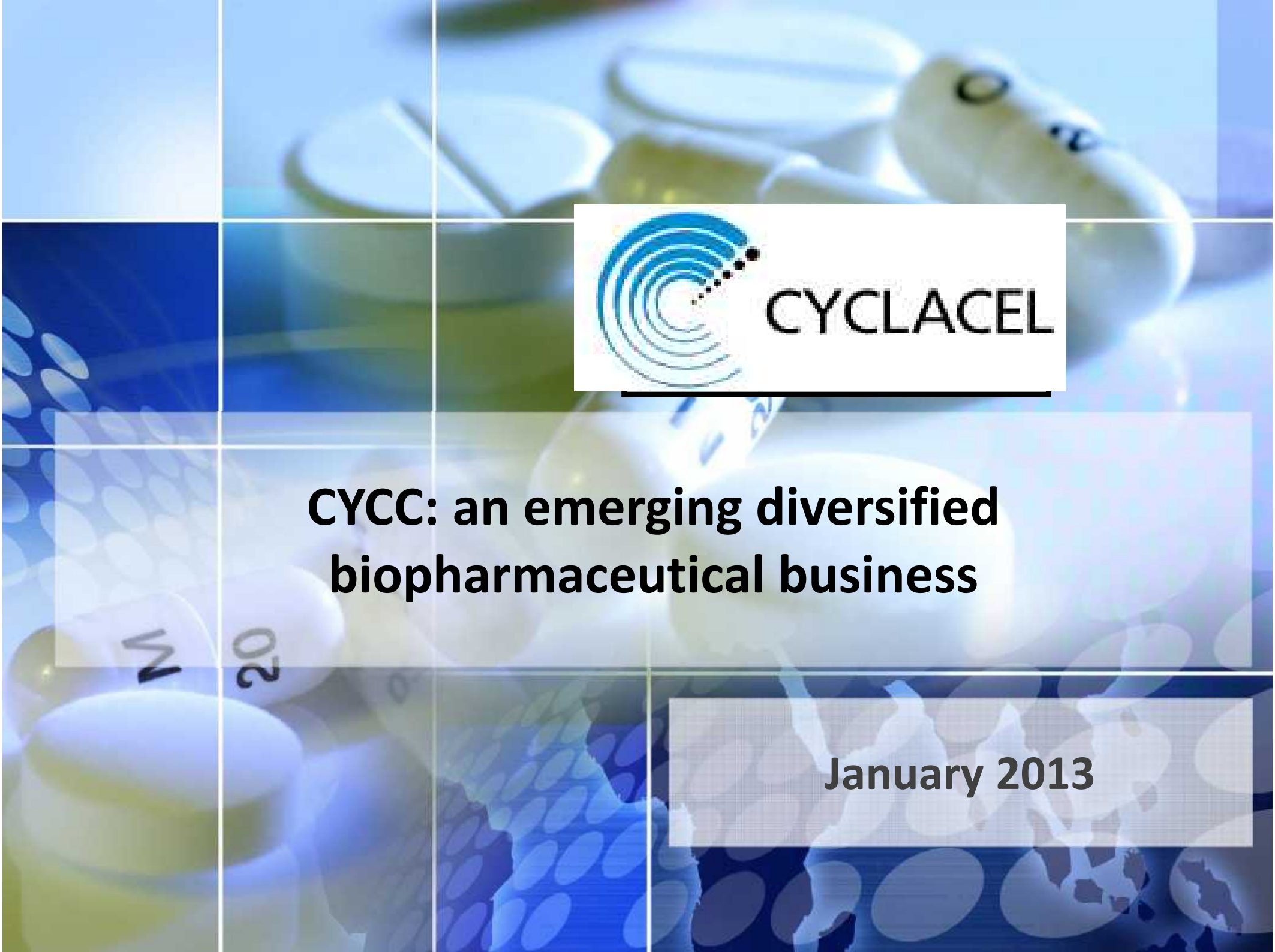


# CYCC: an emerging diversified biopharmaceutical business

January 2013

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# The Case for Sapacitabine

**Oral; well tolerated / Multiyear maintenance dosing achieved**

**Differentiation / High competitive barriers to entry**

- Convert AML → chronic disease

**Significant market opportunity / Large unmet medical need**

- Front-line AML (SEAMLESS registration Ph. 3 under SPA)
- 2nd line MDS after hypomethylating agents
- Solid tumor activity in HRR-defective patients incl. BRCA

