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Celgene Global Health
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The Challenge of Early phase clinical trials For new Cancer Drugs

Joseph S. Camardo, MD. FCPP

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This presentation does not represent an official view of Celgene Corporation

The presentation was developed by Dr. Camardo with help from a colleague, Dr. Jay Feingold, a pediatric hematologist who is Chief Medical Officer for ADC Therapeutics.

Journey of 1000 miles…

- Anti-Tumor Activity is a common observation in Early Trials
  - ✓ Patients are almost always the first study subjects
  - ✓ Sometimes a dramatic response observed in only one or two patients
- Clinical Failure in Phase 3 is also common
  - ➢ Did the drug fail?
  - ➢ Did the trial fail?
  - ➢ Did we misinterpret the early data?

Cancer drugs do not fit the "Tradition"

"Traditional" Development

→Favors Certainty Over Timeline

Generally phase 1,2,3

There are generally Other Good Drugs available

Oncology Development

→ Favors Timeline over certainty

Accelerated Approval is common

ALWAYS a more immediate need

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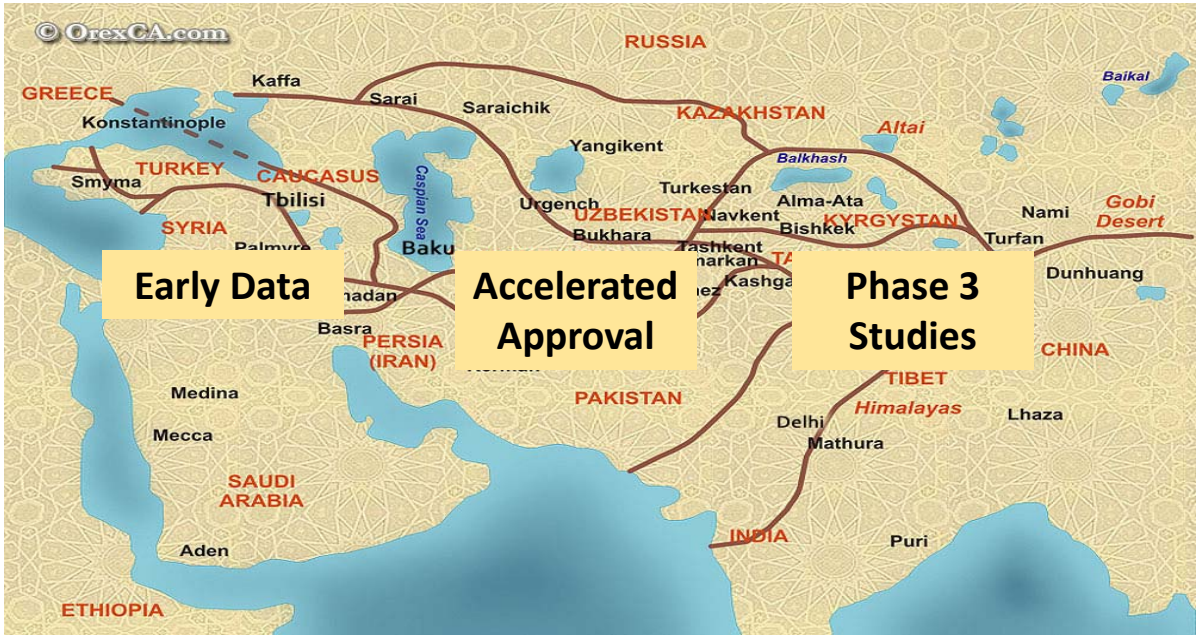
The Long Road

Traditional – Limited Access Highway →



← Oncology – Silk Road

What We Want from Clinical Trials

- Statistically Significant (credible, plausible) Clinical (patient) benefit
  - Improvement compared with a reference treatment
    - Remission, Delay in Recurrence, Improved Survival
- Defined Dose to balance safety and efficacy
  - A Dose Range study showing a dose/response
- Safety
  - Sufficient number of patients to make an estimate of safety risk

What We (usually) Have at "Phase 2"

- Single Arm Study with Surrogate or Comparative Study with limited power
  - Tumor size: Scans and Blood Tests
  - Correlates of uncertain validity (especially for solid tumors)
- Insufficient information about the dose
  - We often favor a high dose
- Insufficient information about Safety
  - Especially for an untested novel drug and target

Drug Development Versus Medical Practice

Doctors often make decisions based on limited, incomplete and sometimes misleading observations

Scientists want complete data, rigorous controls, replicable results, and a “big” effect

Does “art” of medicine have a place in drug development?

