Sunnybrook
HEALTH SCIENCES CENTRE

PHASE II TRIAL OF AZACITIDINE PLUS DEFERASIROX IN HIGHER RISK MYELODYSPLASTIC SYNDROMES (MDS)

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Disclosures for **Anca Prica**

Employment	**None**
Consultancy	**None**
Equity Ownership	**None**
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Patents & Royalties	**None**
Speakers Bureau	**None**
Membership on Board of Directors/Advisory Committee	**None**
Other	**None**
Presentation includes a description of the following off-label use of a drug or medical device	**Deferasirox**

Background

- In MDS – low blood counts including red blood cells leading to anemia
- 2 risk groups: lower and higher
- Higher risk patients:
  - More symptoms, need more support with transfusions
  - Increased risk of becoming AML
  - Shorter life expectancy

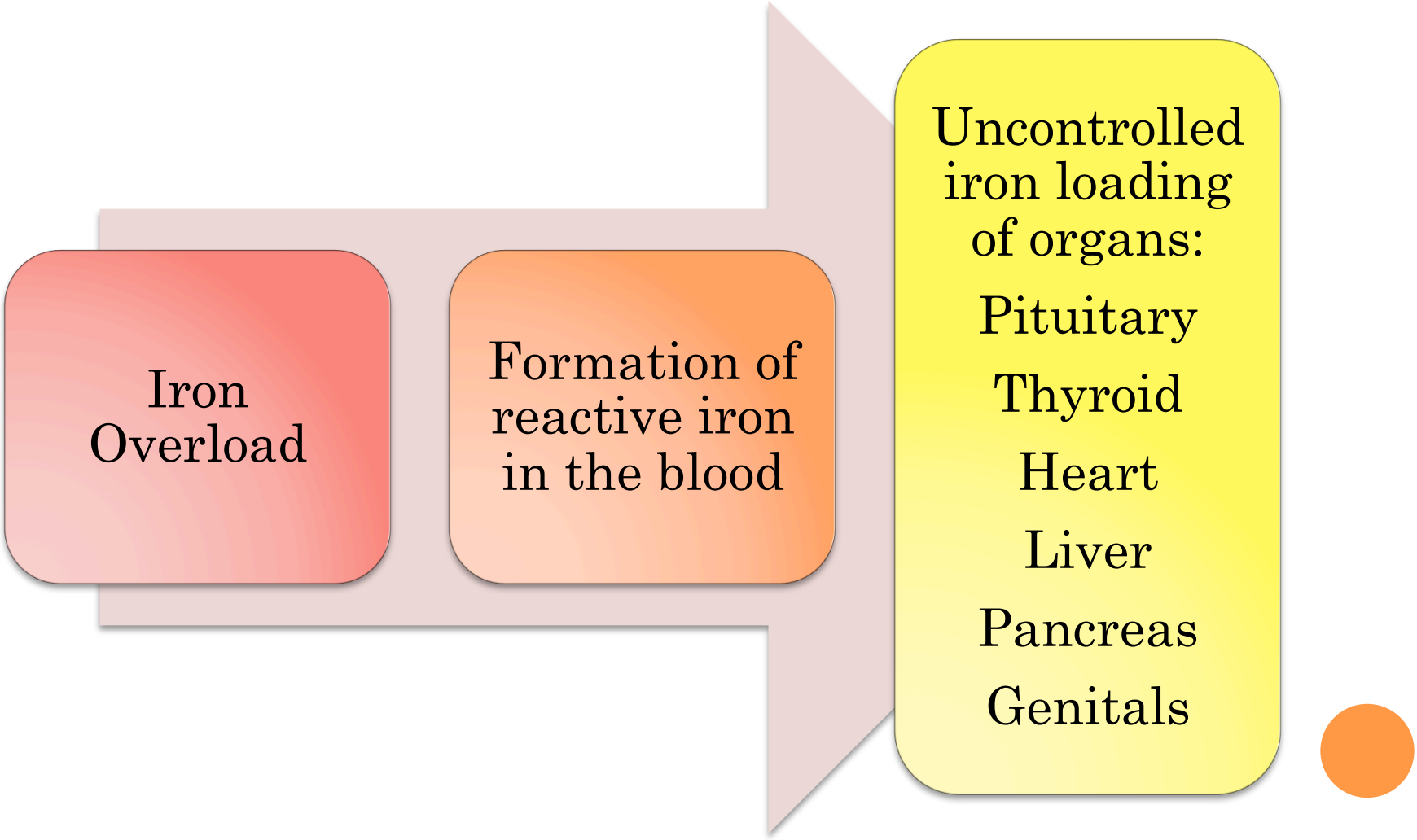
Standard treatment for higher risk MDS

- Azacitidine (Vidaza)
  - Large study on patients with higher-risk MDS showed that patients:
    - Lived longer (about 9 mo longer)
    - Less likely to need transfusions or antibiotics
    - Had an improved quality of life
- However, a large proportion of people still don't respond to the drug or remain transfusion dependant
- Other treatments are needed

Transfusions and Iron overload

- 70% of higher risk patients are transfusion dependant
- Average iron absorption is 1–2 mg/day through gut
- 1 blood unit contains 200-250 mg iron
- **Iron overload can occur after 10–20 transfusions**
- **Measured in the blood as ferritin**

Iron Loading

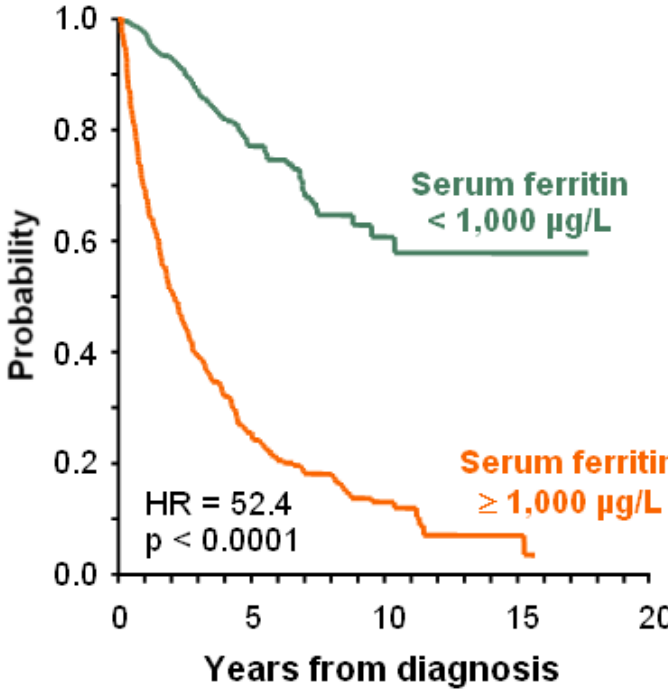


Chelation

- The body cannot remove excess iron on its own
- Chelators are drugs that allow removal of body iron
- Two drugs licensed in Canada
  - desferoxamine (Desferal) given as an infusion overnight
  - deferasirox (Exjade) given orally – newer drug
- have been shown to decrease iron in the blood, but unclear if makes people live longer in MDS (small studies)
- Only studied in lower risk MDS