**Exclusivity / Robust IP position**

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# AML: no Frontline Drugs since 1969

*Mortality ↑↑ with age. Worst prognosis as age ≥ 70 years:*

- Intensive chemotherapy O.S.: ~ 4.6 months *
- Low-dose chemotherapy O.S.: ~ 5.0 months †
- Best Supportive Care O.S.: ~ 3.6 months ◊

*Heterogeneity: prior AHD, cytogenetics, fit vs. unfit, comorbidity*

Typical treatment duration for ara-C i.v. regimens: < 2 cycles

Need new durable activity drugs to drive improved Hazard Ratios in order to impact survival

***…Our solution: sapacitabine oral capsules …***

** Kantarjian, et al, Blood, 2010. † Burnett, et al, Cancer, 2007. ◊ Harousseau, et al, Blood 2009.*

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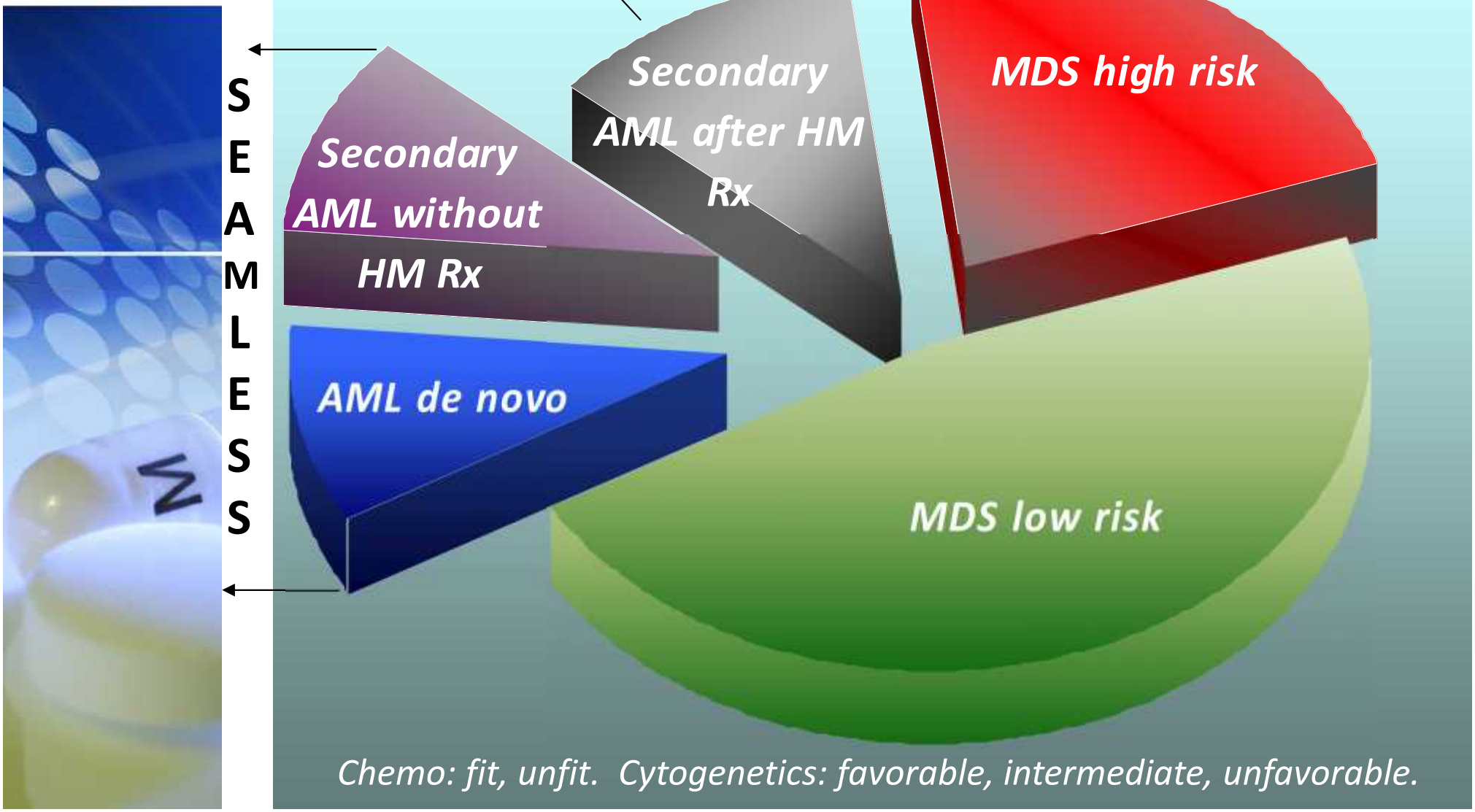
# AML/MDS: Heterogeneous Diseases