How do we make decisions on the Silk Road

Target and Biological Plausibility
Critical and Complete Literature Review
Insight from advisors not involved in the program
Clinical view of treating physicians who enrolled patients

Review of data by the company doctors and scientists

- Pay attention to “stable disease”, does it mean anything?
- Don’t be misled by a Kaplan/Meier Curve that is too good to be true
- Use statistics carefully, easy to be misled in a small study
- Be careful with randomization imbalance
- Evaluate subgroups but be skeptical of good results
- Be conservative with choice of phase 3 population
- Pay attention to small safety signals

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Some history…

Medicines Lost

✓Brivanib

✓Figitumumab

✓MAGE-3

✓Allovectin

Medicines Rescued

✓Iressa

✓Mylotarg

✓CC-223

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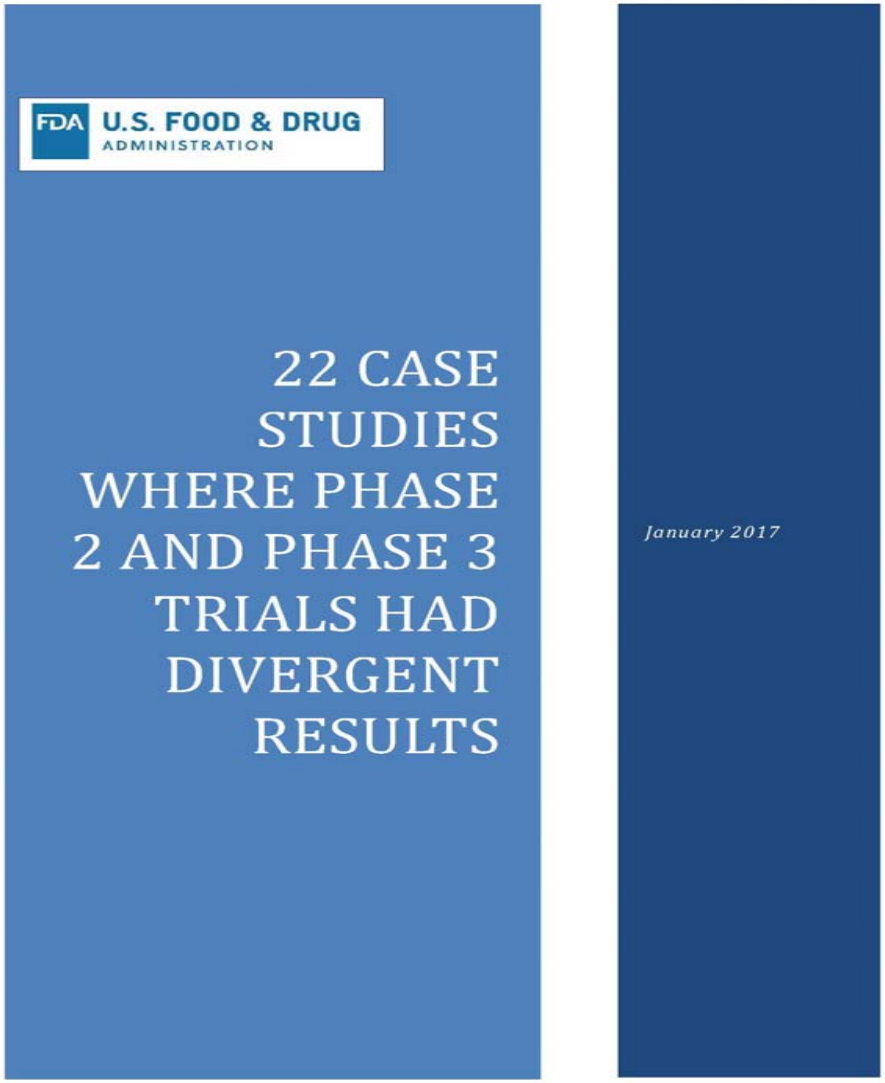


https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf

Summary

To better understand the nature of the evidence obtained from many phase 2 trials and the contributions of phase 3 trials of drugs, vaccines and medical devices, FDA studied 22 recent cases in which promising phase 2 clinical trial results were not confirmed in phase 3 clinical testing. Phase 3 studies did not confirm phase 2 findings of effectiveness in 14 cases, safety in one case, and both safety and effectiveness in seven cases. These unexpected results could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes.

