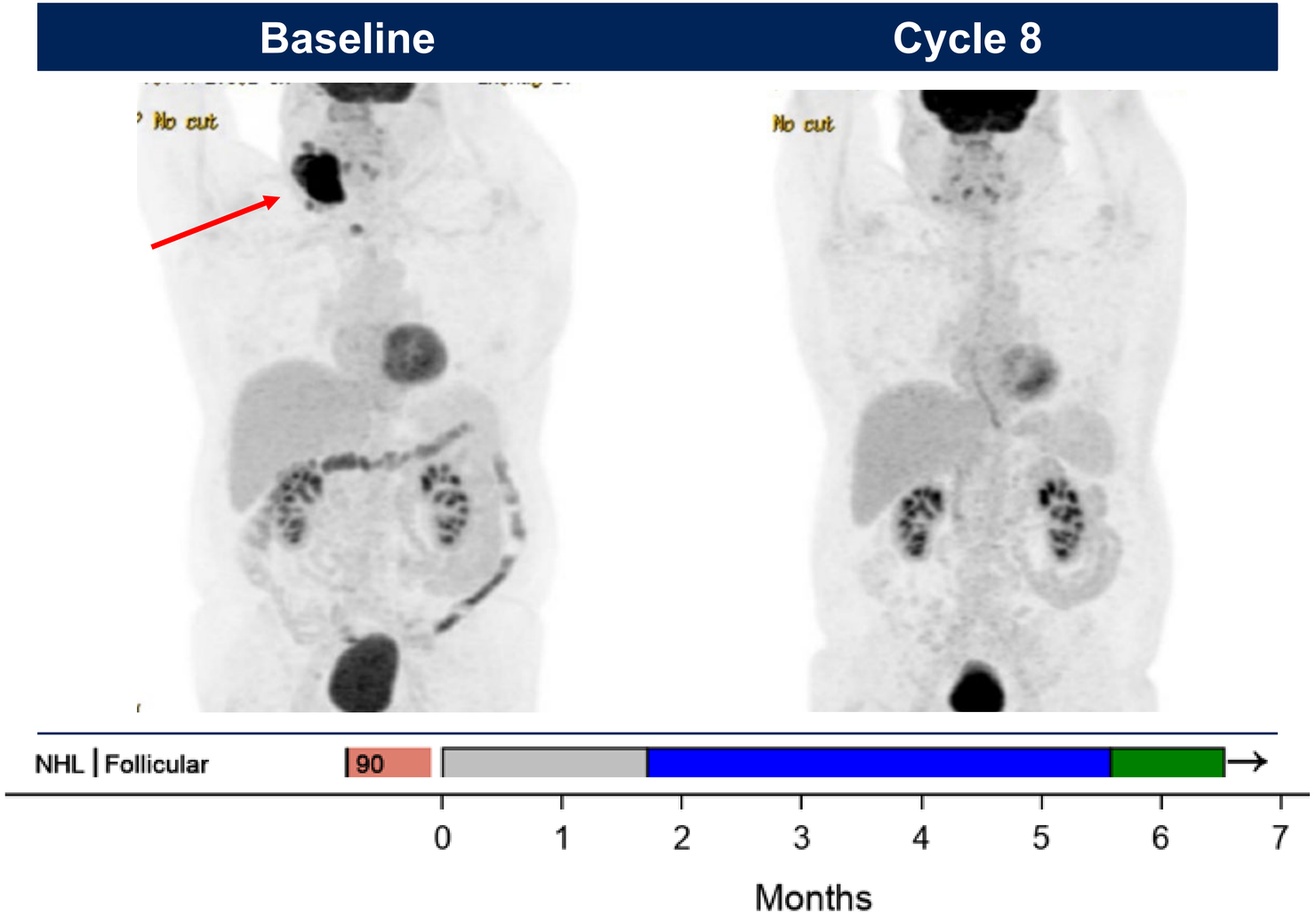
Response #1: DLBCL (Patient 013)

- 81 yo male with DLBCL previously treated with 2 lines of therapy (R-CHOP, R-Benda/XRT)
- Treated with 45 mg PO BID for 5 cycles and then increased to 130 mg PO QD for 2 cycles
- No treatment related adverse events reported in 6+ months on therapy
- He experienced disease progression in the CNS and died after the data cutoff



Response #2: Follicular Lymphoma (Patient 021)

- 59 yo male with follicular lymphoma previously treated with 3 lines of therapy (Rituximab, R-CVP, PI3K inhibitor)
- Treated with 45 mg PO BID for 4 cycles, 130 mg PO QD for 2 cycles, then 200 mg PO QD
- No treatment related adverse events reported in 6+ months on therapy
- Patient's treatment and response is ongoing