SEAMLESS

* *Source: ACS SEER and Cyclacel-commissioned primary market research.*

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# AML/MDS: Threading the Needle

*Most elderly patients unable to sustain intensive chemotherapy*

Single agent therapy given metronomically may be suboptimal

Inducing CR may impede recovery of normal cell counts

CR does not predict for survival

*New drugs must:*

- Ablate blast levels
- Spare normal cells
- Allow count recovery and
- Achieve long treatment duration

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# AML Unmet Medical Need

*Est. **16,000** US prevalence; 12,950 US incidence 2011**

***50% ≥ 70 yrs.**; 66% ≥ 60 yrs.; median age: ~ 67*

| *Treatment* | *Fit for Intensive Chemo* | *Unfit/Refused Intensive Chemo* |
|---|---|---|
| Front line | 7 + 3 | *Clinical trial* **Sapacitabine** |
| Relapsed/ Refractory | *Clinical trial* | *Clinical trial* |

** Source: ACS SEER and Cyclacel-commissioned primary market research. Sapacitabine Phase 2 data on file.*

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# Sapacitabine AML/MDS studies

***> 500 patients already treated across all studies and disease types***

| Study | Preclinical | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|
| AML: Front-line ≥ 70 yrs. n=485 | SEAMLESS RCT | | | |
| AML: Combination with decitabine ≥ 70 yrs. n=46 | SEAMLESS Pilot/Lead-in Single Arm | | | |
| AML: Single agent front-line ≥ 70 yrs. n=105 | Randomized | | | |
| AML: Single agent pre-MDS after HMA failure ≥ 70 yrs. n=60 | Randomized | | | |
| MDS: Single agent refractory to HMAs ≥ 60 yrs. n=63 | Randomized | | | |

** HMAs = hypomethylating agents.*

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# "SEAMLESS" Phase 3 Design

**(Untreated AML: front line; aged ≥ 70 years; n=485)**

- ✓ Design developed in consultation with FDA under a SPA
- ✓ Periodic DSMB reviews & also after 212 events for futility
- ✓ DSMB OK after 119 patients (DEC '12)
- ✓ DSMB OK (OCT '11) *60-day mortality (n=46): 13% vs. FDA hurdle of 37%*
- P = 0.05; HR = 0.725. As of DEC '12 surpassed 130 patients

**A. Alt. sapacitabine + decitabine** (n~243)

***Primary Endpoint: overall survival***

**B. Decitabine** (n~243)

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# SEAMLESS Ph 3 Early Indicators

*Required reduction in risk of death: 27.5%*

A. Sapacitabine/ Decitabine O.S. (n=46): **~ 9.4 months** *

C. Decitabine O.S. (n=95): **~ 6.3 months** †

- *Intensive chemotherapy O.S. (n=446): ~ 4.6 months* ◊

*60-day mortality:*

A. Sapacitabine/ Decitabine: **13%** *

C. Decitabine: **20%** †

- *Intensive chemotherapy: 36%* ◊

** Interim data from pilot, lead-in study of Arm A in SEAMLESS; aged 75 or older; subject to change. ASH 2012, Abs. 2630; 72% aged 75 or older. † Kantarjian, et al, JCO, 2012; aged 75 or older. ◊ Kantarjian, et al, Blood, 2010. Kantarjian et al, The Lancet Oncology, 13:11:1096-1104, 2012. Caveat: cross-study comparison.*