These case studies demonstrate that large phase 3 randomized controlled trials can generate critical evidence across all types of products, patients, and diseases. Both safety and efficacy failures occurred even when the phase 2 studies were relatively large, and even when the product was already approved for another condition. In some cases, the phase 3 study revealed that short-term results found in the phase 2 study were not associated with a long-term benefit or that the product had toxicity that was not uncovered in the phase 2 study.

Brivanib: Growth Factor Inhibitor

Phase 2: 55 patients with advanced Hepatocellular Carcinoma previously untreated
CT/MRI showed one complete response, three partial responses, 24 stable disease
Second cohort: 46 patients who failed sorafenib (intolerance): two partial responses, 19 stable disease

Phase 3: 1100 patients with no prior treatment, randomized to brivanib or sorafenib
Median survival 9.5 months (B) 9.9 months (S): did not meet non-inferiority objective

395 patients previously treated with sorafenib randomized to B or placebo
No improvement in survival
Unknown results from third phase 3

Adjuvant treatment to chemoembolization: terminated with no improvement in survival

Allovectin: Intralesional HLA-B7/beta 2 microgloblulin plasmid with cationic lipids

Phase 2: 77 patients at 16 centers

7 patients with complete or partial response, 4.8 months duration

Phase 3: 390 patients Failed to demonstrate statistically significant improvement compared with first-line chemotherapy for objective response rate (ORR), or survival

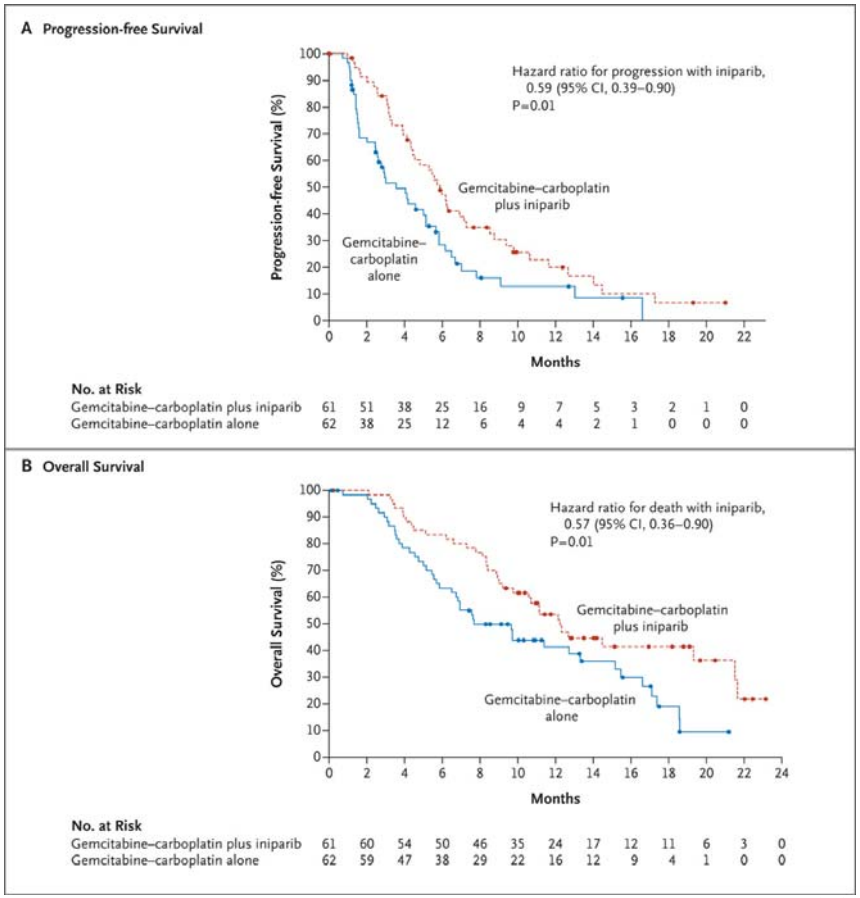
Iniparib: The Fairy Tale Dream Comes to an End