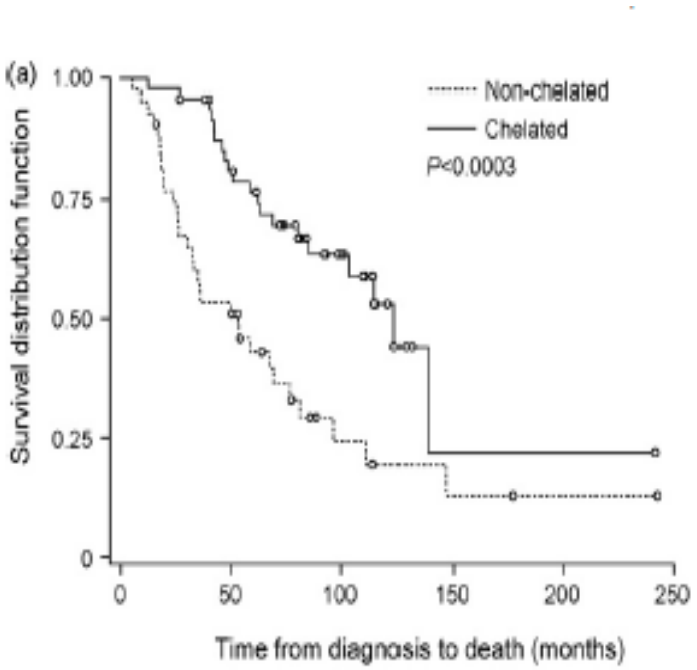
Bad Effects of iron Loading

Worse survival if ferritin >1000



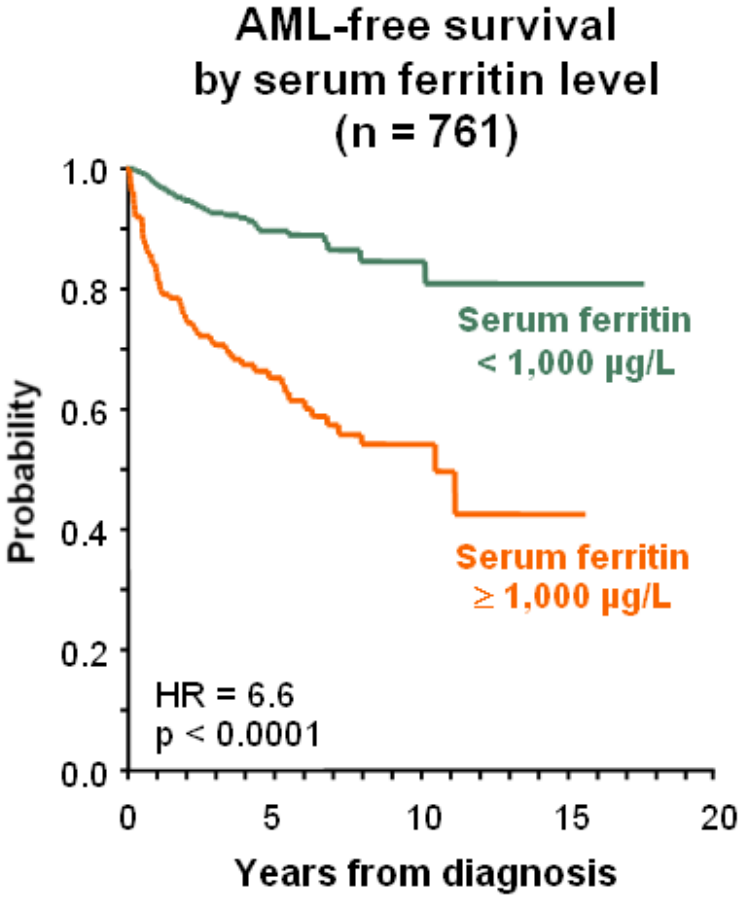
Sanz et al., Blood 2008 112 (abstract 640)