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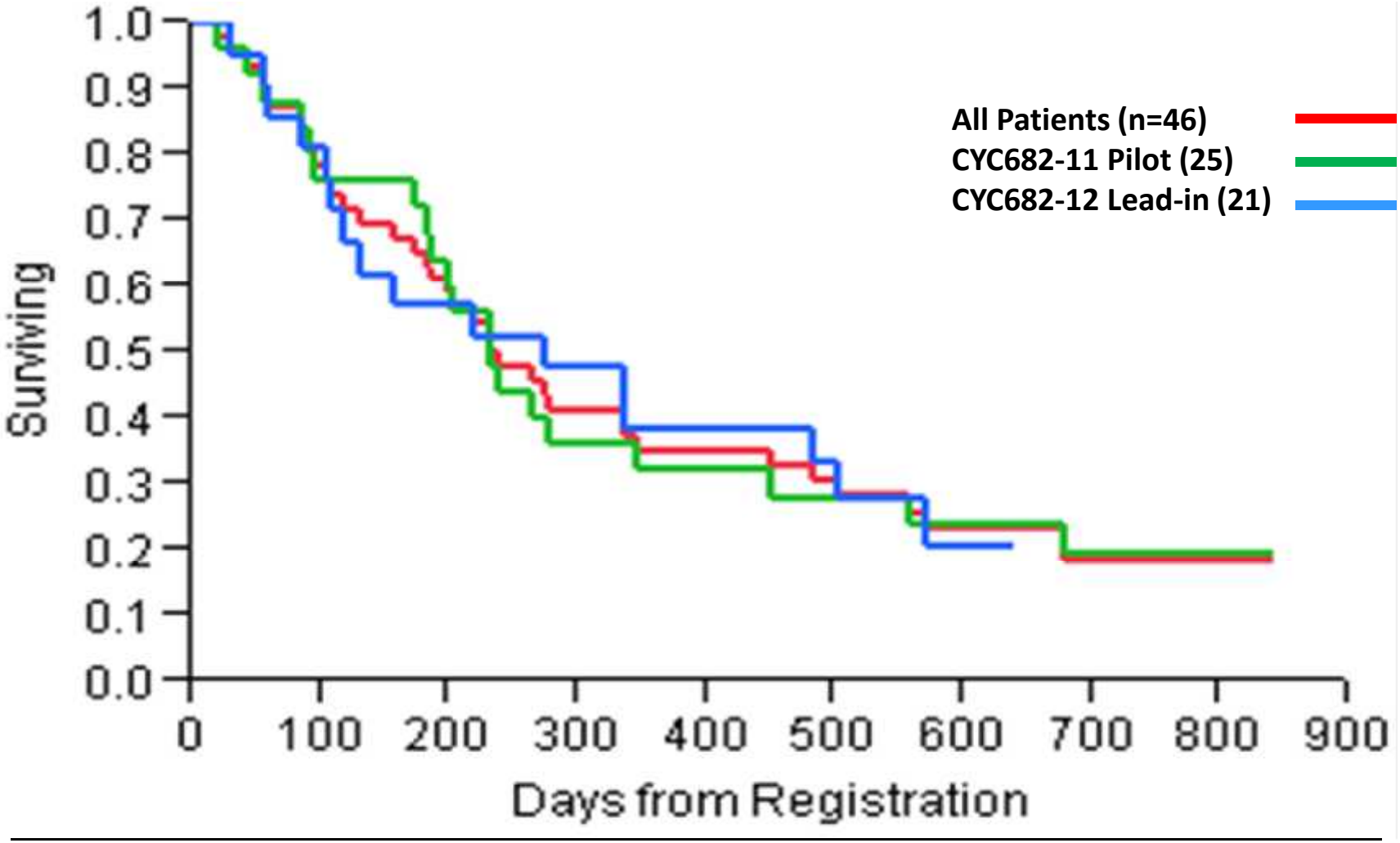
# SEAMLESS Pilot/Lead-in Study

