



CYCLACEL

**Innovative medicines for cancer and other diseases
using cell cycle & DNA damage response biology**

Biotech Showcase - January 2017



Disclaimer

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Cyclacel Highlights

Drugs against cancer based on cell cycle control biology

DNA damage modulation with sapacitabine oral capsules

- Ph 3 readout in front-line AML patients

DNA damage response with sapacitabine + seliciclib

- Oral combination: Ph 1 benefit in BRCA +ve patients

Transcriptional CDK2/9 inhibitor program

- Seliciclib (Ph 2) and CYC065 2nd gen CDK inhibitor (Ph 1)

Strong financial position & experienced management

- Est. capital through 2018 (beyond Ph 3 AML data readout)

Addressing large markets with limited competition

Source: Cyclacel press releases and data on file.



Translating Cancer Biology into Medicines

Profs David Lane (*p53*) & David Glover (*Polo & Aurora kinases*)

- Exploit cell cycle biology to disrupt cancer cell immortality:
 - *DNA DAMAGE RESPONSE* Modulating cancer cell DNA repair
 - *CELL CYCLE CONTROL* Breaking cancer cell addiction to oncogenes

Drug portfolio strategy

- Small molecules, enzyme targets (*DNA pol- α* , *CDK*, *PLK*)
- Phase 1 through Phase 3 trials completed
- Target profile: orally available, chronic treatments
- Low intensity treatment experience & patient QoL
- High value therapeutics

Source: Cyclacel data on file.



Pipeline

Program	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Marketed
Sapacitabine	AML	SEAMLESS Phase 3 registration study				
Sapacitabine	MDS	Phase 2 randomized study				
Sapacitabine + Seliciclib	Solid Tumors	Phase 1 BRCA +ve				
CYC065 CDK Inhibitor	Cancer	Phase 1 solid tumors				
CYC140 PLK Inhibitor	Cancer					

Investigator Sponsored Trials (IST)

Seliciclib	Cushing's disease & Rheumatoid Arthritis				
Seliciclib	Cystic Fibrosis				

AML = acute myeloid leukemia. MDS = myelodysplastic syndromes. IND = investigational new drug.

The clinical problem of elderly AML



***High Intensity iv Therapy +
Low Quality of Life + Old Age + Frailty
= High Mortality***



Predicament of 70+ year old AML Patient



- Newly diagnosed: multigenetic, heterogeneous disease
- Old age, frailty and comorbidity

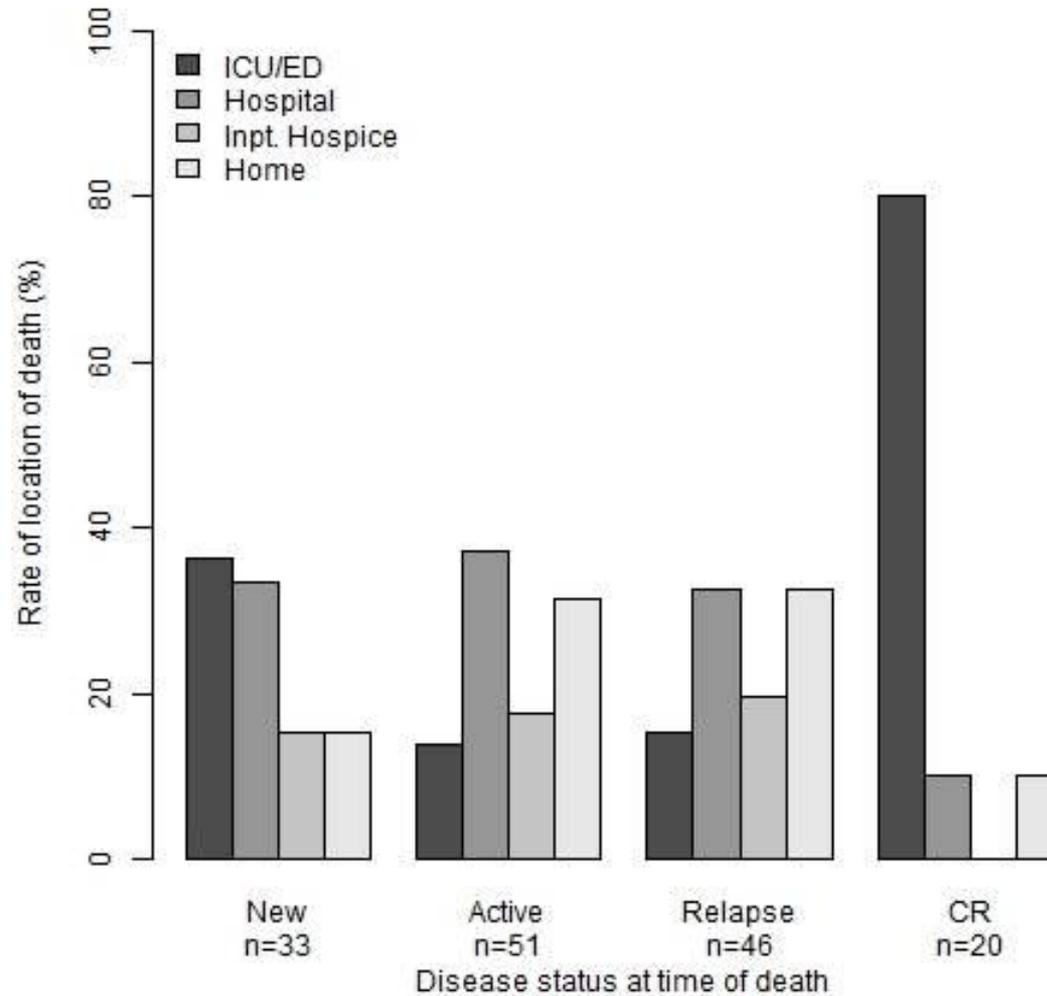
Options:

- 47-year old intensive iv chemotherapy regimen ("7+3")
- Investigational clinical trial
- Hospice or terminal care at home

- Median survival of 3 - 6 months
- 60-day mortality of ~ 20 - 36%



End of Life with AML: MGH 2007-2012



* Source: Foster J et al, Abstract 3318, ASH 2015.

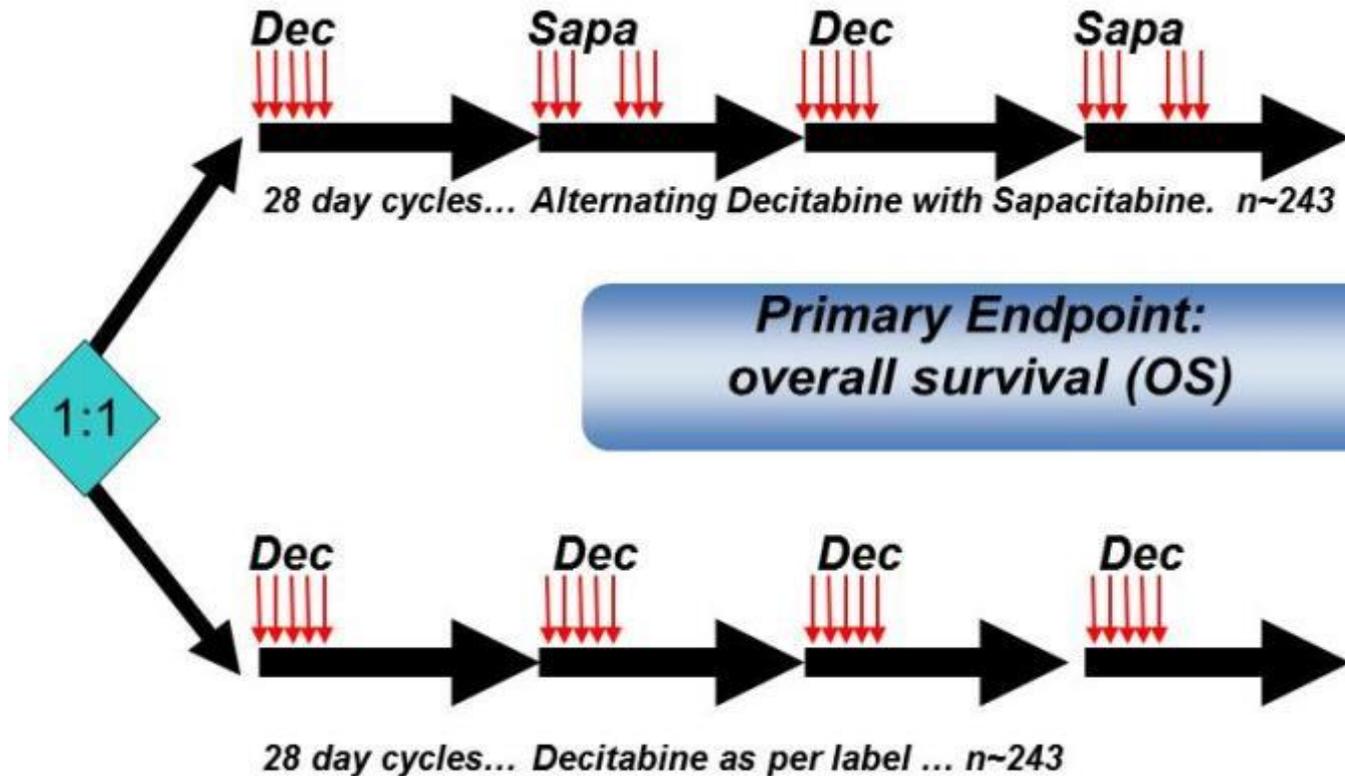


Our solution

***Low Intensity Therapy +
Stay-at-Home Treatment =
Extended survival + High Quality of Life***

SEAMLESS Phase 3 - *Low Intensity Strategy*

(Untreated AML: front line; ≥ 70 years; $n=485$; $p=0.05$; $HR=0.725$)



