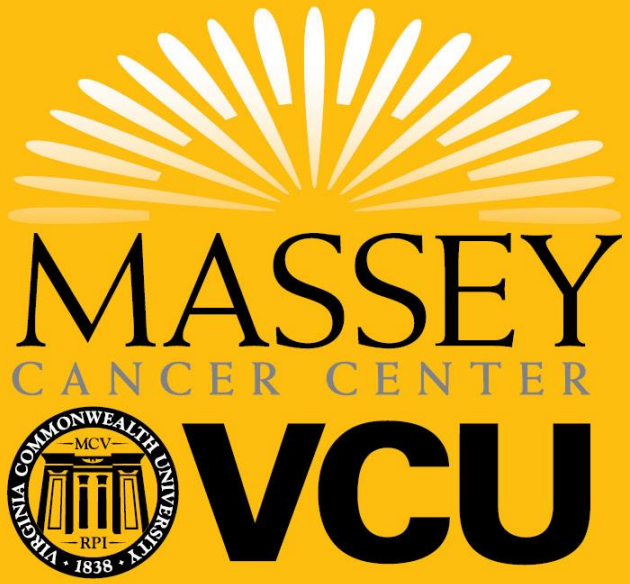

PHASE I CLINICAL TRIALS

GOALS

- Phases of Clinical Trials
- Unique aspects of Phase I Trials
- Benefits and Barriers to enrollment

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PHASE 3 CLINICAL TRIAL

- Purpose:
  - To compare the new treatment with the current standard treatment
- Number of people taking part:
  - From 100 to several thousand

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PHASE 2 CLINICAL TRIAL

- Purpose:
  - To determine if the new treatment has an effect on a certain cancer
- Number of people taking part:
  - Less than a 100

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PHASE I CLINICAL TRIALS

- Purpose:
  - To find a safe dose
    - Maximum tolerated dose (MTD)
  - To determine toxicity of the new treatment
    - Dose Limiting Toxicity (DLT)
  - To assess for early efficacy signals
- Number of people taking part:
  - 15 to 30

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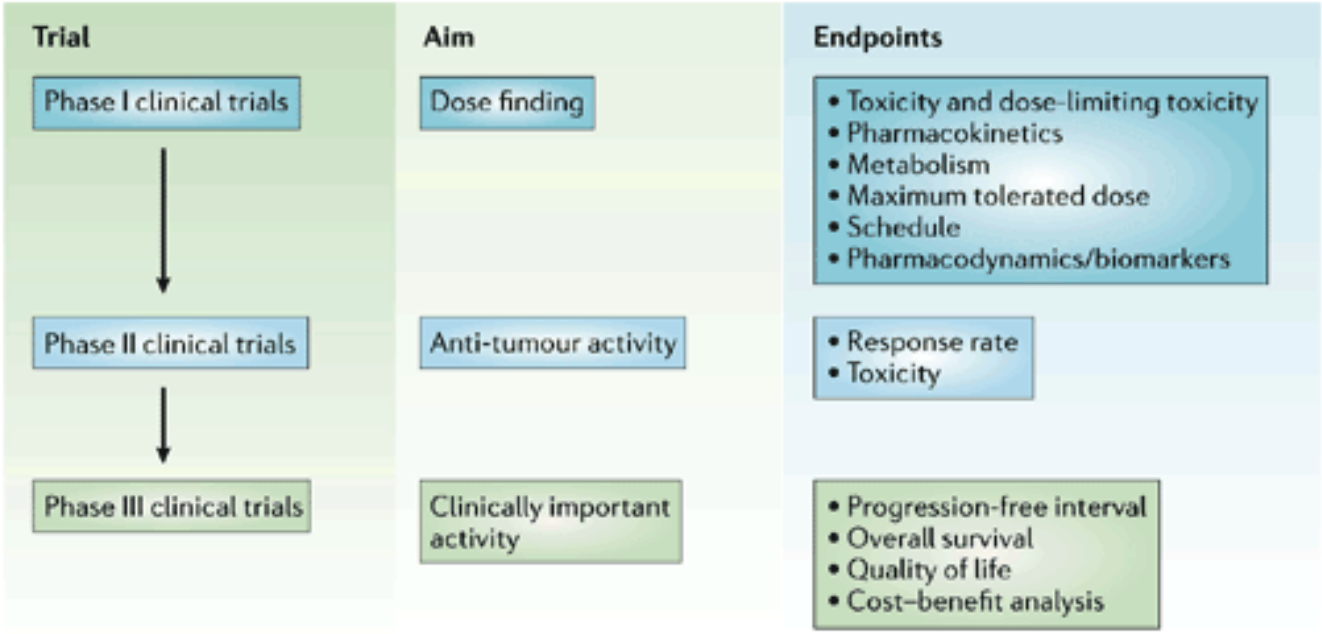

