CLL Global Research Foundation 2021 Perspectives

29 July 2021

Important Tests for Selecting Treatment in CLL

- Del(17p) status by FISH: can change[2]
  - Know % of cells with deletion
- *TP53* mutation status: can change[2]

- IGHV mutation status (for first line): does not change[1]

- *BTK* and *PLCG2* mutation status (in BTKi treated): can change[3]

1. Crombie. Am J Hematol. 2017;92:1393. 2. Chauffaille. Hematol Transfus Cell Ther. 2020;42:261. 3. Hallek. Am J Hematol. 2019;94:1266.

WW Standard First-line Treatments for CLL by Patient Characteristics and Goals

- **First-line treatments**
  - **Del(17p) / M-*TP53* – 5% - Durable disease control, NO CHEMOTHERAPY**
    - BTKi + Obin; reserve BCL2i-based for debulking
  - **Older, Unfit – 75% - Deep remission *vs.* Durable control (BTKi) (no chemo)**
    - **UM-IGHV** – patient preference and comorbidities important
      - BCL2i + Obin – fixed duration
    - **M-IGHV**
      - BCL2i + Obin – fixed duration
  - **Young, Fit – 20% - Deep remission *vs.* Durable control (BTKi)**
    - **UM-IGHV**
      - BCL2i + Obin – fixed duration
    - **M-IGHV**
      - BCL2i + Obin – fixed duration
      - FCR-based chemoimmunotherapy

Standard Treatments for Rel / Ref CLL by Disease Characteristics

- **Relapsed / Refractory CLL - Durable disease control**
  - Del(17p) / m-*TP53*
  - Age / comorbidities
  - Prior CIT
  - Prior BTK-inhibitor ± CIT
  - Fludarabine-refractory (CIT)
  - Ibrutinib-refractory
  - Idelalisib-refractory

Treatment Options:

- BTK-inhibitor
- BCL-2-inhibitor ± rituximab
- PI3K-inhibitor + rituximab
- Lenalidomide ± CD20 mAb
- ~~Chemoimmunotherapy~~
- Allo-SCT
- Clinical Trial

Defining “Cure”

- Complete elimination of all leukemia, never to return; patients with normal life span for all treated
  - FCR in mutated-IGHV - ?
- Remission with no future need for treatment, normal life span
  - Leukemia may persist, but does not grow to require treatment
- Normal life span, despite treatment needed
  - Current targeted therapy

CLL Notable Clinical Advances – 2020/2021

1. Updated report of long remissions in pts with CLL treated with VEN-based treatments (CLL14 and MURANO trials)
   - Focus on undectable minimal residual disease (uMDR) as treatment endpoint
2. ACA/ZAN vs. IBR – as effective, maybe better; less atrial fibrillation
3. Updated reports on efficacy of combined targeted treatments – encouraging early results
   - BTKi+BCL2i ± CD20 mAb
4. Update on pirtobrutinib (LOXO-305; reversible BTKi) clinical activity in pts with resistant CLL and with Richter's transformation
5. Clinical activity of liso-cel (CD19-CAR-T cells; JUNO) in pts with resistant CLL – durable remissions in heavily pre-treated patients