Phase 2: 123 patients with triple-negative breast cancer randomized to gemcitabine/carboplatin (GC) with (GCI) or without (GC) addition of iniparib
Extension of Progression-Free Survival (PFS) from 3.6 to 5.9 months
Extension of Overall Survival (OS) from 7.7 to 12.3 months (p=significant)

Phase 3: Open trial of 519 patients randomized to GC or GCI
NO difference for OS (HR .88)
NO difference for PFS (HR .79, did not meet criteria for significance)

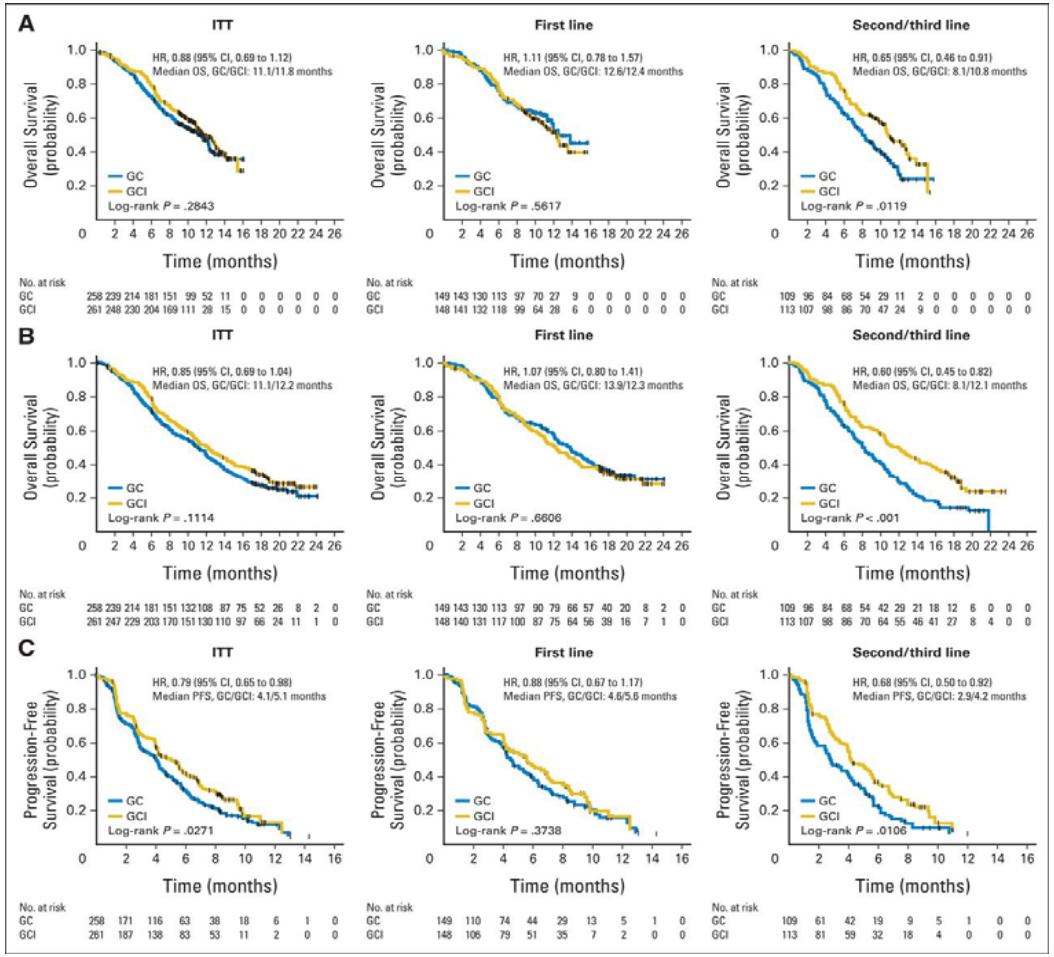
Authors: Crossover Design, Confounding Variables

Kaplan–Meier Estimates of Progression-free and Overall Survival Rates, According to Treatment Group.