Jayson *et al. Nature Reviews Cancer* **6**, 330–336 (April 2006) | doi:10.1038/nrc1842

nature REVIEWS CANCER

DRUG DEVELOPMENT EXAMPLE

- Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the bcr-abl tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001;344:1031-1037.
- Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. New Engl J Med. 2002;346:645-652.
- O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003 Mar 13;348(11):994-1004.

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PHASE I CLINICAL TRIALS

- Mechanism for laboratory research to be translated into clinical practice
- Generally open-label
- Limited number of institutions
- Resources for closer observation/monitoring

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TYPES OF PHASE I TRIALS

- Disease specific phase I studies
- All-comer phase I trials
- New agent alone
- Combination of new agents
- New agent with standard chemotherapy/agent

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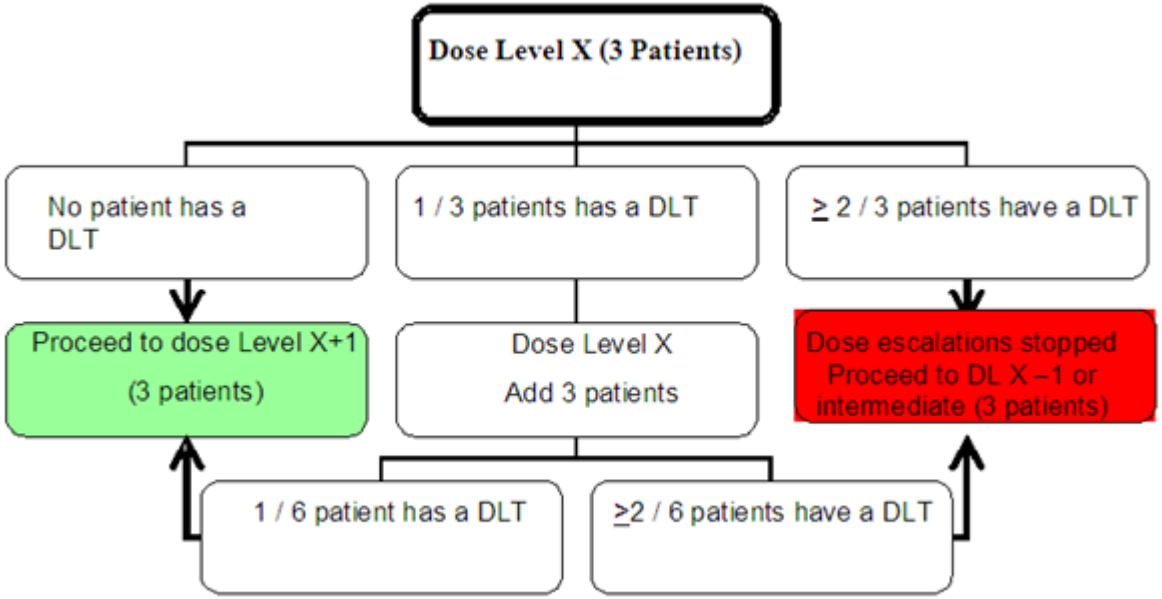
TRIAL DESIGN

- 3+3 Design is most common



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PHARMACOKINETICS

- Determine how rapidly a drug is cleared from the circulation
- Challenging to collect
  - May require some longs days and/or frequent visits during the first cycle of therapy

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BENEFITS TO PATIENTS

- Improved Quality of Life and Psychological Benefit
  - Defined treatment plan
  - Routine contact with clinicians
  - Control over disease
  - Access to palliative care

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BENEFITS TO PATIENTS

- Direct Medical Benefit
  - Potential for significant therapeutic impact
    - Imatinib
    - Pembrolizumab
  - Older analyses found approximately 5% of patients had objective response
  - New analyses – about 11% with objective response and up to 18% when combined with FDA-approved drug