CLL Clinical - What to Watch - 2021/2022

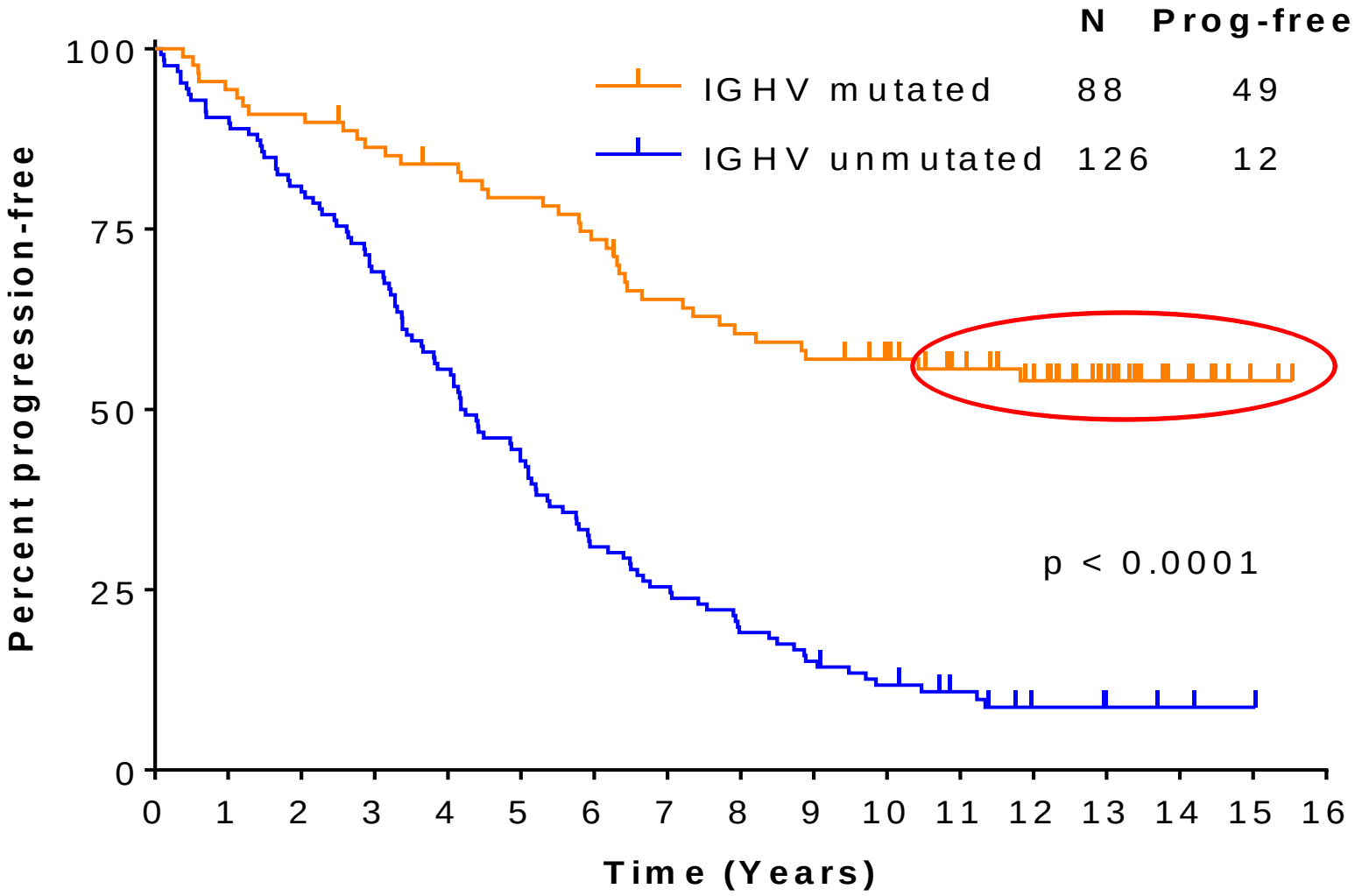
1. Developing and optimizing targeted therapy combinations – goal of undetectable-MRD as treatment endpoint
   - Identifying high-risk subgroups of pts and potentially cured pts based on pre-treatment disease characteristics
   - Non-chemotherapy curative strategies
   - Transition focus from “maintenance” to “curative”
2. New treatments: pirtobrutinib; CAR-T (CD19 and newer targets-ROR1); bi-specific antibodies (CD20xCD3-mosunetuzumab); many others in early development (CYC065, NX-2127,…)
3. Develop more effective treatments for pts with Richter’s transformation
4. Clarifying and correcting immunologic deficiencies in pts with CLL
   - COVID impact in CLL population
   - Reduce infection rate
   - Reduce rate of second cancers

CLL Research Needs - 2021/2022

1. Developing curative treatments
2. Improved outcomes for patients with del(17p)/mutated-TP53
3. Improved outcomes for patients with Richter's Transformation
4. Correcting immune dysfunction
    a. Improving outcomes with COVID (vaccination and infections)
    b. Improving outcomes with vaccination and infection risk
    c. Reducing risk for second cancers