O'Shaughnessy J et al. N Engl J Med 2011;364:205-214.

Fig 2. Kaplan-Meier curves of overall survival (OS) and progression-free survival (PFS) with 50% (primary analysis; A and C) and with 70% (updated analysis; B) of survival events. GC, gemcitabine and carboplatin; GCI, gemcitabine, carboplatin, and iniparib; HR, hazard ratio; ITT, intention to treat.



Published in: Joyce O'Shaughnessy; Lee Schwartzberg; Michael A. Danso; Kathy D. Miller; Hope S. Rugo; Marcus Neubauer; Nicholas Robert; Beth Hellerstedt; Mansoor Saleh; Paul Richards; Jennifer M. Specht; Denise A. Yardley; Robert W. Carlson; Richard S. Finn; Eric Charpentier; Ignacio Garcia-Ribas; Eric P. Winer; *Journal of Clinical Oncology* **2014,** 32, 3840-3847.
DOI: 10.1200/JCO.2014.55.2984

Figitumumab (IGF-1R Inhibitor)

Phase 2:

Higher ORR with addition of Figitumumab to carboplatin and paclitaxel, compared with carboplatin and paclitaxel in patients with Non Small Cell Lung Cancer

Phase 3:

1264 patients with Non Small Cell Lung Cancer
Figitumumab added to standard regimen showed trend toward **decreased overall survival and increased number of adverse events.**

Phase 2 paper was retracted because procedure for tumor measurement was not followed

Tumor reduction not confirmed
Corrected data showed a LOWER response rate from Phase 2

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MAGE: Non Small Cell Lung Cancer (post surgery)

Phase 2: MAGE-A3-positive lung tumors (resected)

182 patients randomized to vaccine or placebo

Improvement in Disease-Free survival (DFS) and Overall Survival

Phase 3: MAGRIT

2,272 patients with resected MAGE A3 positive lung cancer, randomized to Vaccine or placebo on same dose/schedule as phase 2

DFS 60.5 months compared with 57.9 months (NS)

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Some history…

Medicines Lost

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Medicines Rescued

✓Iressa

✓Mylotarg

✓CC-223

Iressa: (gefitinib, EGFR inhibitor)

Early Studies: Dramatic anti-tumor effects in about 10 percent of patients

- Accelerated Approval based on Overall Response
- Failed to confirm clinical benefit (PFS or OS)
- Withdrawn in US

Translational research showed that patients with a response to gefitinib

- had identifiable mutations of the EGFR
- most of these mutations occurred in patients from Asia (Japan)

<u>This was an early and critical example of the role of a mutation in the response to a specific targeted therapy</u>

Iressa: (gefitinib, EGFR inhibitor)

Additional Phase 3 Studies were completed in patients with EGFR mutations associated with response to gefitinib

IRESSA submitted for review and approval

IRESSA Approved for:

first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors harbor specific types of epidermal growth factor receptor (EGFR) gene mutations, as detected by an FDA-approved test.

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EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

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Sean Tracy,1 Heidi Greulich,1,2 Stacey Gabriel,4 Paula Herman,1
Frederic J. Kaye,5 Neal Lindeman,6 Titus J. Boggon,1,3
Katsuhiko Naoki,1 Hidefumi Sasaki,7 Yoshitaka Fujii,7
Michael J. Eck,1,3 William R. Sellers,1,2,4†
Bruce E. Johnson,1,2† Matthew Meyerson1,3,4†

SCIENCE VOL 304 4 JUNE 2004

Mylotarg

Gemtuzumab-ozogamicin: CD33 directed cytotoxic drug for AML

Accelerated approval in 2000 for older patients with CD33 positive recurrent/refractory AML

Based on response rate (CR (complete) or CRp (without platelet recovery)