## Kaplan-Meier Survival Plot (n=46)

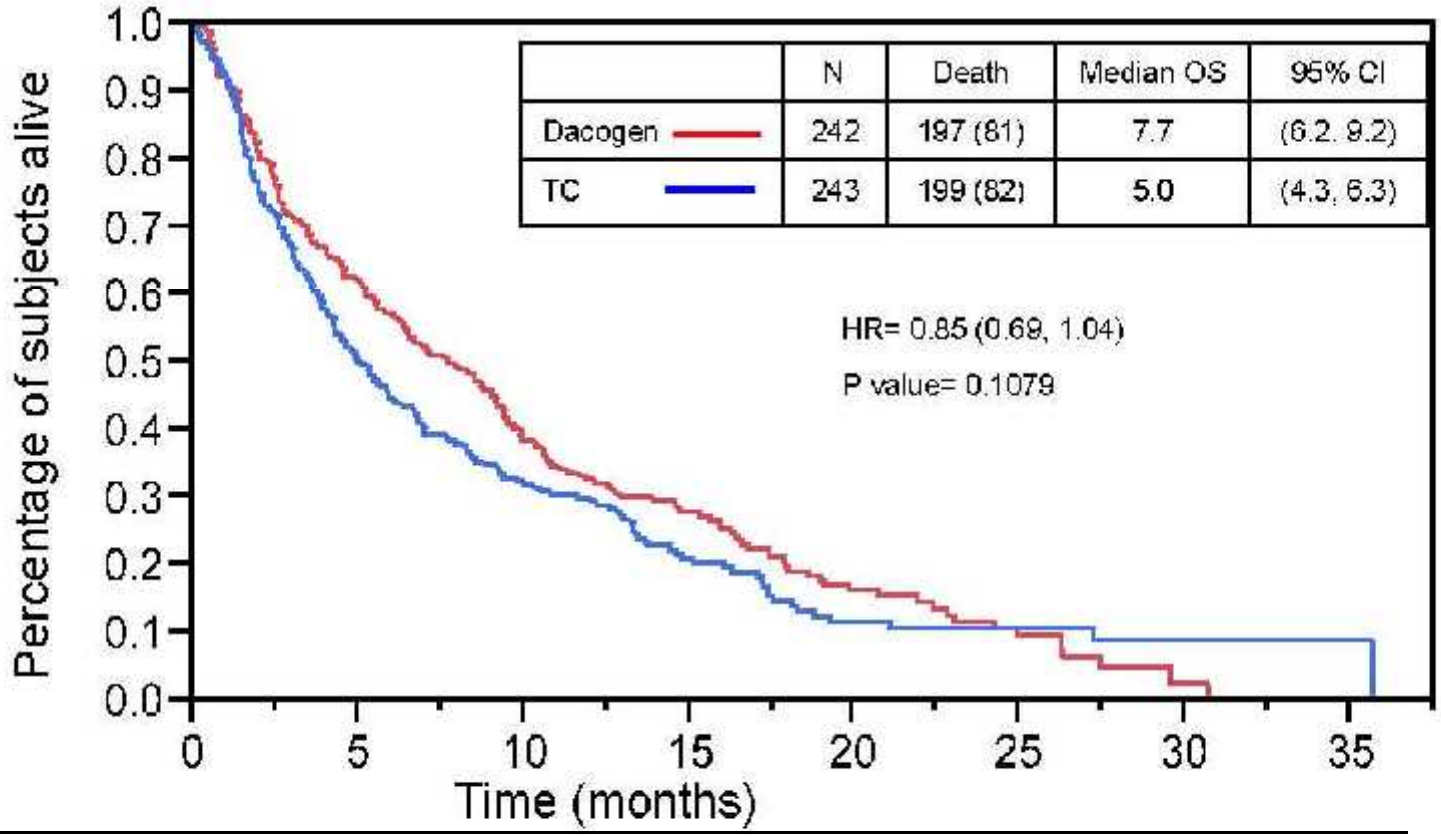



| No. at risk | 3M | 6M | 12M | 18M | 24M |
|---|---|---|---|---|---|
| | 38 (83%) | 30 (65%) | 16 (35%) | 12 (26%) | not reached |