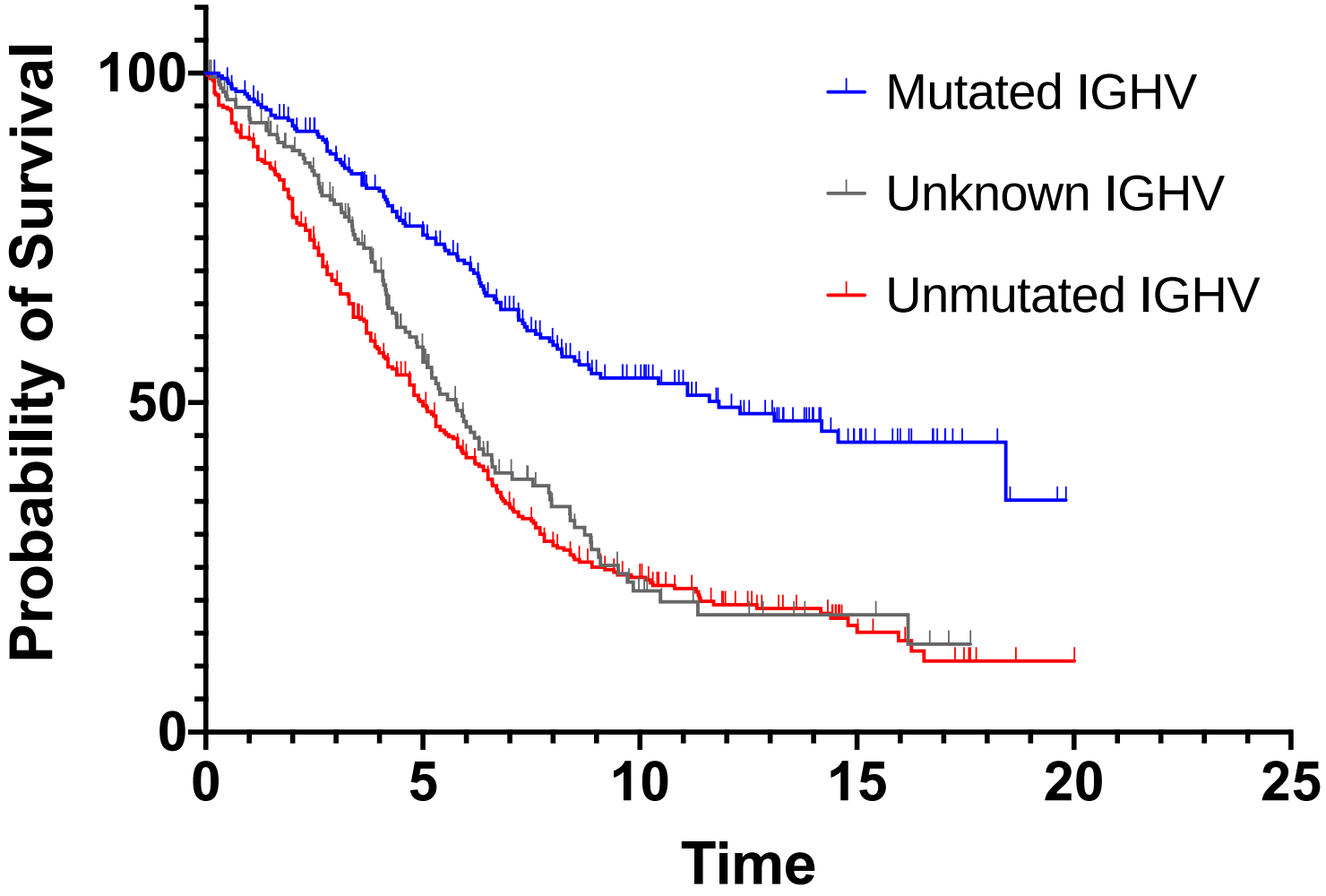
FCR Cure slides

IGHV-Mutated patients have prolonged PFS after First-line FCR



Thompson, *Blood* 2016