Confirmatory studies initiated in **first-line indication**

MRC study (Daunorubicin/Ara-C, 7 + 3) with or without Mylotarg

Clinical benefit demonstrated in defined subset of patients

SWOG study (7 + 3) with or without Mylotarg

Halted for excess mortality in Mylotarg group

Withdrawn from US (based on SWOG)

Mylotarg

Additional studies performed by Pfizer Approved based on new phase 3 studies at lower dose (from label)

237 patients with newly diagnosed AML who could not tolerate or chose not to take intensive chemotherapy, randomized to Mylotarg or Best Supportive Care

Overall Survival improved from 3.6 months to 4.9 months

57 patients who had first relapse

26 percent of patients had complete remission

median duration 11.6 months

Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial.

Burnett AK[1], Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH, Yin JA, Hunter A, Goldstone AH, Wheatley K.

Abstract

PURPOSE:

Antibody-directed chemotherapy for acute myeloid leukemia (AML) may permit more treatment to be administered without escalating toxicity. Gemtuzumab ozogamicin (GO) is an immunoconjugate between CD33 and calicheamicin that is internalized when binding to the epitope. We previously established that it is feasible to combine GO with conventional chemotherapy. We now report a large randomized trial testing the addition of GO to induction and/or consolidation chemotherapy in untreated younger patients.

PATIENTS AND METHODS:

In this open-label trial, 1,113 patients, predominantly younger than age 60 years, were randomly assigned to receive a single dose of GO (3 mg/m(2)) on day 1 of induction course 1 with one of the following three induction schedules: daunorubicin and cytarabine; cytarabine, daunorubicin, and etoposide; or fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin. In remission, 948 patients were randomly assigned to GO in course 3 in combination with amsacrine, cytarabine, and etoposide or high-dose cytarabine. The primary end points were response rate and survival.

Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial.

RESULTS:
The addition of GO was well tolerated with no significant increase in toxicity. There was no overall difference in response or survival in either induction or consolidation. **However, a predefined analysis by cytogenetics showed highly significant interaction with induction GO (P = .001), with significant survival benefit for patients with favorable cytogenetics, no benefit for patients with poor-risk disease, and a trend for benefit in intermediate-risk patients.** An internally validated prognostic index identified approximately 70% of patients with a predicted benefit of 10% in 5-year survival.

CONCLUSION:
A substantial proportion of younger patients with AML have improved survival with the addition of GO to induction chemotherapy with little additional toxicity.