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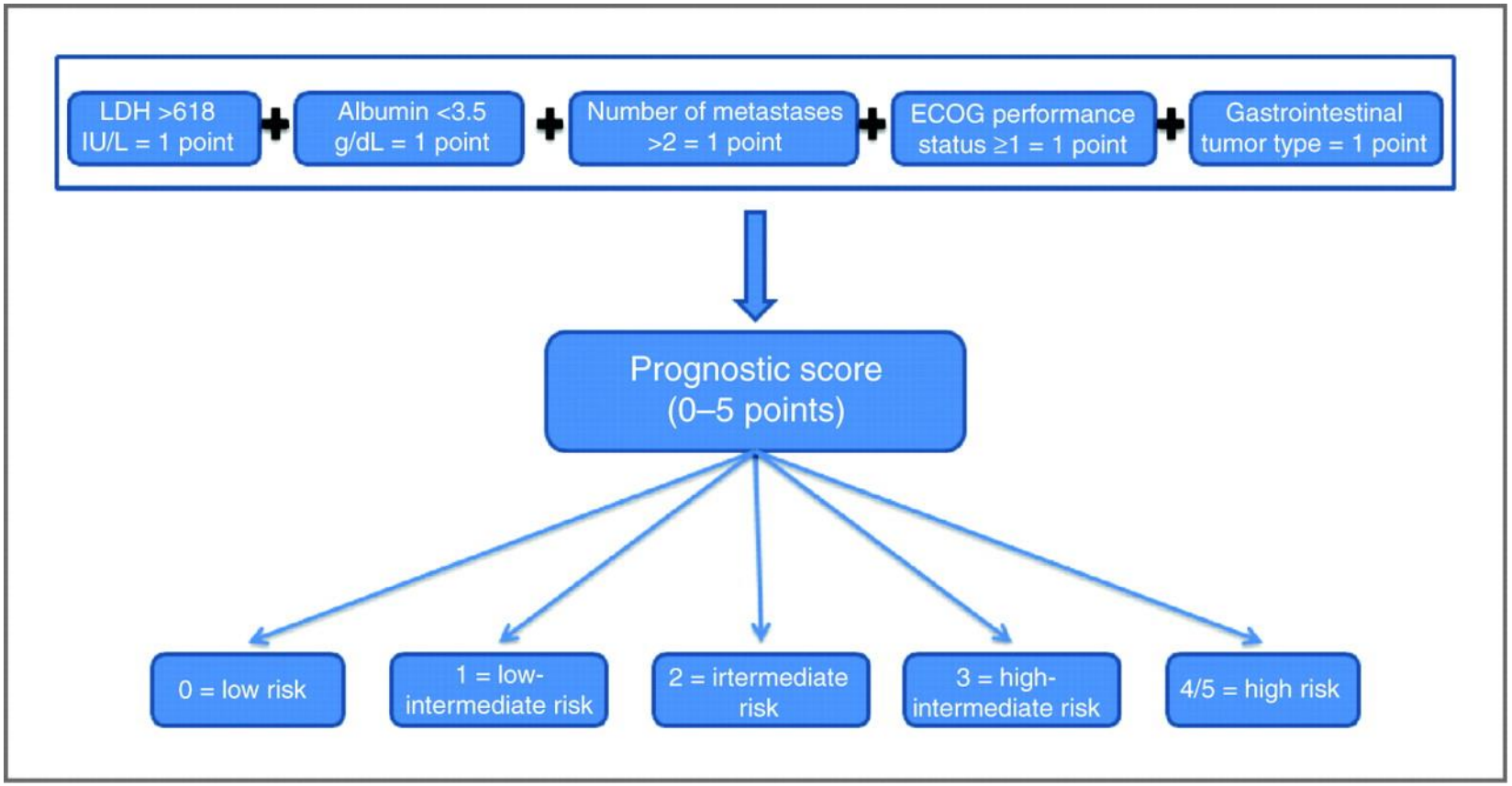
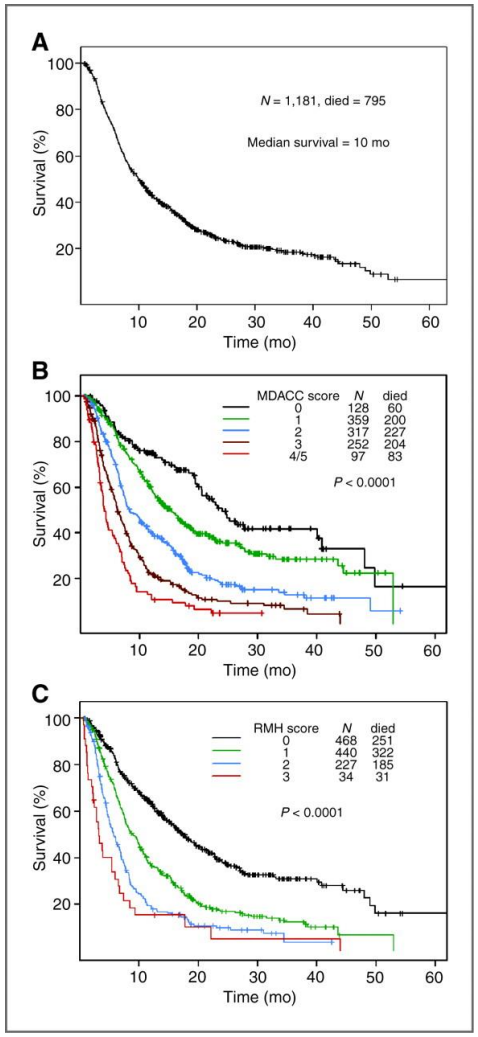
Proposed algorithm to assign patients to 1 of the 5 risk groups that predict survival characterized by summing the number of risk factors present at the time of first visit to the phase I clinic.