Long-term follow-up of 804 patients treated on FCR and FCR-like studies

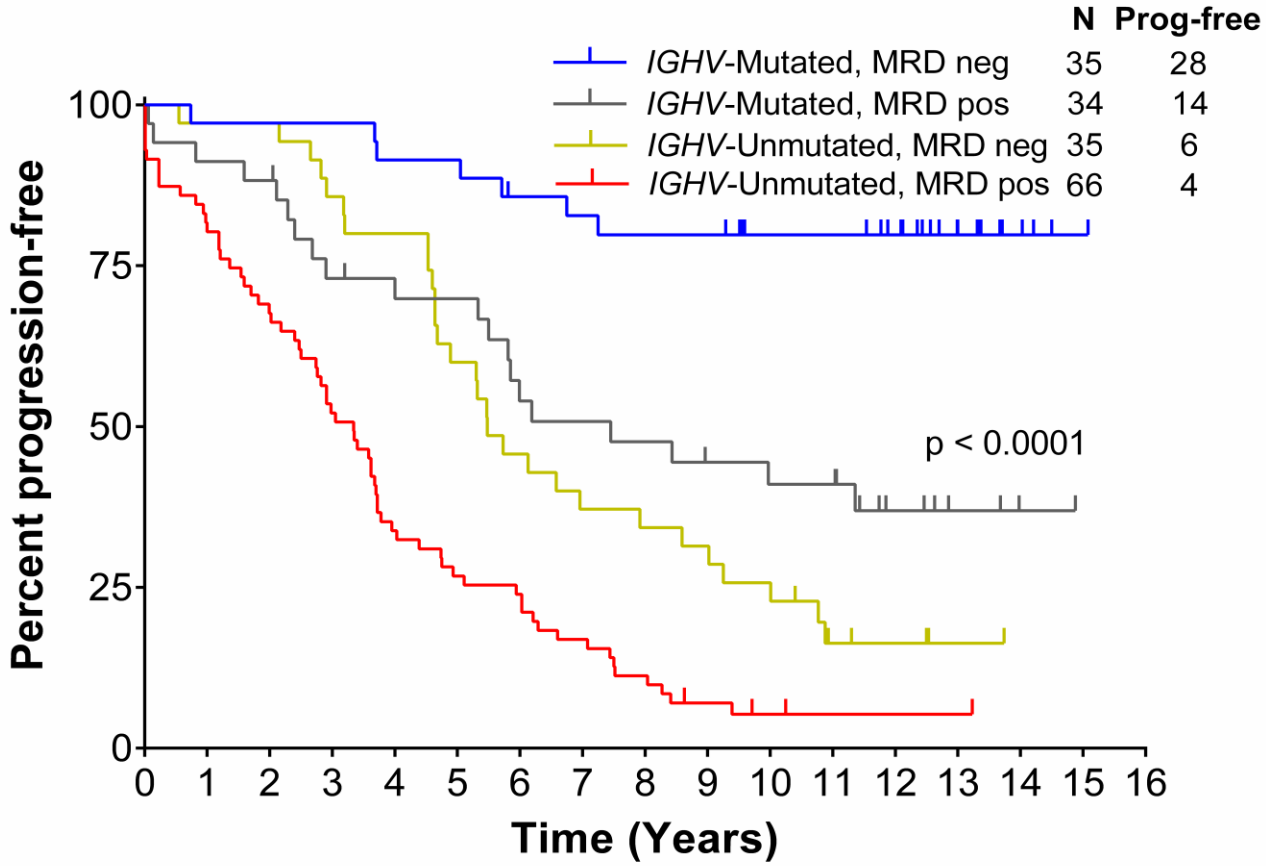


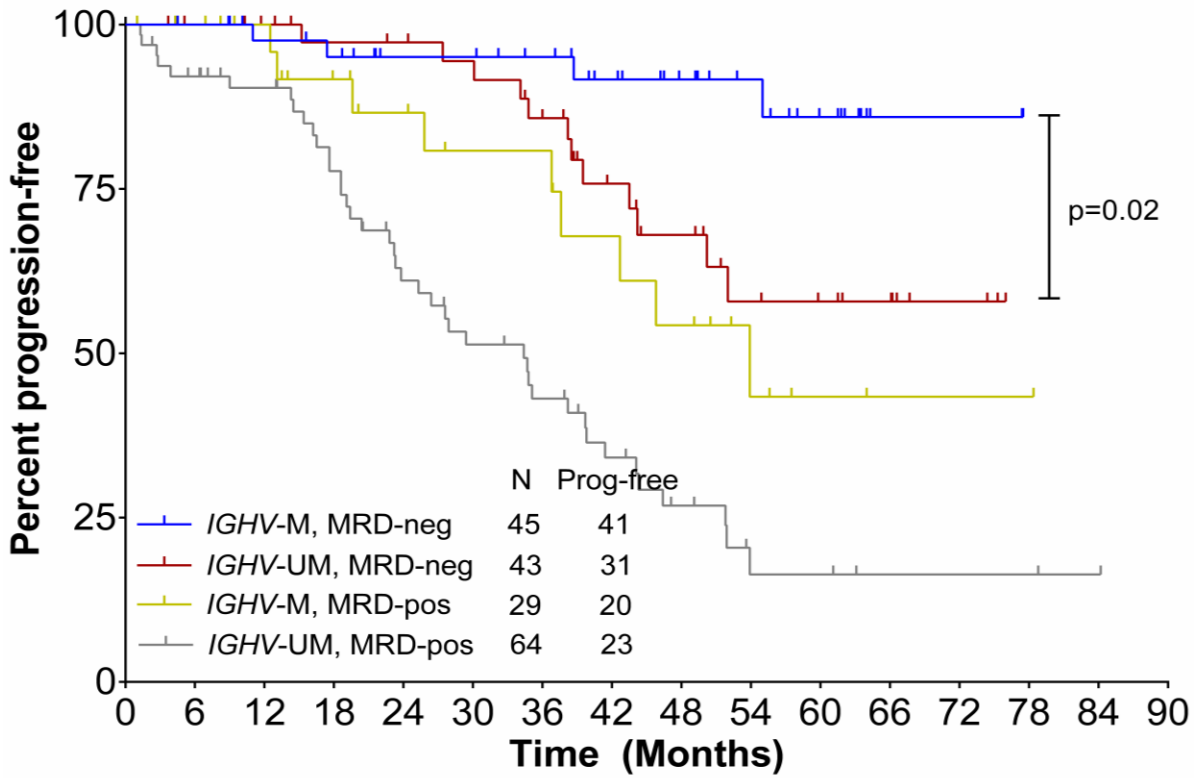
At risk at 10y:

1. Mutated 71/257.
2. Unknown 16/177.
3. Unmutated 59/370

Thompson PA, 2020. Unpublished data

The Importance of MRD





Thompson PA et al. *Blood* 2016; Thompson PA et al. *Leukemia* 2018

Long-term outcomes after FCR

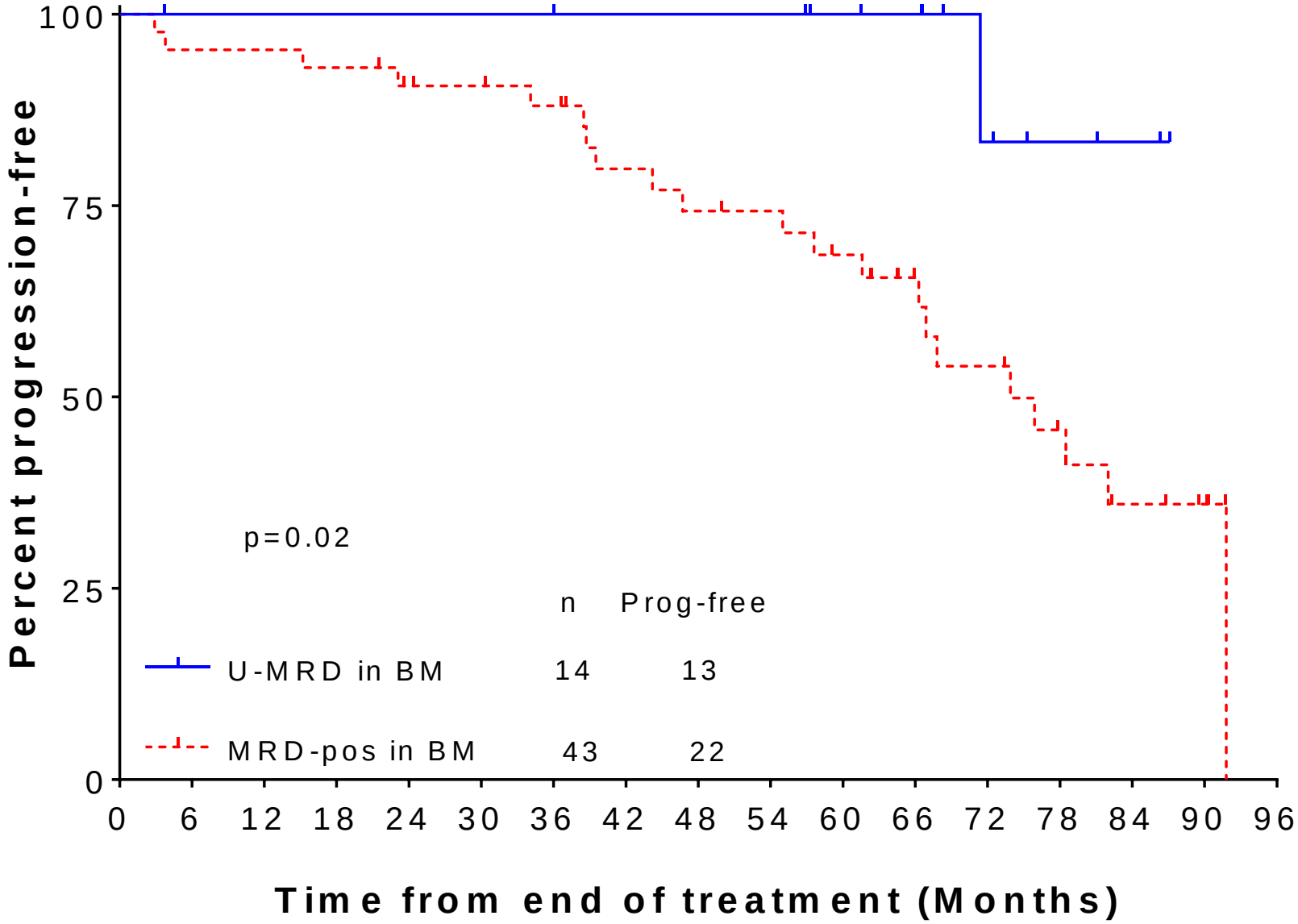
Most common causes of death:

1. CLL remained the most common cause of death (58.1%).
2. Other cancers (18.4%).
3. RT (15.4%).
4. Infection in remission (6.6%).