- ✓ In consultation with FDA under SPA
- ✓ Fully enrolled at 110 US & European hospitals



SEAMLESS Phase 3 Assumptions & Events *

≥27.5% reduction in risk of death

Median OS of:

- 8 months for experimental arm
- 6 months for control arm

Completed enrolment in December 2014

Required number of events reached

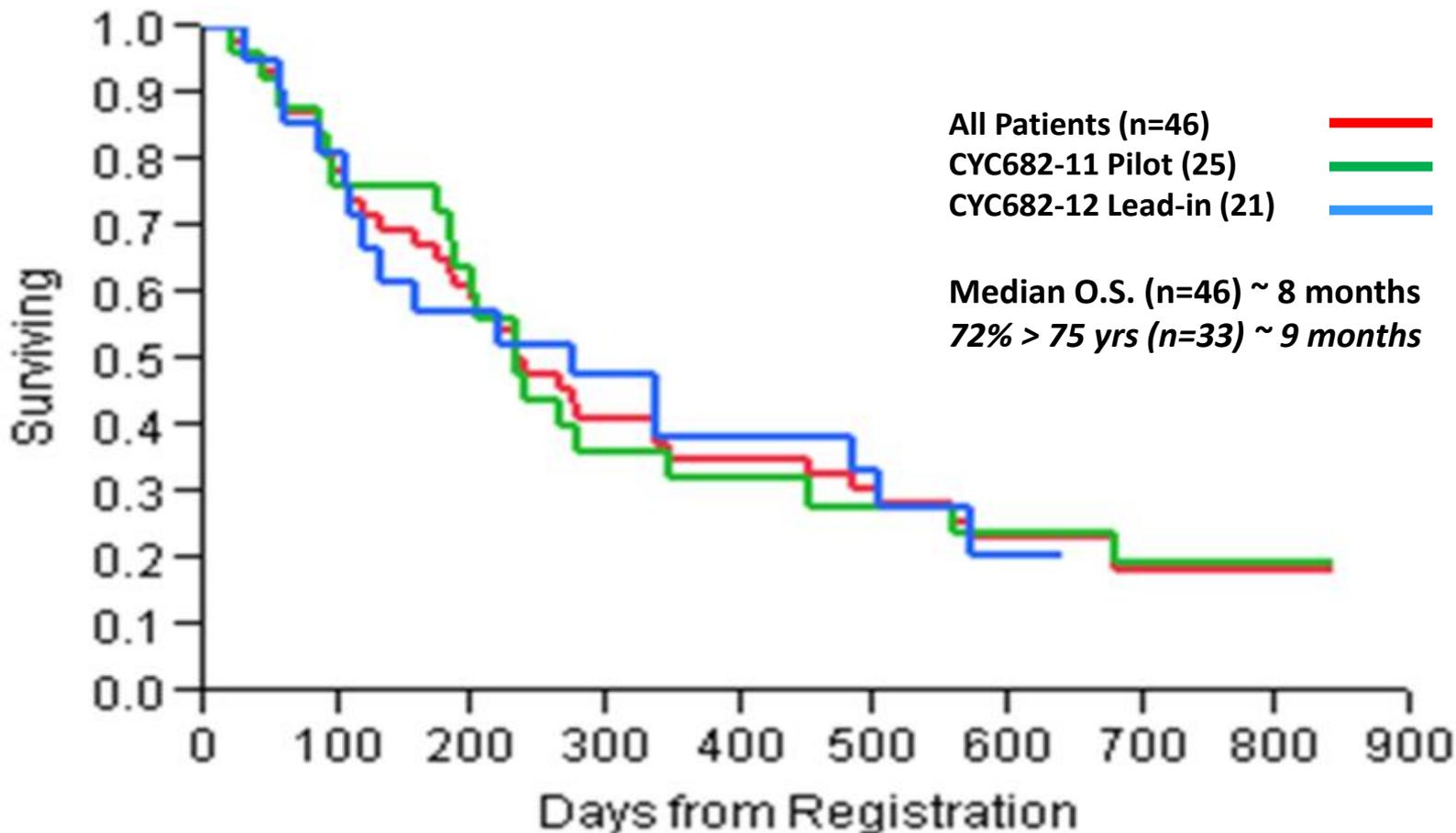
- Preparation for final analysis and reporting SEAMLESS outcomes underway

Anticipate reporting primary and secondary endpoints and submissibility to regulatory authorities in early 2017

* Source: Cyclacel data on file.

