



CYCLACEL

Translating cancer biology into medicines

NASDAQ CYCC September 2017

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- Apply deep understanding of cell cycle biology to disrupt
 - a. cancer cell **resistance**
 - b. **DNA repair** or evasion
- Pioneer in Cyclin Dependent Kinase inhibitors
- Focus on molecularly-defined patient populations
- Rationally designed clinical programs in solid and blood cancers
- Experienced management
- Estimated capital through YE 2019

Development Pipeline



Program	Target/Indication	Preclinical	Phase 1/1b	Phase 2	Phase 3 or pivotal	Commercial Rights
CYC065 iv and oral CDK2/9 inhibitor	Solid tumors (FiH)	RPh2D				Worldwide
	Mcl-1 ↑ RR CLL ± Bcl inhibitor	CYC065+venetoclax RR CLL				
	Cyclin E Ovarian,breast, etc.	CYC065	Ovarian			
	DDR*: BRCA+ve Breast,ovarian,pancr.	CYC065 + sapacitabine				
	DDR*: BRCA+ve Breast,ovarian,pancr.	+ PARPi				
sapacitabine nucleoside analogue	DDR*: BRCA+ve Breast,ovarian,pancr.	sapacitabine + seliciclib				Worldwide (except Japan)
	AML unfit for chemo, ≥ 70y	Data Analysis				
CYC140 PLK1 inhibitor	Solid and blood cancers	IND-ready	Ph1 FIH			
Investigator sponsored trials (IST)	Seliciclib (CYC202)	Cushings disease, RA, cystic fibrosis				Worldwide
	CYC065 MYCN amplified	CYC065	Neuroblastoma			
	CYC065 MCL-1 ↑	CYC065	MLL-r leukemias			

Current status

Planned studies

Data Dependent

* DDR=DNA Damage Response

Cyclin Dependent Kinase Inhibitor Transcriptional Regulation Program

2001 Nobel Prize for Physiology & Medicine culminating in approved Rx

Paradigm-shift in breast cancer: CDK4/6i-based combinations with AI

- IBRANCE® (palbociclib, PFE, approved 2015, ~\$2.1bn 2016 sales)
- KISQALI® (ribociclib, NVS, approved 2017)

CYCC's CDK2/9i strategy: overcome **resistance** via regulating transcription

- Seliciclib 1st Gen, signals of anticancer activity (Ph 2)
- CYC065 2nd Gen, more potent, better profile than seliciclib (Ph 1)

- CDK4/6 inhibitors → senescence → eventually resistance
- In many cancers resistance correlated with:
 - ↑ expression of pro-survival proteins (Bcl-2, Bcl-XL, **Mcl-1**, etc.) and/or
 - addiction to oncogenes (incl. **MYCN**, **cyclin E** amplification)
- First Bcl-2 inhibitor: venetoclax (ABBV, for CLL, does not ↓ Mcl-1)
- Competitive race to develop Mcl-1 inhibitors
- CYC065:
 - *1st CDKi to ↓ Mcl-1 in patients with signals of clinical benefit*

* Source: Cyclacel data on file.

n=24 heavily pretreated patients with advanced solid tumors

- Determined safety, DLT, PK in 7 DL, est. RP2D; DL7 MTD reversible neutropenia
- Treated n=10 in DL6 cohort
- Demonstrated target engagement and consistent **Mcl-1 suppression** over 24h after single dose in 7/9 evaluable DL6 patients
- Anticancer activity observed in 3 patients with:
 - **Mcl-1 ↑ ovarian tumor,**
 - **Myc ↑ laryngeal cancer, and**
 - **cyclin E / Mcl-1 ↑ amplified ovarian tumor**

Hematological malignancies:

- 1 Combination with **venetoclax**, i.e. relapsed/refractory CLL (Mcl-1 ↑)

Solid tumors:

- 2 Selected Cyclin E ↑ solid tumors, i.e. breast, uterine (USC)
- 3 Selected Mcl-1 ↑ solid tumors, i.e. ovarian

CDK4/6 isoform

palbociclib (PFE) ribociclib (NVS) Approved in combination with letrozole for ER +ve Her2 -ve advanced or met BC ~

abemaciclib (LLY) Ph3

trilaciclib (GTHX) Ph1/2

CDK2/9 transcriptional isoform

CYC065 (CYCC 2G) Ph1 completed

seliciclib (CYCC 1G) Ph2

dinaciclib (pan CDK, MRK) Ph3

BAY1143572 (CDK9, BAY) Ph1

Other (pan CDK or selective):

SY1365 (CDK7, Syros);

voruciclib (CDK4/6/9, MEI Pharma)

DNA Damage Response (DDR) Clinical Program

DNA Damage Response (DDR):

Overcoming Cancer DNA Repair & Evasion



Cancer cells evolve, eventually becoming immortal by blocking DNA repair

SoC for HR deficient cancers (incl. BRCA1, -2): PARP inhibitors in ~ 50% of patients

CYCC DDR strategies:

- CYC065 CDKi: modulate DNA repair via HR, NHEJ, etc. pathways
- ↓ expression of HR DNA repair genes (BRCA1 and BRCA2)
- Sapacitabine best clinical data: in BRCA +ve patients with various cancers

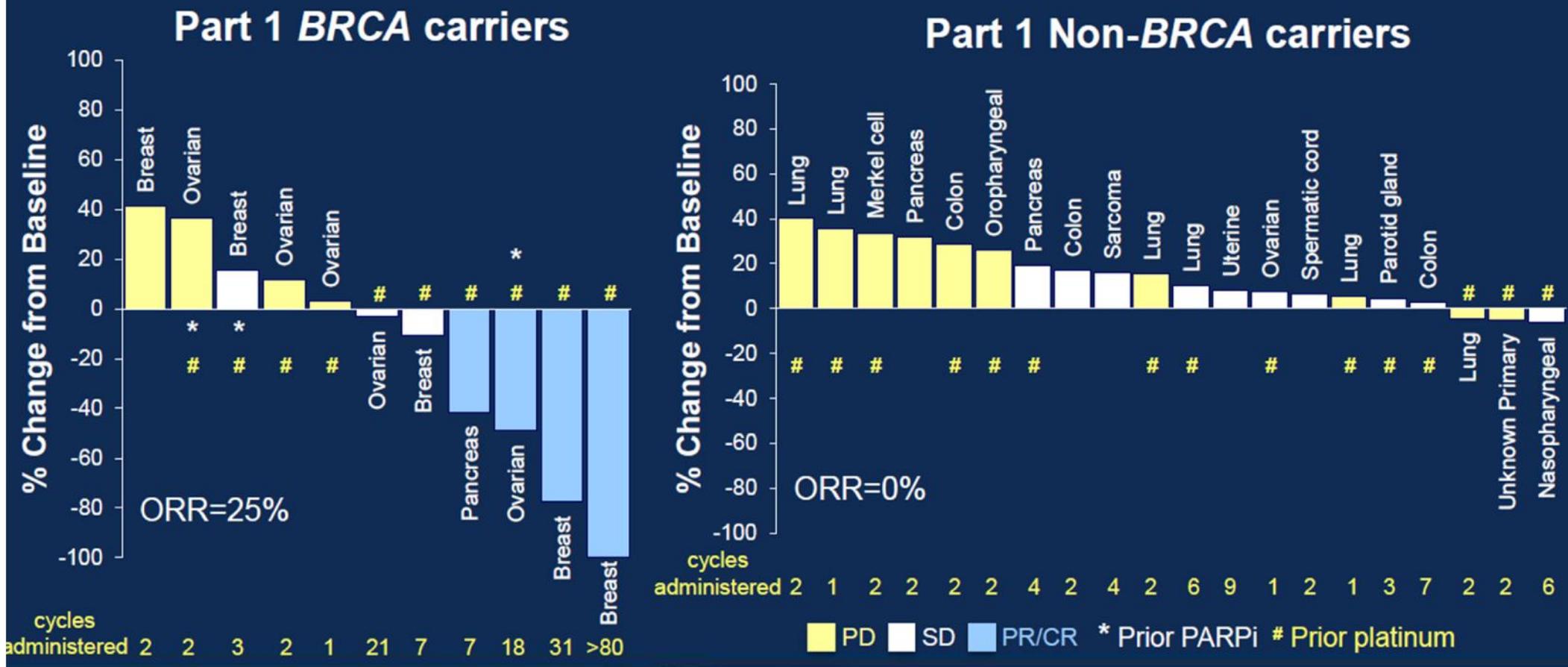
Clinical translation possibilities:

- Single agent in sensitive cancers
- Combinations with SoC

RECIST Evaluable BRCA Carriers

Cancer	Best Response	Prior Treatment	Total cycles
<i>Part 1</i>			
<i>(n=16)</i>			
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
<i>Part 2</i>			
<i>(n=28)</i>			
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

Best Response (all cycles)



PRESENTED AT: ASCO ANNUAL MEETING '16

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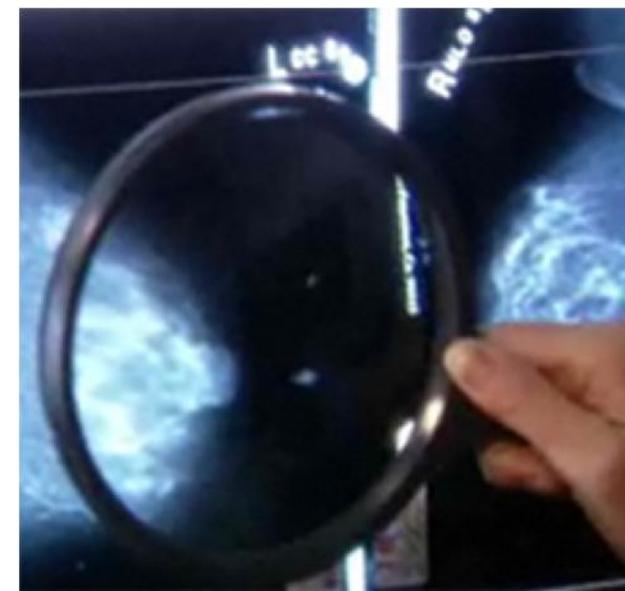
* Source: Tolaney S et al, JCO 34, 2016 (suppl; abs. 2503).

DDR: Rational combo of sapacitabine + CDK2/9 inhibitor

*Activity in HR-repair deficient tumors **



- All-oral regimen, complementary mechanisms:
sapacitabine's dual MoA of DNA SSBs[#] and cell cycle arrest plus CDKi modulation
- Parts 1 & 2 durable clinical benefit (PRs & prolonged SD) in patients with BRCA +ve:
breast, ovarian, pancreatic cancers
- Part 3 to start: revised schedule including BRCA +ve ovarian, pancreatic cancer patients



Potential line extensions with CYC065 in lieu of seliciclib



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

Sapacitabine in AML

Sapacitabine in AML (SEAMLESS Ph 3 data)

Optionality from potential regulatory submission



- ✓ Increase in median OS (primary endpoint) did not reach stat sig
- ✓ Doubling of CR rate (secondary endpoint)
- ✓ Improved median OS in large (2/3 of study) prospectively defined subgroup based on WBC level
- Karyotype analysis in progress followed by final analysis
- Determine submissibility to regulatory authorities
- Pre-submission End of Phase 3 meetings

Source: Cyclacel press releases and data on file.