14/300 patients developed MDS/AML (4.7%).

This has likely changed dramatically with more effective salvage treatments.

We Can do better with MRD



Thompson PA et al. *Blood* 2019

Key Questions

- Update all long term outcomes for FCR-treated patients. MDA in a unique position to describe “life after FCR”
- Are these patients truly “cured.” i.e. Do they have MRD using NGS?
- If MRD+, what happens to MRD over time.

COVID and CLL

Dr Philip Thompson

7/29/21


IF 2020 WAS
A SCENTED CANDLE
memegenerator.net

Early US experience of COVID outcomes in CLL

- 198 patients (predominantly USA).
- 39% untreated, 61% previously treated.
- Median age 63.
- Median CIRS score 8.
- Majority of patients on treatment were receiving BTKi monotherapy.

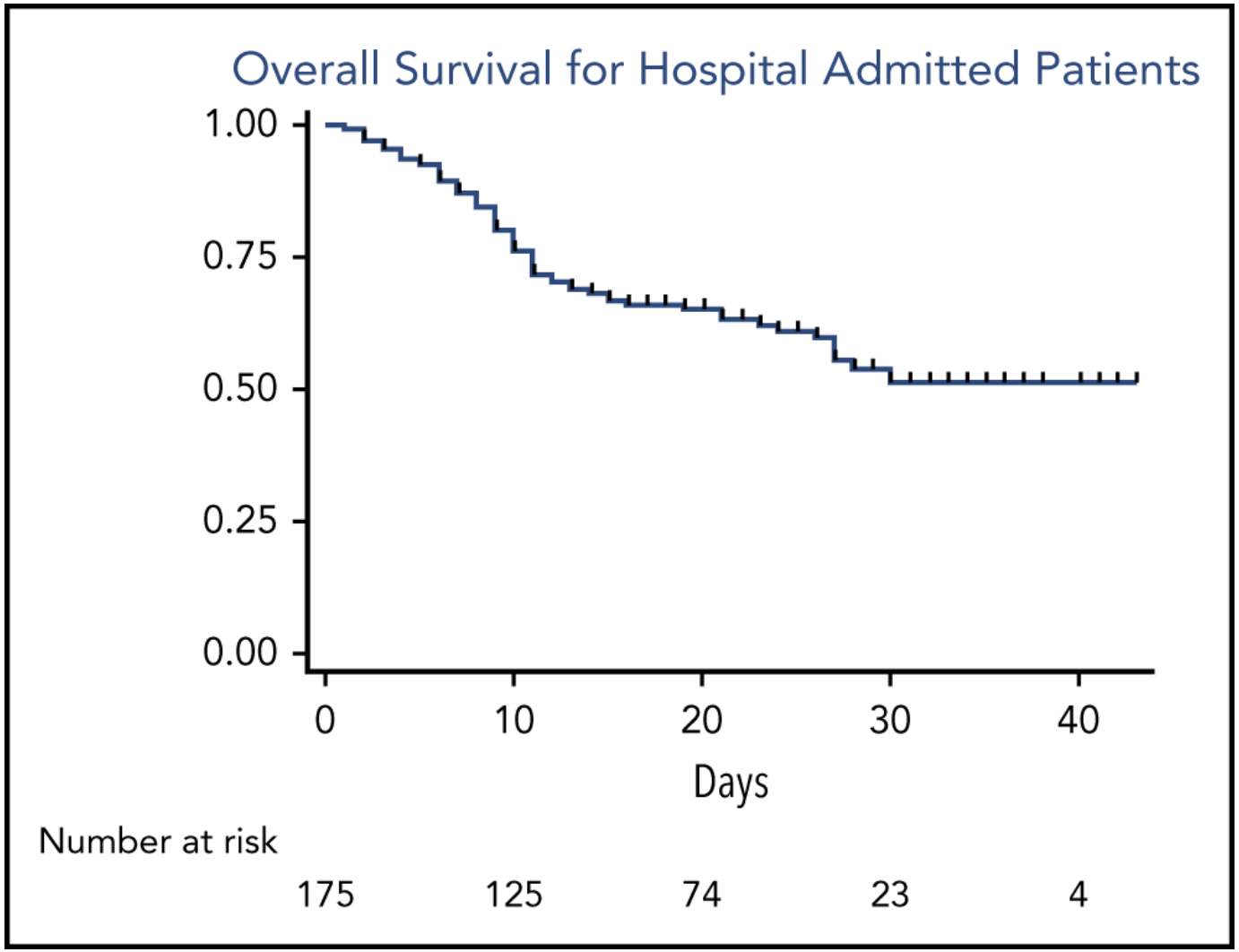
Anthony R. Mato et al Blood, 2020,

Outcomes

- 90% hospitalization.
- 33% mortality rate.
- Worse outcomes in patients with age >/=75, high CIRS score.
- No difference according to BTKi vs not.