SEAMLESS Pilot/Lead-in Study

Kaplan-Meier Survival Plot



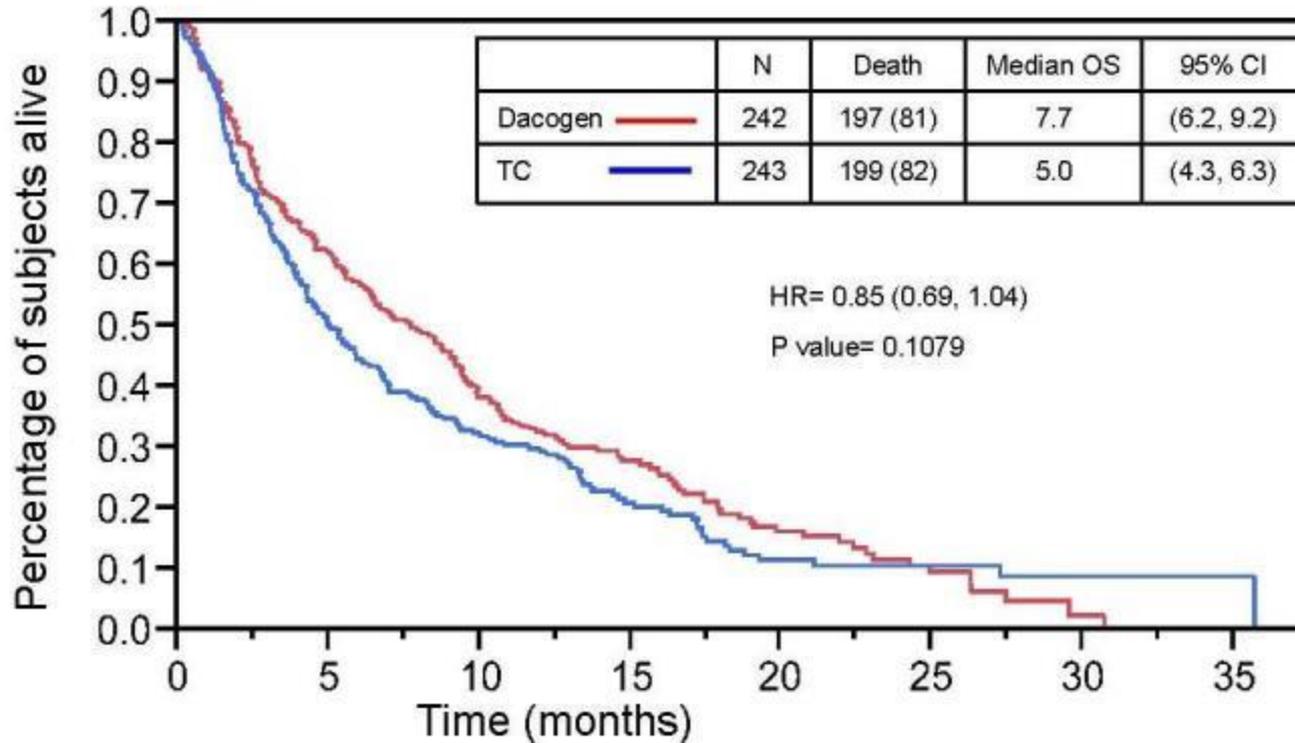
No. at risk	3M	6M	12M	18M	24M
	38 (83%)	30 (65%)	16 (35%)	12 (26%)	not reached

* Source: Ravandi F, et al, American Society of Hematology Annual Meeting Dec. 2012, Abstract #2630.





K-M Plot, Pre-specified OS final Analysis (DACO-016: Cut-off Oct. 28, 2009)



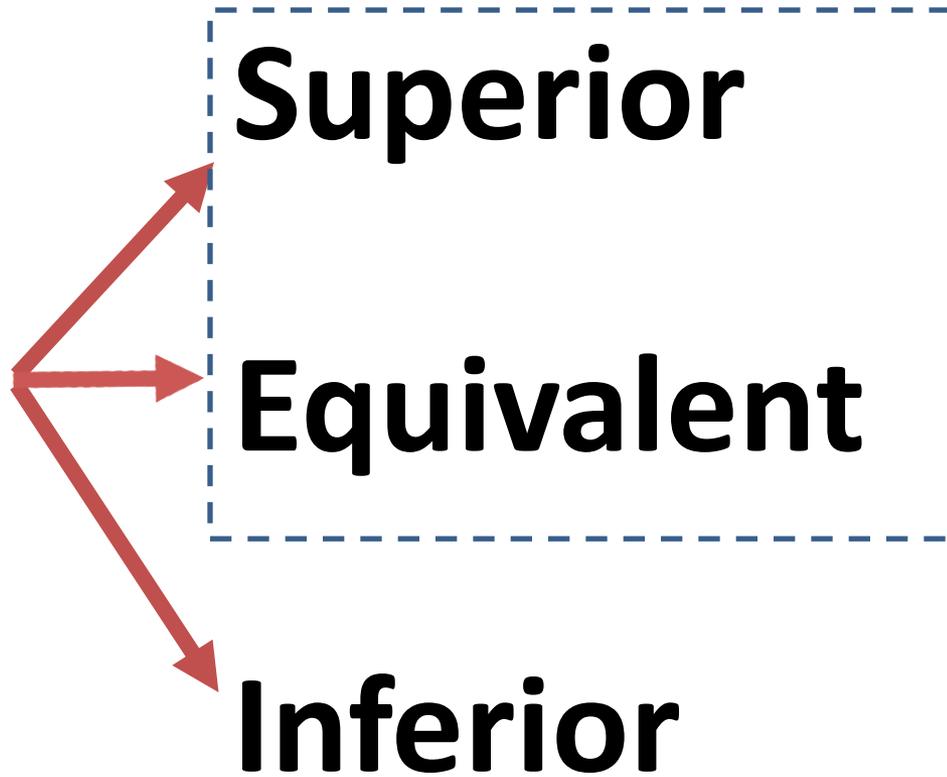
No. of subjects at risk	6M	12M	18M	24M	30M	36M
Dacogen	242	137	65	28	12	1
TC	243	107	55	19	07	4