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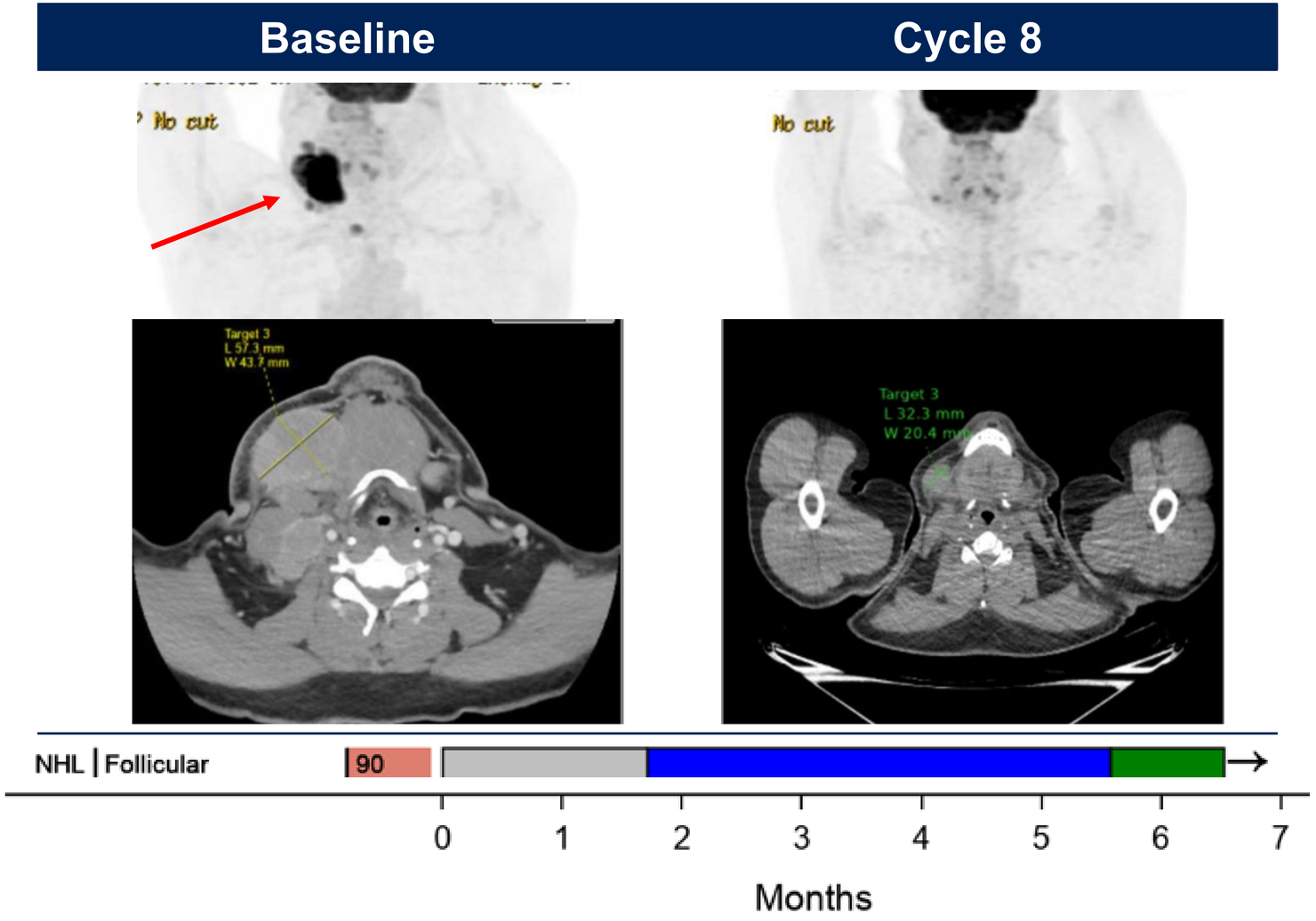
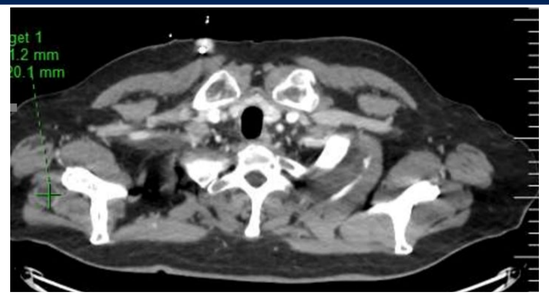
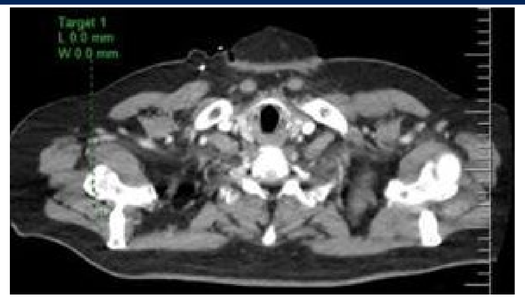
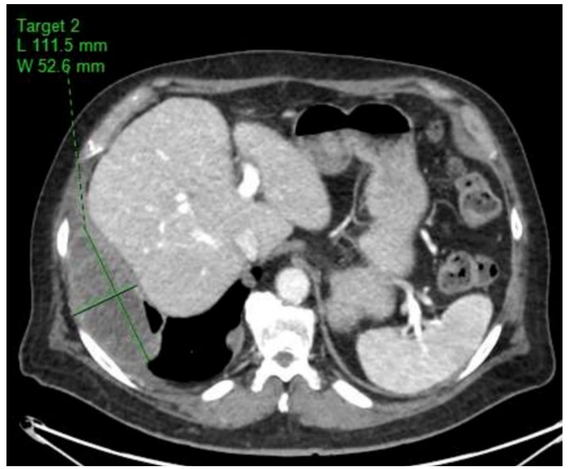
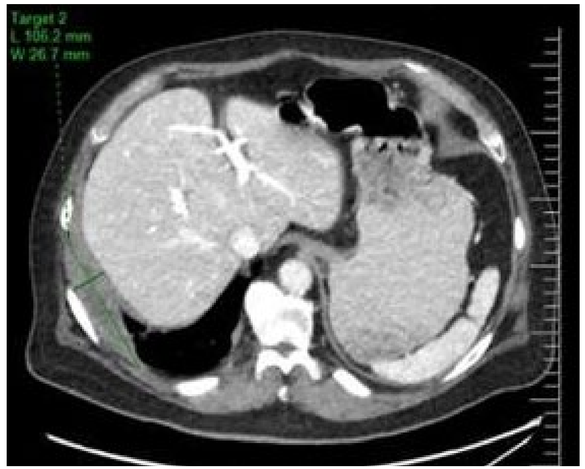
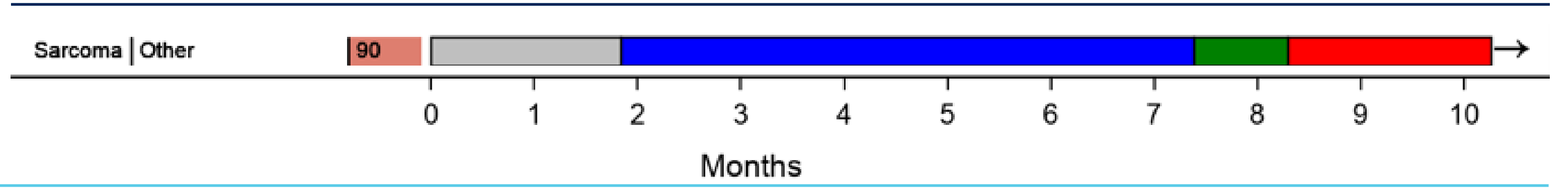


Response #3: Myxofibrosarcoma (Patient 006)

- 73 yo male with myxofibrosarcoma previously treated with 4 lines of therapy
- Treated with 45 mg PO BID for 8 cycles, 90 mg PO QD for 1 cycle, then 130 mg PO QD for 1 cycle
- No treatment related adverse events reported in 10+ months on therapy
- He experienced disease progression and has subsequently discontinued treatment after the data cutoff

Site	Baseline	Cycle 7
Chest Wall Posterior R Shoulder		
Pleura Right Costophrenic		



Conclusions: CYT-0851 Phase 1 Interim Analysis

- CYT-0851 has been evaluated in 8 dose-escalation cohorts with no DLTs. Escalation is ongoing to define the MTD.
- Treatment-related adverse events occurred infrequently and were low-grade and manageable.
- The pharmacokinetic profile exhibits dose proportional exposure and a long half-life supporting once-daily oral administration with predicted PD effects.
- Responses were observed in DLBCL, FL, and soft tissue sarcoma with tumor shrinkage in pancreatic cancer and ovarian cancer at biologically-active doses.

CYT-0851 is the first DDR-targeted agent with monotherapy activity in solid tumors and NHL and a non-myelosuppressive safety profile

Acknowledgments

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