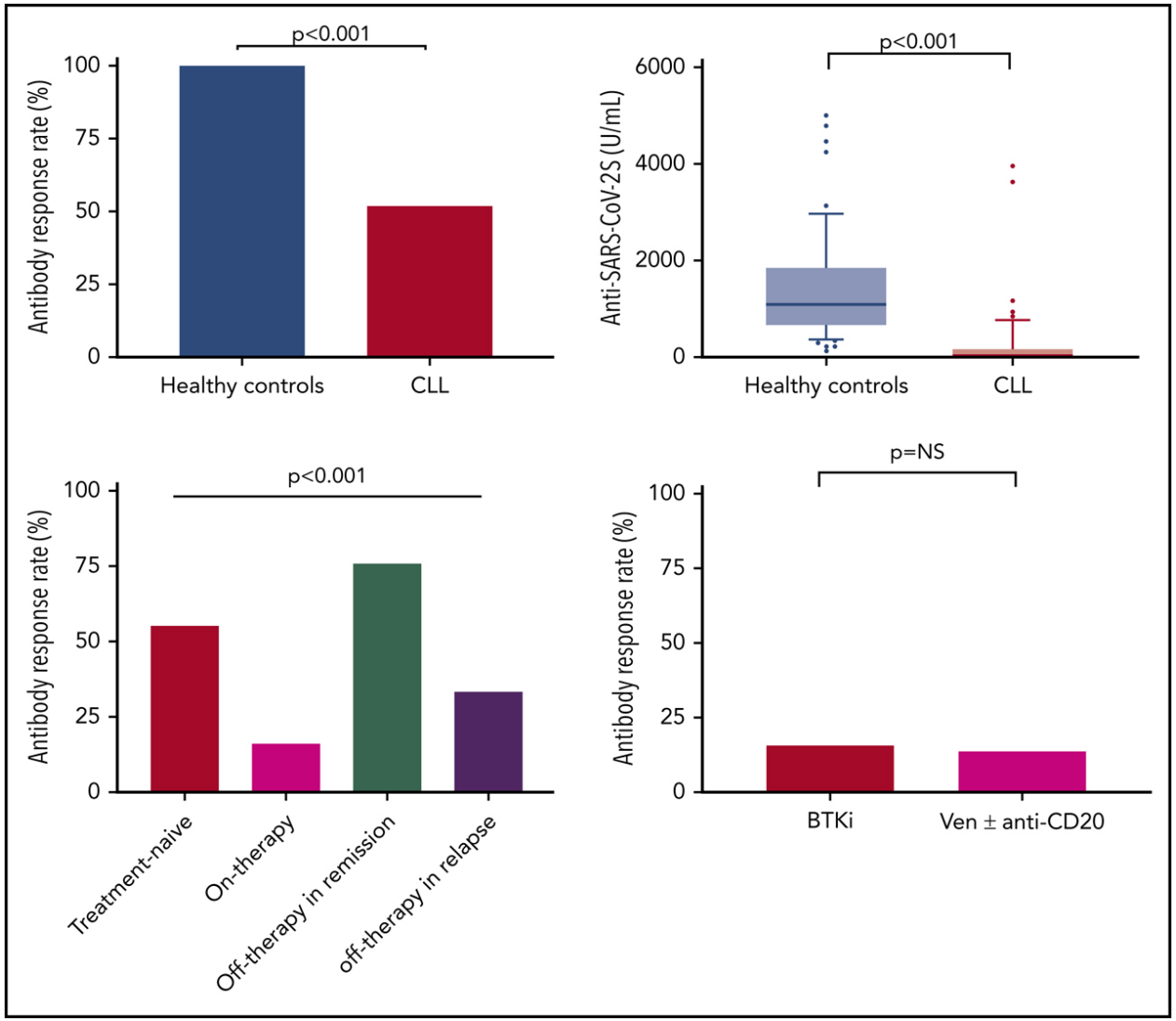
Anthony R. Mato et al Blood, 2020,

Outcomes of COVID-19 in patients with CLL: a multicenter international experience