Jennifer Wheler et al. Clin Cancer Res 2012;18:2922-2929

Clinical Cancer Research
AACR American Association for Cancer Research

A, Kaplan–Meier survival curve for overall survival in 1,181 patients.



Jennifer Wheler et al. Clin Cancer Res 2012;18:2922-2929

Clinical Cancer Research
AACR American Association for Cancer Research

BENEFITS TO PATIENTS

- Reduced Risk
  - Risk-benefit ration has improved over time
  - Treatment related death rate has decreased significantly.
    - 1% from 1991 and 1994
    - 0.06% between 1999 and 2002

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From: **Trends in the Risks and Benefits to Patients With Cancer Participating in Phase 1 Clinical Trials**

JAMA. 2004;292(17):2130-2140. doi:10.1001/jama.292.17.2130

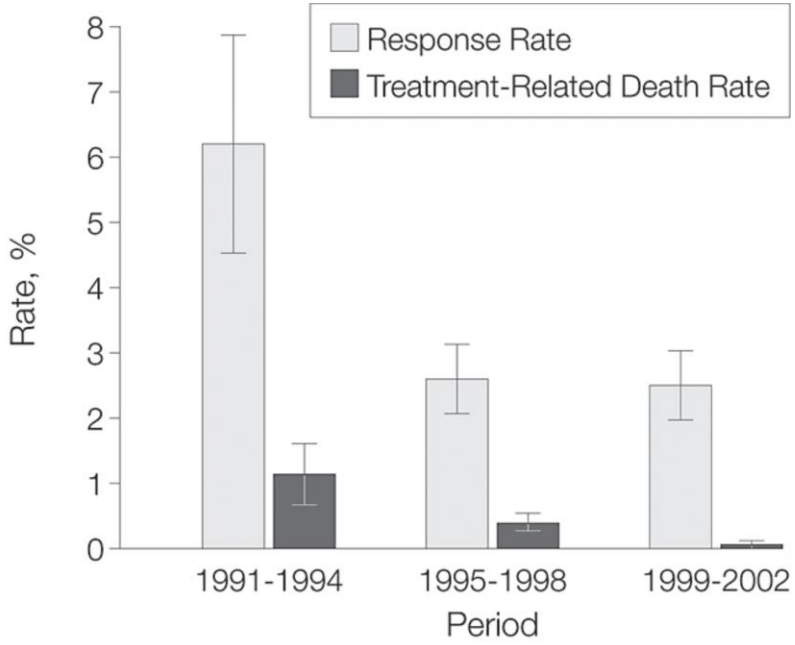

Figure Legend:

The contribution of trial-level data to the period average was weightedby the number of enrollees. Error bars indicate SE.

BARRIERS TO ENROLLMENT

- Declined participation
  - ~15% rate
  - Pursue other treatments
  - Quality of life purposes
  - Uncertainty of benefit and toxicity
  - Trial burden
  - Desire to have more active treatment

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BARRIERS TO ENROLLMENT

- About 13% were recommended another treatment
- Lack of availability in ~10%
  - Need more trials and spots
- Ineligible
  - Multiple primary cancer
  - Poor performance status
  - Heavily pre-treated (~13% of excluded) as some trials limit # of lines of therapy