Financials

June 30, 2017 *pro forma* cash & cash equivalents: \$27.4m¹

Current Operating cash burn (excludes non-cash items)

- ✓ 2014: ~ \$18.7m annual²
- ✓ 2015: ~ \$14.5m annual²
- ✓ 2016: ~ \$10.1m annual²
- 2017: ~ \$ 8.0m annual³

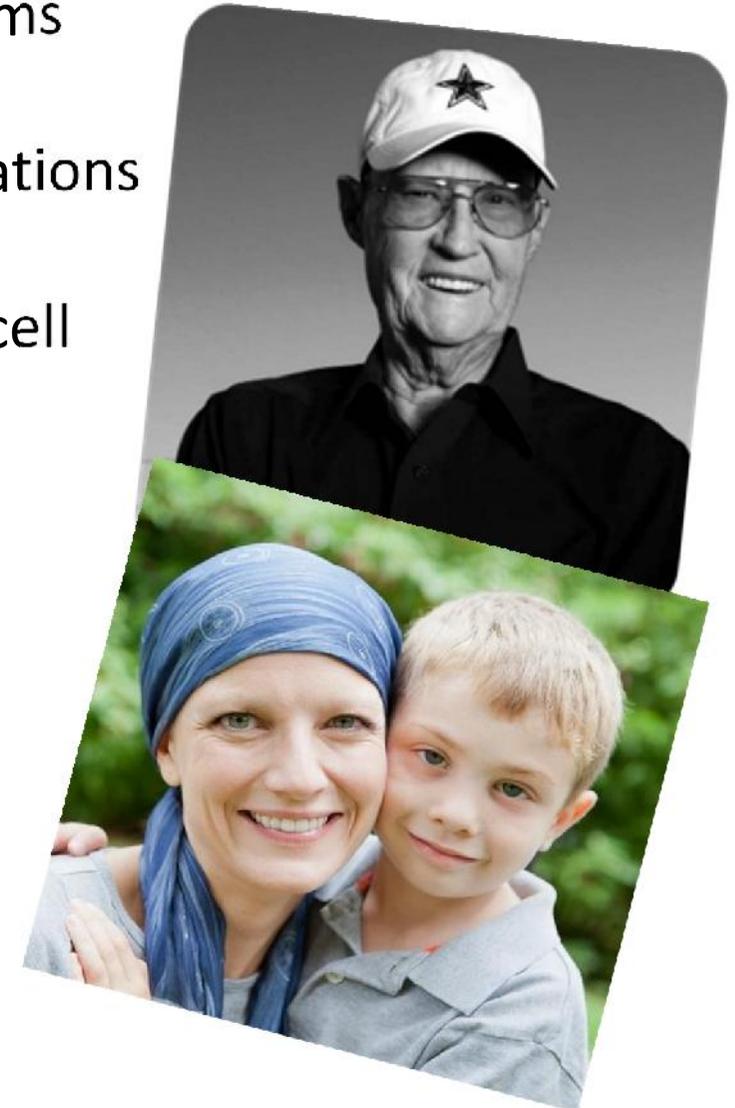
Fully diluted shares: ~ 20.0 million^{1,4}

No debt

1. Cyclacel press release
2. 10-K
3. Company estimate
4. Common stock outstanding: 11.4m

Investment Thesis

- Clinical stage CDKi and DDR oncology programs
- Targeting molecularly-defined patient populations
- Treat difficult cancers and overcome cancer cell resistance & DNA repair
- CDK inhibitors: validated drug class
- Competitively positioned
- Significant market opportunities



Key Milestones



- Start CYC065 Ph 1b in RR CLL combo with venetoclax
- Sapacitabine/selaciclib update BRCA +ve breast cancer
- Start Part 3 in BRCA +ve cancers beyond breast
- CYC140 (PLKi) IND submission
- CYC065 Phase 1 data solid tumors
- Sapacitabine SEAMLESS determine submissibility

THANK YOU

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