Anthony R. Mato et al Blood, 2020,

COVID19 vaccine response in CLL patients



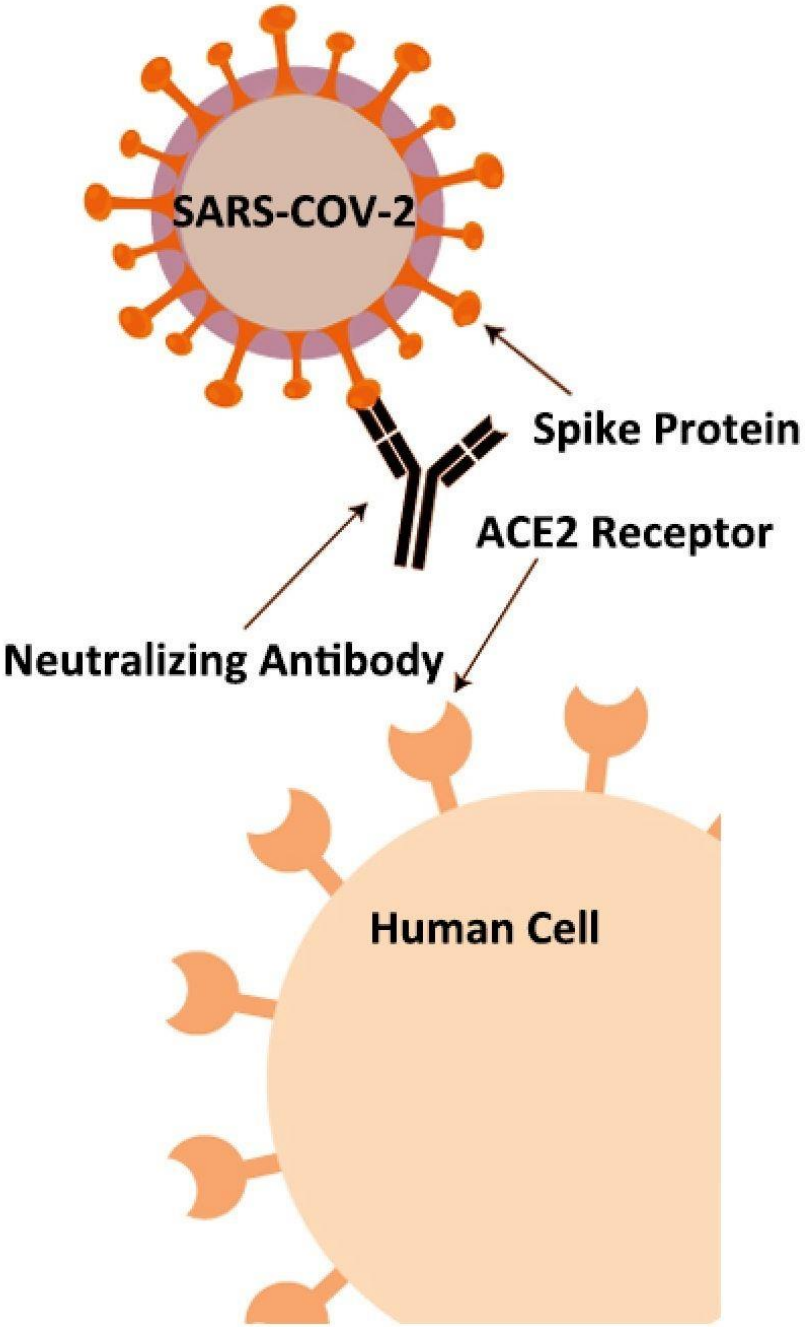
Herishanu et al. *Blood* 2021.

Major unknowns

- How well do anti-spike protein antibody levels correlate with neutralizing antibody titers?
- How important are T cell responses and are they more preserved in our patients (especially those on ibrutinib)? Potent memory T cell responses are induced in healthy adults by Pfizer vaccine[1]
- How well will “boosters” work? How many doses? Should we stop therapy for immunization in very stable patients?

Sahin et al. Nature 2021

How Neutralizing antibodies work



Evaluating response to vaccination

- Planned to enroll 500 patients at multiple centers around USA. Currently we are at ~210-230 (several centers did not enroll).
- Pre-vaccine N- and quantitative S-antibody testing, looking for prior COVID.
- Post-vaccine serial analyses of quantitative S antibody titers.

1. Pre-dose 2.
2. 1m, 6 and 12m post-dose 2.

- Subgroup of 80 patients:

1. Neutralizing antibodies 1 month post-dose 2.
2. T cell responses 1 month post-dose 2.

- Correlations between S antibody titers and neutralizing antibodies/T cell responses.

Future Directions

- Given smaller than planned total accrual and our knowledge that patients are having booster shots, we are amending the protocol to capture patients pre- and post-booster dose, to evaluate T cell and NA titers in these patients.

Thank you!

wwierda@mdanderson.org