* Source: FDA Briefing Document, Dacogen ODAC, February 9, 2012. Of 242 treated with decitabine 39% were aged 75 years or older.





Possible SEAMLESS Outcomes





AML Market Opportunity Parameters

- US incidence: ~ 20,000; EU: ~ 22,000 patients
- Aged 70 years or older ~ 50% or 21,000 EU/US patients
- Assume 80% unfit/refuse intensive chemotherapy: available EU/US population of ~ 16,800 patients
- Indicative US annual cost of branded azacitidine or decitabine: ~\$45,000-\$65,000.

† Source: NCI SEER database, 2015 and Cyclacel proprietary market research.



Sapacitabine Competitive Positioning

- 1st line eAML: no approved drug since 1969
- Only orally-administered, low intensity drug
- Durability
- Well tolerated
- Convenience
- Line extensions (MDS, BRCA +ve cancers)
- Market research suggests ↑ unmet need





Cyclin Dependent Kinase Inhibitors:

Emerging novel oncology drug class

First CDK inhibitor approved in 2015 for breast cancer

Translating the 2001 Nobel Prize for Physiology & Medicine into treatments

Cyclacel's portfolio of CDK2/9 inhibitors:

- Seliciclib (Phase 2)
- CYC065 (Phase 1)



CDK Inhibitor Landscape *

CDK4/6 isoforms

- **palbociclib (PFE)**
Approved in combination with letrozole for ER +ve Her2 -ve advanced BC
- **abemaciclib (LLY; also CDK9)** Ph3
- **ribociclib (NVS)** Ph3

CDK2/9 “transcriptional” isoforms

- **seliciclib (CYCC)** Ph2
- **CYC065 (CYCC)** Ph1
- **dinaciclib (pan CDK, MRK)** Ph3
- **BAY1143572 (CDK9, BAY)** Ph1

* Source: Cyclacel data on file.

Activity in HR-repair deficient tumors *

All-oral combo sapacitabine+seliciclib:

- durable clinical benefit (PRs & prolonged SD) in patients with BRCA +ve:
 - **breast,**
 - **ovarian,**
 - **pancreatic cancers**

...Opening new opportunities for line extensions...

* Source: Tolaney S et al, J Clin Oncol 34, 2016 (suppl; abstr 2503); Shapiro et al, AACR Proceedings, 2013, LB-202. HR=homologous recombination.

Sapacitabine & Seliciclib Ph 1 Best Responses *

RECIST Evaluable BRCA Carriers

Cancer	Best Response	Prior Treatment	Total cycles
Part 1 (n=16)			
Breast	CR	adriamycin, cyclophosphamide, paclitaxel, cisplatin	>80
Breast	PR	adriamycin, cytoxan, paclitaxel, carboplatin	31
Ovary	SD	paclitaxel, carboplatin, gemcitabine	21
Ovary	PR	paclitaxel, carboplatin, gemcitabine, topotecan, iniparib	18
Breast	SD	tamoxifen, raloxifene, anastrozole, adriamycin, Cytoxan, paclitaxel, carboplatin, navelbine	7
Pancreas	PR	gemcitabine, 5-FU, oxaliplatin	7
Part 2 (n=28)			
Breast	PR	adriamycin, cytoxan, paclitaxel, capecitabine, irinotecan, ABT-888 (PARP inhibitor), MPDL3280A	>19
Ovary	SD	paclitaxel, carboplatin, doxil	22
Breast	SD	adriamycin, cytoxan, capecitabine, faslodex	12
Ovary	SD	paclitaxel, carboplatin, doxil, gemcitabine, topotecan, cytoxan, avastin	11
Ovary	SD	paclitaxel, carboplatin, doxil, olaparib (PARP inhibitor), cediranib	8
Ovary	SD	paclitaxel, carboplatin	4
Ovary	SD	paclitaxel, carboplatin, doxil, gemcitabine, alimta, cytoxan, avastin, olaparib (PARP inhibitor)	4
Pancreas	PR	gemcitabine, abraxane, docetaxel	4
Pancreas	SD	gemcitabine, cisplatin, abraxane, folfox, TH-302	4