Better survival with chelation



Rose et al, Leuk Res. 2010. 34(7):864-870

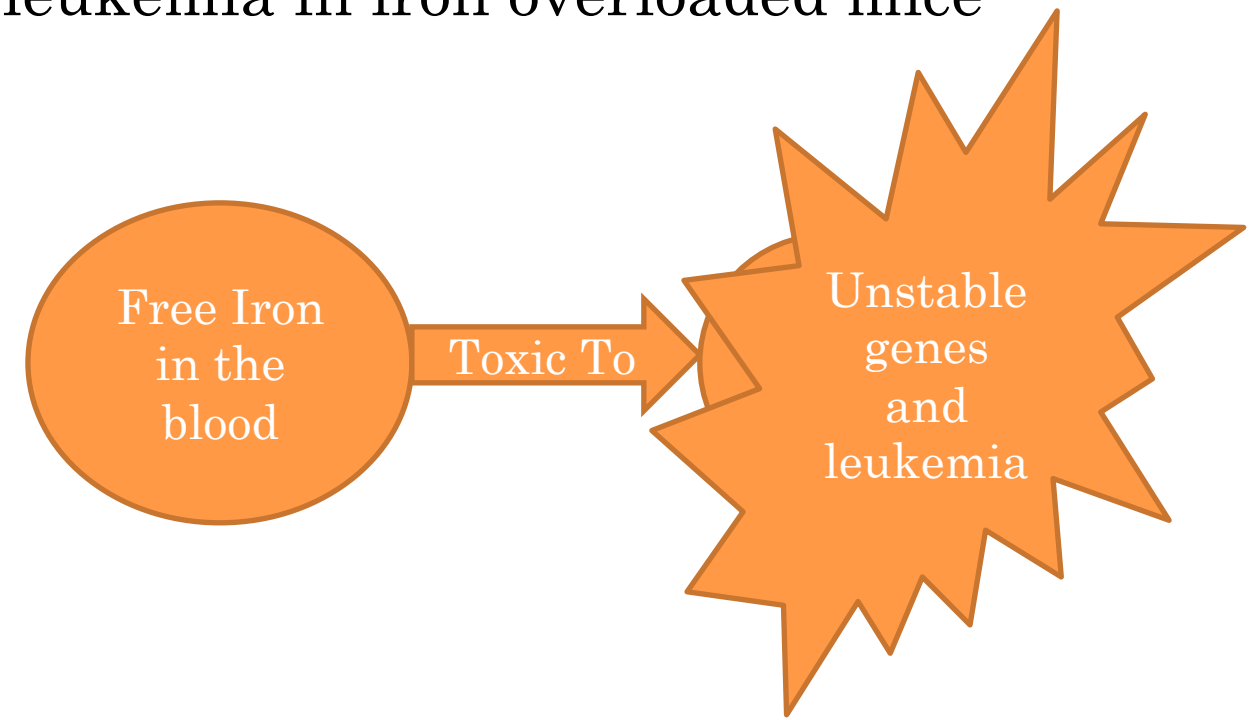
Iron overload may be associated with increased leukemia



Sanz G, et al. Blood. 2008;112:[abstract 640].

HOW?

- Dr. Wells and his team have shown progression to leukemia in iron overloaded mice



Iron chelation improves Anemia

- Large trial evaluation of Exjade
- Subset of lower risk MDS patients
- 23% of patients had a response in their red blood cell counts
- ?Mechanism – reversal of toxic effects of iron on bone marrow stem cells

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Clinical trial objectives

- Primary
  - Determine proportion of patients with blood count improvement with the addition of Exjade to Vidaza
- Secondary
  - Determine safety of Exjade + Vidaza
  - Assess
    - markers of iron overload such as reactive iron in the bone marrow

Eligibility

- Inclusion
  - Adults >18 yrs of age
  - Higher risk MDS
  - Vidaza X 6 cycles with no blood count improvement, but stable disease as per IWG criteria
  - Ferritin >500
- Exclusion
  - Kidney abnormalities
  - Liver abnormalities