** 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)




| | N | Death | Median OS | 95% CI |
|---|---|---|---|---|
| Dacogen | 242 | 197 (81) | 7.7 | (6.2, 9.2) |
| TC | 243 | 199 (82) | 5.0 | (4.3, 6.3) |

| No. of subjects at risk | | 6M | 12M | 18M | 24M | 30M | 36M |
|---|---|---|---|---|---|---|---|
| Dacogen | 242 | 137 | 65 | 28 | 12 | 1 | 0 |
| TC | 243 | 107 | 55 | 19 | 07 | 4 | 0 |

** Source: FDA Briefing Document, Dacogen ODAC, February 9, 2012.*

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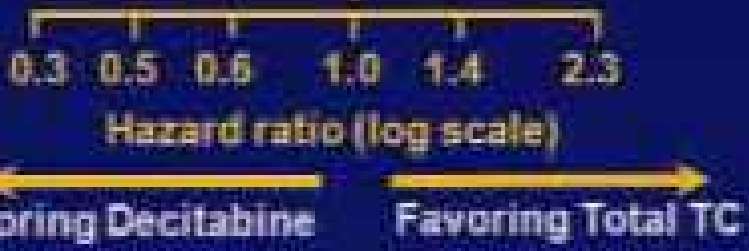
# OS, Exploratory Analysis (CCO 2010)

| Exploratory Subgroup | HR (95% CI | Total TC Event/N | Total TC Median, mo | Decitabine Event/N | Decitabine Median, mo | P |
|---|---|---|---|---|---|---|
| All patients | 0.82 (0.68, 0.99) | 227/243 | 5.0 | 219/242 | 7.7 | .037 |
| Age, years | | | | | | |
| <70 | 1.01 (0.70, 1.45) | 62/70 | 4.9 | 65/71 | 9.1 | .961 |
| 70–74 | 0.79 (0.56, 1.11) | 69/74 | 5.7 | 69/76 | 8.0 | .165 |
| ≥75 | 0.72 (0.54, 0.98) | 96/99 | 4.5 | 85/95 | 6.3 | .035 |
| Type of AML | | | | | | |
| De novo AML | 0.71 (0.56, 0.91) | 149/157 | 5.2 | 137/155 | 8.2 | .006 |
| Secondary AML | 0.92 (0.66, 1.29) | 77/84 | 4.9 | 82/87 | 7.1 | .636 |




CCO=clinical cutoff.

# Landmark Analysis

*Caveat: Cross Study Comparison* *

| *(months)* | *Decitabine (DACO-016) ≥65 yrs, n=242* | *Sapacitabine/ decitabine (SEAMLESS pilot/lead-in) ≥70 yrs, n=46* | *Decitabine (DACO-016) ≥75 yrs, n=95* | *Sapacitabine/ decitabine (SEAMLESS pilot/lead-in) ≥75 yrs, n=33* |
|---|---|---|---|---|
| **Median O.S.** | **7.7 *** | **8.5** | **6.3 *** | **9.4** |
| | | | | |
| **3** | **72%** | **83%** | **-** | **-** |
| **6** | **57%** | **65%** | **50%** | **-** |
| **12** | **32%** | **35%** | **-** | **36%** |
| **18** | **21%** | **26%** | **-** | **-** |
| **24** | **15%** | ***Not reached*** | **-** | ***Not reached*** |

*† Source: ASH 2012 Abs. 2630 and 3623. * Kantarjian et al JCO 2012 DACO-016 Decitabine Ph 3 for Elderly AML.*