ED AT: ASCO ANNUAL MEETING '16

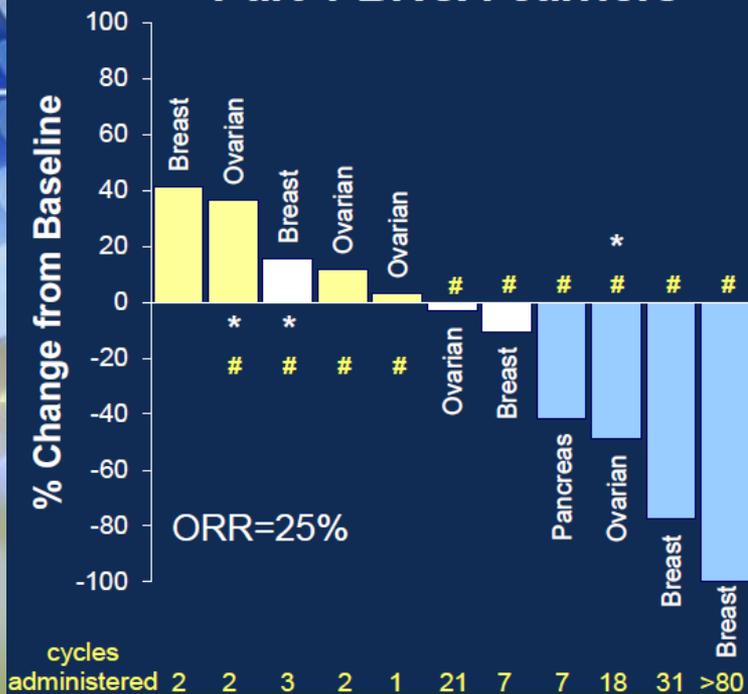
Presented by: Sara M. Tolaney, MD, MPH

* Source: Tolaney S et al, J Clin Oncol 34, 2016 (suppl; abstr 2503).

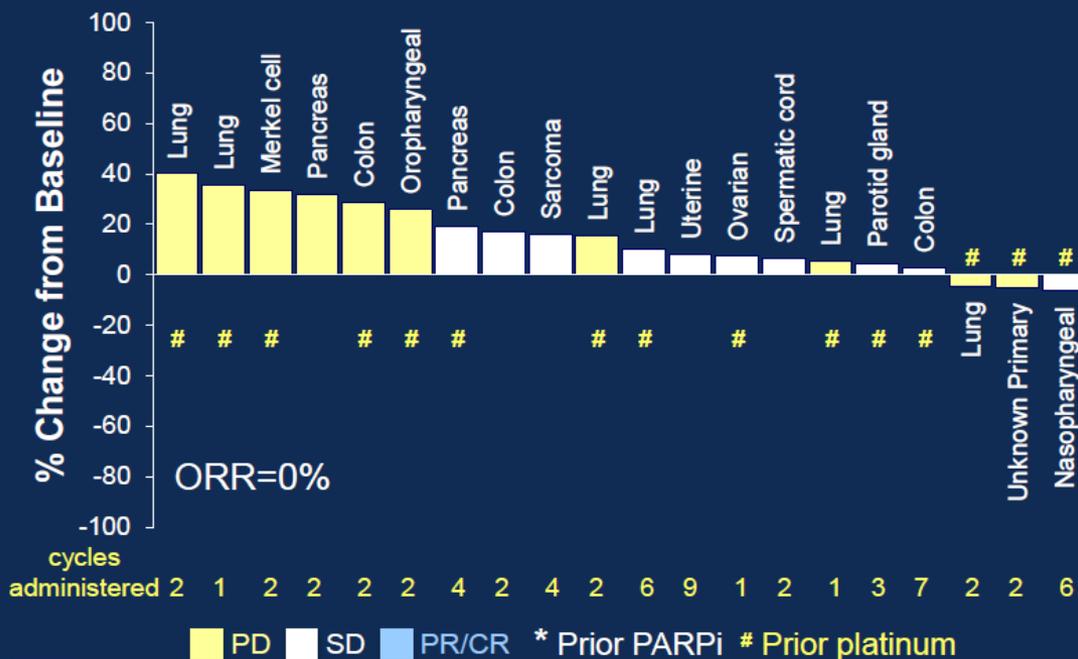
Sapacitabine & Seliciclib Phase 1 BRCA +ve Benefit*

Best Response (all cycles)