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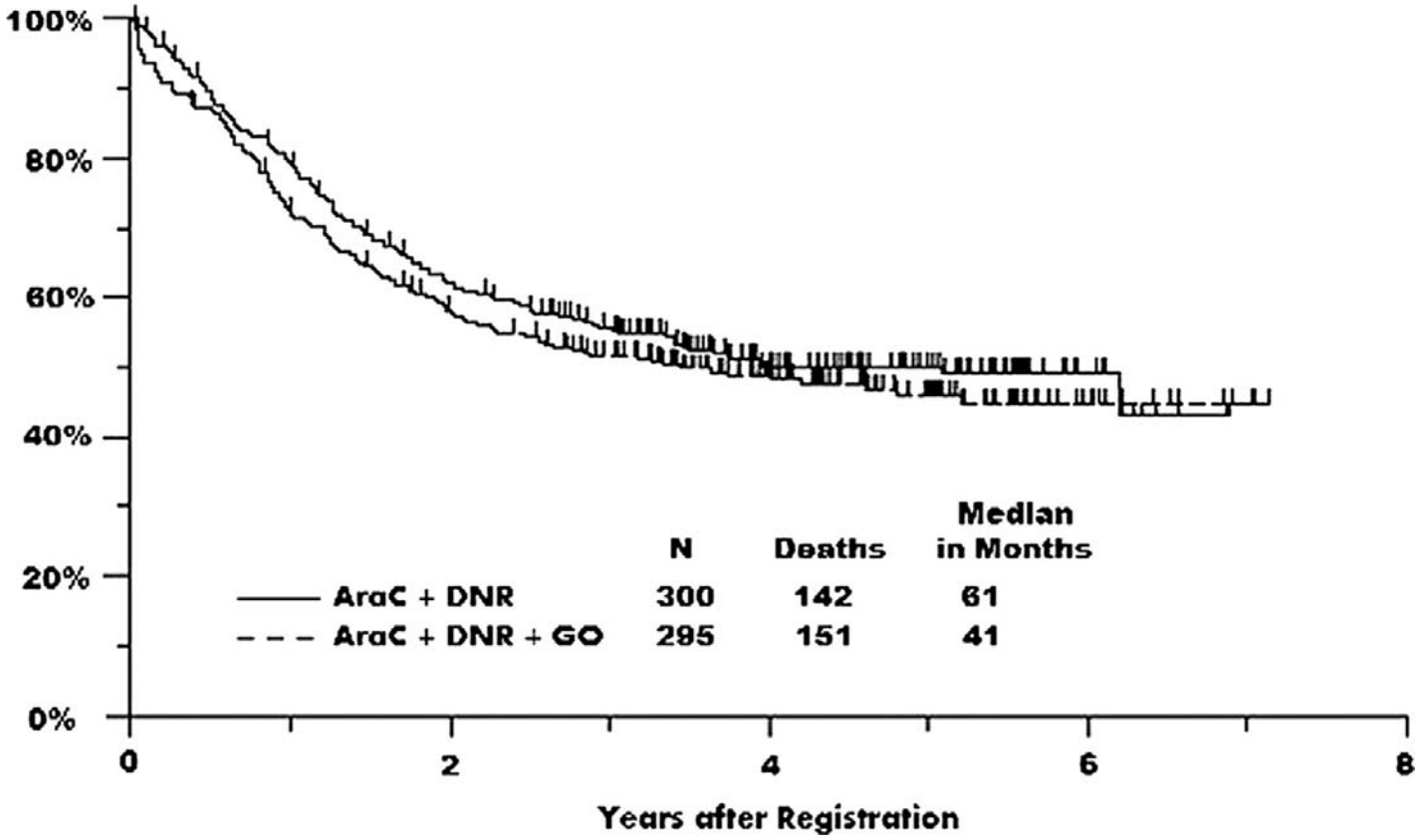
A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia

Stephen H. Petersdorf, Kenneth
J. Kopecky, Marilyn Slovak, Cheryl Willman, Thomas Nevill, Joseph Brandwein, Richard A. Larson, Harry P. Erba, Patrick J. Stiff, Robert K. Stuart, Roland B. Walter,
Martin S. Tallman, Leif Stenke and Frederick R. Appelbaum
Blood 2013 121:4854-4860
https://doi.org/10.1182/blood-2013-01-466706

The rate of fatal induction toxicity was significantly higher in the DA-GO group. In this study, the addition of GO to induction or postconsolidation therapy failed to show improvement in CR rate, disease-free survival, or overall survival.

Overall Survival by Induction Arm
All Patients



CC-223

CC 223 is a mTOR inhibitor with activity against TORC1 and TORC2
in development for Hepatocellular Carcinoma (HCC)

Celgene halted development
Competitor trial with mTOR inhibitor did not reach endpoint BUT
observed activity in subgroup of patients with hepatitis B

<u>HCC caused by Hepatitis B remains a common problem in China</u>

CC-223 now in development in China/Asia for HCC

Licensed to Antengene

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Penn Museum

From the Han period pairs of qilin-a mythical hybrid of a lion and a dragon-were placed at the avenue leading to grave.

The qilin glorified the deceased while protecting the tomb from evil spirits.

What is this?

Wormwood, (Qinghaosu)

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Winner of the Nobel Prize

Artemisinin: The Modern Malaria Treatment

For nearly two millennia, Chinese healers turned the leaves of a fern-like weed into a tea to cure fevers and other ailments.

During the 1970s, Chinese scientists discovered a compound that killed the malaria parasite.

Today, artemisinin is the main ingredient in the most effective treatment for malaria

Where in the World Will Science & Medicine Flourish?

- Where ideas are encouraged
- Where skills are developed
- Where the government is committed to science
- Where the money is available
- Where there are dedicated scientists
- Where there is an internet connection
- Where there is a desire

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Where is There a Need for New Medicine

Wherever People Live…

无论在何处…(No matter where they are)

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Thank You!

谢谢!