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# MDS Unmet Medical Need

*Est. 300K incidence in US & EU in 2008**

***45,000 US Medicare patients (aged ≥65 years) filed claims for MDS in 2003****

| *Treatment* | *Low Risk* | *High Risk* |
|---|---|---|
| 1st line | ***lenalidomide #*** | ***azacitidine#*** ***decitabine*** |
| 2nd line | *Clinical trial* | **Sapacitabine** *Clinical trial* |

*…NCCN guidelines for 1st line hypomethylating agents: **4-6 cycles** …‡*

*Median OS int-2/high-risk MDS after **treatment failure** of HM agents: **4.3-5.6 months**†*

** Source: Cyclacel est. & Golberg, S, et al, JCO, 2010. # Revlimid®, Celgene. Vidaza®, Celgene. & Dacogen®, Eisai. Dacogen and Vidaza are hypomethylating (HM) agents. ‡ NCCN Guidelines MDS v.2.2011 p. 19. † Prebet T, Gore S, et al, JCO 2011; Jabbour E, Garcia-Manero G, et al, Cancer 2010.*

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# MDS: Unmet Need after Frontline Failure

*MDS intermediate-2 and high-risk by IPSS experimental standard of care options after frontline failure:*

- Azacitidine 2nd line: ~ 5.6 months †
- Decitabine 2nd line: ~ 4.3 months †
- Low-dose chemotherapy O.S.: - no data -
- Best Supportive Care O.S.: - no data -

*No maintenance regimen available for HMA responders*

***…Our solution: sapacitabine oral capsules …***

- Sapacitabine 2nd, 3rd, 4th line: ~ 8-10 months *

*† Prebet T, Gore S, et al, JCO 2011; Jabbour E, Garcia-Manero G, et al, Cancer 2010. * Depending on schedule; interim data (unaudited) of an ongoing study, presented at The Eighth Annual Hematologic Malignancies Conference (October 2012).*

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# Sapacitabine Phase 2 MDS Data: 682-06, Part 4

**(MDS: 2nd, 3rd or 4th line; aged ≥ 60 years; n=63) ***

| | *Total (63)* | *Arm G (21)* | *Arm H (21)* | *Arm I (21)* |
|---|---|---|---|---|
| Prior Azacitidine | 30 | 9 | 10 | 11 |
| Prior Decitabine | 15 | 4 | 3 | 8 |
| Prior Aza + Decitabine | 18 | 8 | 8 | 2 |
| Median OS days (# alive) | **252** (14) | **291** (7) | **274** (4) | **227** (3) |
| *Med. OS blasts 10-19%* | ***274*** *(11)* | ***240*** *(6)* | ***307*** *(4)* | ***153*** *(1)* |
| 30-day deaths | 3 | 1 | 1 | 1 |
| 60-day deaths | 8 | 3 | 2 | 3 |
| Received ≥ 6 cycles | 17 | 7 | 6 | 4 |

** Interim data (unaudited) as of October 2012 of an ongoing study, presented at The Eighth Annual Hematologic Malignancies Conference (October 10-14, 2012), Houston, Texas.*

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# Sapacitabine Mid-Stage P2 Data

**AML: 1-year survival = 30%*, median OS ~ 7 months***

- ≥ 70 years; 80% untreated; 20% first relapse; 55% de novo; 45% preceded by AHD, such as MDS

**MDS: 1-year survival=29-35%; CR=7%, median OS ~9 m***

- ≥ 60 years; previously treated: azacitidine (43%); decitabine (34%); both (23%); triple refractory incl. lenalidomide (16%)

**NSCLC: PRs (squamous, undifferentiated)**

**BRCA +ve solid tumors: activity signal including PRs in breast, pancreatic, ovarian cancers**

** Source: Garcia-Manero, G et al, ASH 2009, ASH 2010, ASCO 2012, company PRs and Cyclacel interim data on file.*

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# "LI-1" Phase 2/3 IST Design

**(Untreated AML/high-risk MDS: front line aged ≥ 60 years)**

- ✓ Pick a Winner Program & LI-1 protocols: UK LLR and NCRI
- ✓ Adaptive design: 5 investigational drugs vs. Low-dose ara-C
- ✓ Interim DMEC based on CR; exc. sapacitabine on 1-yr. survival
- ✓ DMEC did not recommend sapacitabine single agent continues