Treatment Plan

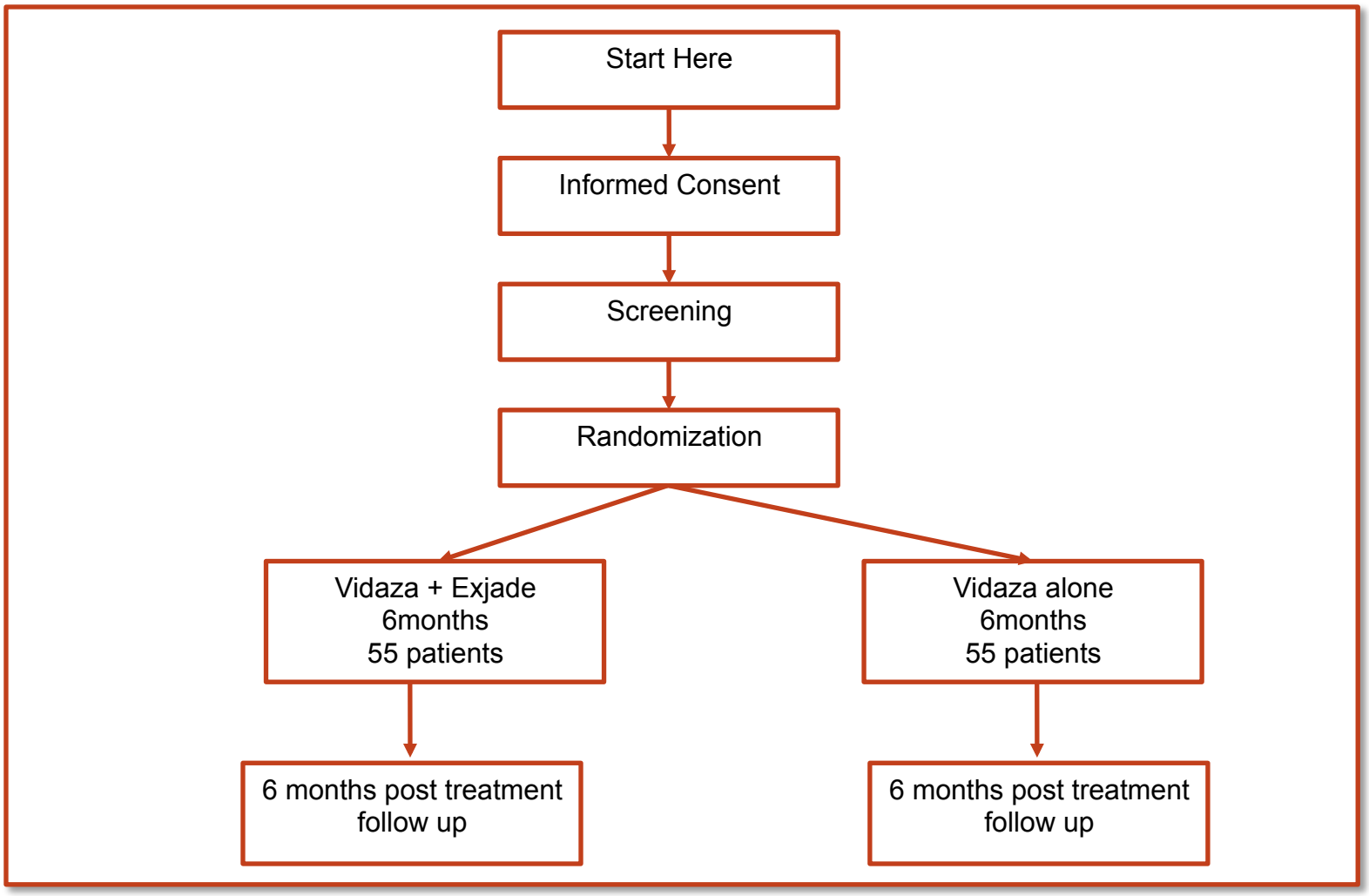
- Continue Vidaza
- Half the patients: Add Exjade for 6 months
- Half the patients: Continue azacitidine alone for an extra 6 months
- Dose changes as needed
- At study end
  - Stop Exjade
  - Continue Vidaza

Response assessment

- IWG criteria:

Red blood cell response	**Increase in red blood cell count by 15 or ⇩≥4 transfusions/8wks**
Plt response	**⇧ by 30 if >20 at start or 100% if 10 to >20**
Neut response	**≥ 100% and absolute > 0.5**
Stable disease	**Bone marrow evaluation – no progression**

- Bloodwork weekly for the first 8 weeks, then every 2 weeks until study completion.
- BM at study entry, half way through at 3 months and at study completion or patient withdrawal
- Side effects monitored every month


Start Here
Informed Consent
Screening
Randomization
Vidaza + Exjade
6months
55 patients
Vidaza alone
6months
55 patients
6 months post treatment
follow up
6 months post treatment
follow up

Where?

- 1st stage:
- 26 patients (half in each group)
- At Sunnybrook Hospital/Odette Cancer Centre
- If responses, would expand to multiple centres through Canada

Status

- Still in the planning stages
- Working on the final approval for the protocol
- Hope to start enrolling in about 6-9 months

Thank you

- AAMAC – providing funds for fellowship award and to help complete this research
- CIHR
- Dr. Buckstein and Dr. Wells
- Novartis Oncology
- In advance, you, the patients