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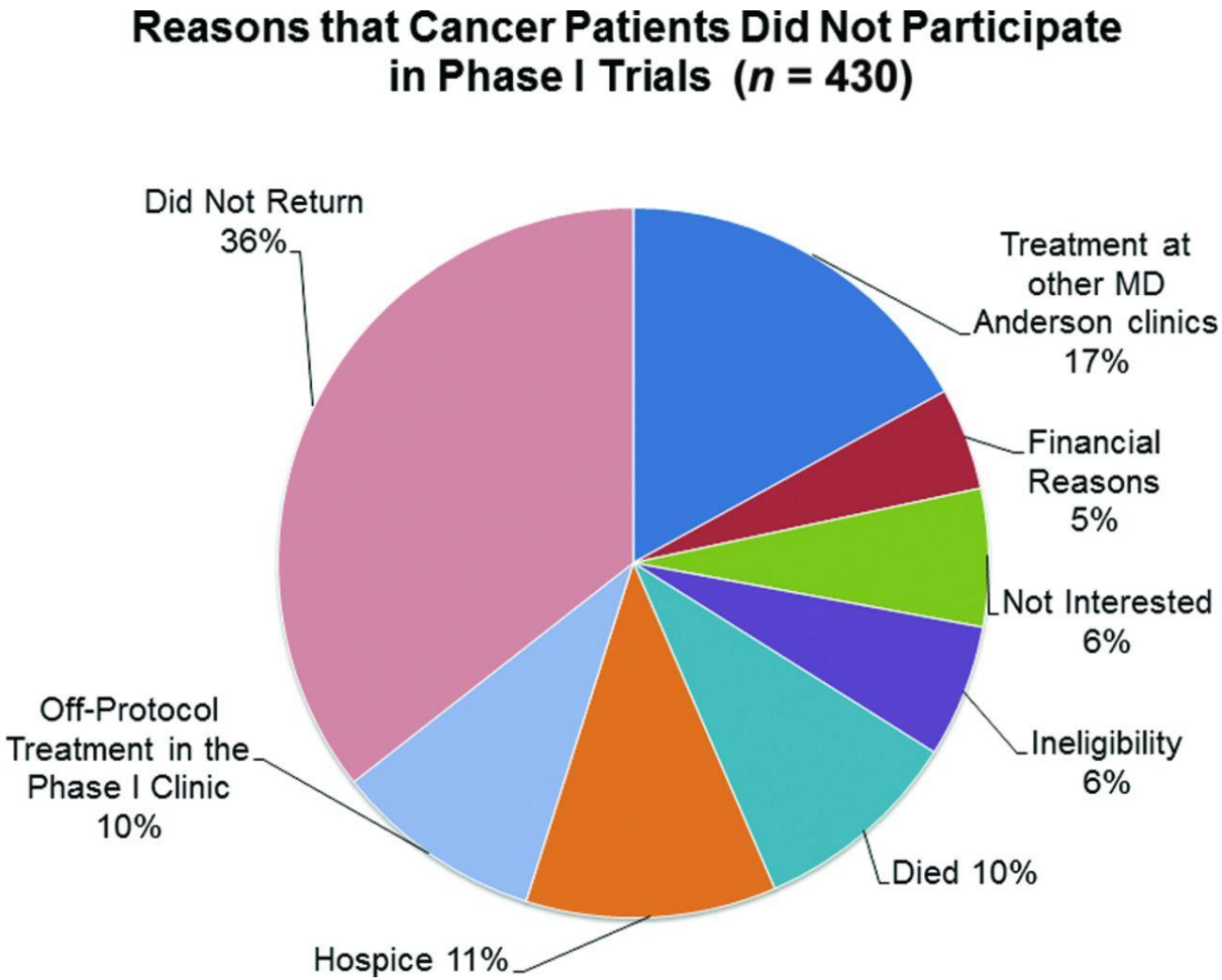
Pie chart shows percentages of patients with cancer who were first seen in the phase I clinical trials facility at MD Anderson Cancer Center from August 1, 2011, to February 29, 2012, according to reason for failure to enroll onto a phase I clinical trial.



Siqing Fu et al. The Oncologist 2013;18:1315-1320

FAQS FROM PATIENTS/TEAMS

- Is there a placebo?
- How often will I need to come in for visits?
- How will you know if the treatment is working?

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ASCO RECOMMENDATIONS

- Improve Coverage of Phase I Trials
- Improve Patients' Understanding of Goals of Phase I Trials
- Increase Enrollment onto Phase I Clinical Trials
- Improve Phase I Trials Research Process

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TAKE HOME PEARLS

- Think about trials early in course
- Communication with phase I team is beneficial to all

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QUESTIONS?

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