Part 1 BRCA carriers



Part 1 Non-BRCA carriers



PRESENTED AT: ASCO ANNUAL MEETING '16

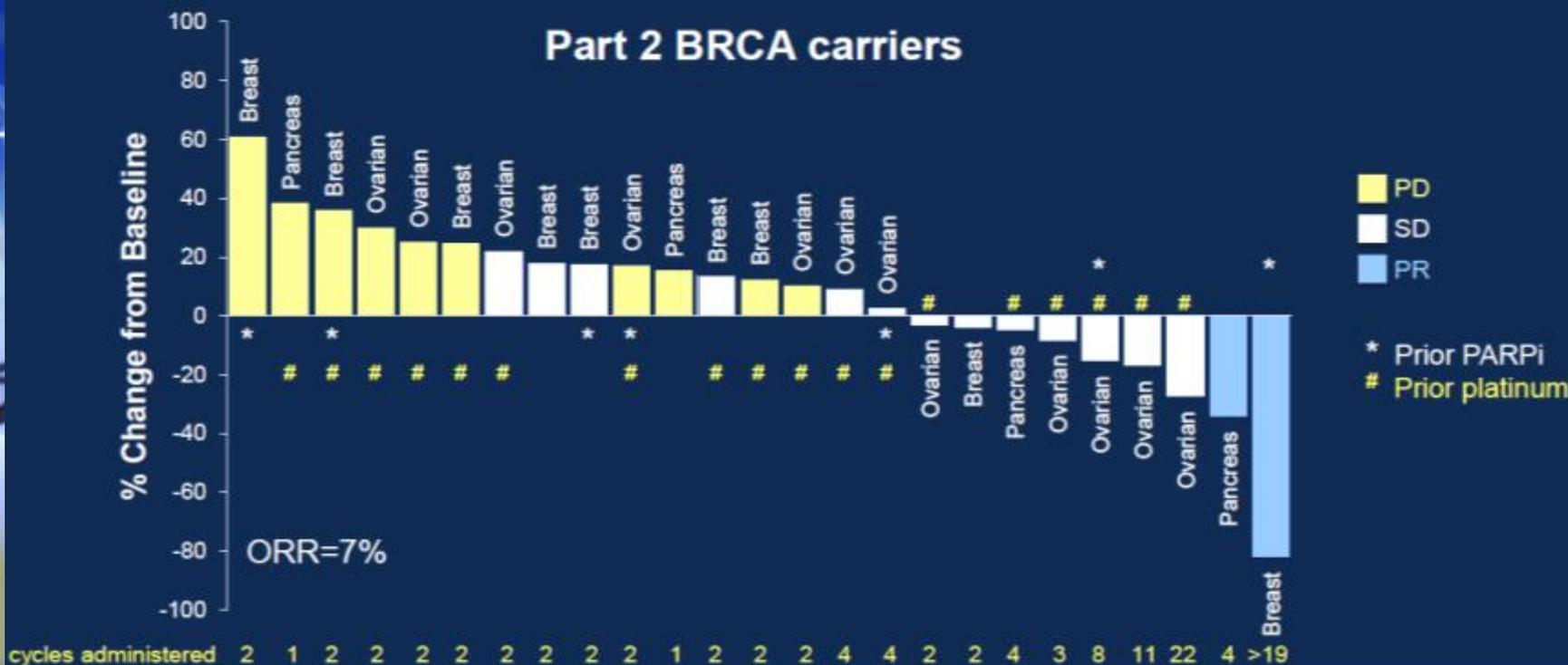
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Sapacitabine & Seliciclib Phase 1 BRCA +ve Benefit*

Best Response (all cycles)



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* Source: Toloney S et al, J Clin Oncol 34, 2016 (suppl; abstr 2503).



CYC065 CDK Inhibitor Overview

Intravenous or oral, potent & selective CDK2/9 inhibitor

Active in:

- Hematological malignancies (AML, MLL-r)
- BRCA /HRD +ve solid tumors; sapacitabine combination
- HER2 +ve solid tumors; trastuzumab combination

Therapeutic strategy: modulation of resistance

Significant market opportunity & unmet medical needs

Source: Cyclacel press releases and data on file.



Cancer Cells are Addicted to Oncogenes

Cancer propagated by:

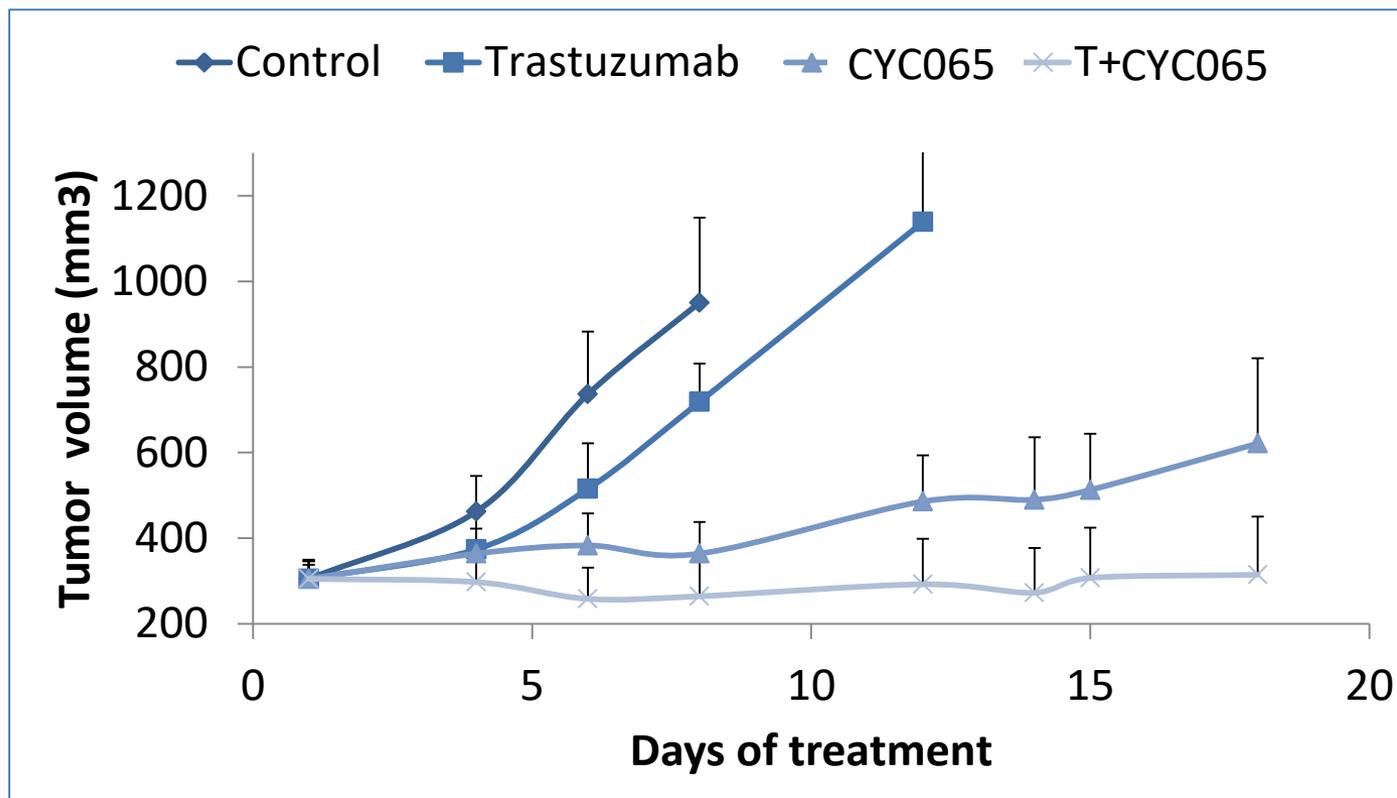
- Inactivation of tumor suppressor genes (i.e. p27, p53);
- Activation of continuously expressed oncogenes required for cancer maintenance (i.e. KRAS, MYC):

➤ ONCOGENE ADDICTION

- Pharmacologic inhibition of oncogenes → **apoptosis or senescence & innate immune response** → cell death

Source: Weinstein I, Science 2002;297:63. Pelengaris S, et al, Cell 2002;109:321. Xue Lowe et al Nature 2007 doi:10.1038/nature05529. Cyclacel data on file.

CYC065 Activity in HER2⁺, Cyclin E-addicted, Trastuzumab-resistant Breast Cancer



CYC065 single agent and in combination with trastuzumab *in vivo* tumor growth inhibition & regression (combination) of BT474R trastuzumab resistant HER2⁺ BC cell line.

Source: Scaltriti et al 2011 PNAS 108 3761



Financial Position & Capitalization

Pro Forma Cash & cash equivalents: \$19.5m¹

Operating cash burn (excludes non-cash items)

✓ 2013: ~ \$18.2m annual²

✓ 2014: ~ \$18.7m annual²

✓ 2015: ~ \$14.5m annual²

✓ 2016: (est.) ~ \$11.0m annual³

Fully diluted shares: ~ 4.6 million⁴

No debt

1. \$18.0m, Sept. 2016 10-Q and \$1.5m, ATM proceeds Oct. 2016 2. 10-K 3. Company estimate. 4. Sept. 2016 10-Q; common stock outstanding: 4.3m.



Key Catalysts

- Sapacitabine SEAMLESS: topline data readout and determination of submissibility
- Pre-submission regulatory consultations
- Sapacitabine & seliciclib solid tumors updated data
- Sapacitabine MDS combination after HMA failures
- CYC065 (CDK) First-in-Human Phase 1 study data



Investment Thesis

1st oral, low intensity Rx for elderly AML

Novel clinical & labeling strategy

Large market size + line extensions

**Transcriptional CDKi oncology program
with two promising clinical agents**

Thank you for your support

ir@cyclacel.com