**A. Sapacitabine** (n~55)

***Interim Analysis Threshold: doubling 1-year survival***

**B. Low-dose cytarabine** (n~55)

** Source: [http://www.controlled-trials.com/ISRCTN40571019](http://www.controlled-trials.com/ISRCTN40571019) and investigator communication.*

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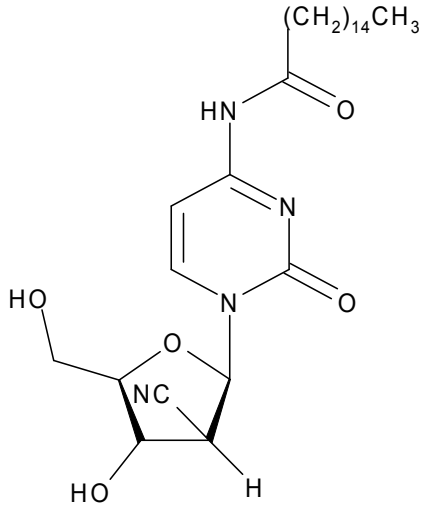
# Changing the Paradigm

*"Sapacitabine is one of the most exciting drugs in development for AML since cytarabine, the current standard of care."* †

**Hagop Kantarjian, M.D.**
**Chairman & Professor, Leukemia Department**
**The University of Texas M D Anderson Cancer Center**




† *Source: CYCC Analyst Note 11/07, Lazard Capital Markets.*

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# Sapacitabine Exclusivity

Potentially first front-line AML drug in > 40 years

Long Patent Life to 2027 (recent US patent to 2030)

Orphan designation in US & EU for both AML & MDS

Ph 2 responders: median # cycles = 12; O.S. = 525 days

Maintenance potential with an oral drug

*Source: Kantarjian et al, The Lancet Oncology, 13:11:1096-1104, November 2012.*

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# Nucleoside Analogue Landscape

***Ara-C (cytarabine), Clolar®, Dacogen®, Vidaza®***

- Approved for AML, MDS, pediatric ALL
- i.v. administration
- ~$850 million in 2011E
- No activity in solid tumors

***Gemzar® (gemcitabine)***

- Approved for bladder, breast, NSCLC, ovarian, pancreas cancer
- i.v. administration
- ~$1.6 billion in 2010E
- No activity in leukemia

***Sapacitabine is unique among nucleoside analogues as it is orally active in <u>both</u> hematological malignancies and solid tumors***

** Trademarks: Clolar®: Genzyme; Vidaza®: Celgene; Dacogen®: Eisai, Gemzar®: Lilly.*

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# 2013 Key Milestones

*Sapacitabine*

- SEAMLESS Phase 3 enrollment update
- Next periodic DSMB review of SEAMLESS
- Updated Phase 2 data in MDS after HMAs
- Registration plan for MDS after HMAs
- Updated Phase 1 data sapacitabine & seliciclib in patients with solid tumors

*Other*

- Markman hearing on romidepsin IP litigation

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# CYCC Business Overview

**Novel, cell cycle biology-based, oral drugs for cancer**

**Sapacitabine pipeline within a drug:**

- AML, MDS, HRR-defective solid tumors (incl. BRCA carriers)

**Pipeline of other orally available, cell cycle modulating drugs:**

- CDK (seliciclib, CYC065), Aurora and PLK inhibitors

**Experienced management team associated with development & commercialization of several novel drugs**

**Cash through 2014 (~ $18 million SEP ’12 #)**

*# Source: 10-Q company filing Q3 2012.*

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# Sapacitabine Differentiation

Only oral drug in Front-Line AML; well tolerated

Only Rx being tested in patients aged ≥ 70 years

Ph 3 based on Ph 2 random. survival & SPA with FDA

MoA: Homologous Recombination Repair pathway

Paradigm shift: convert AML → chronic disease

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# Cyclacel Pharmaceuticals

*Cell cycle pioneers*

*Improving patient lives*

*With orally-available*

*Innovative medicines*

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