Industry Perspective: Minimal (Measurable) Residual Disease in Chronic Lymphocytic Leukemia

Davy Chiodin with Nadia Ono

Regulatory Science – Acerta (A Member of the AstraZeneca Group)

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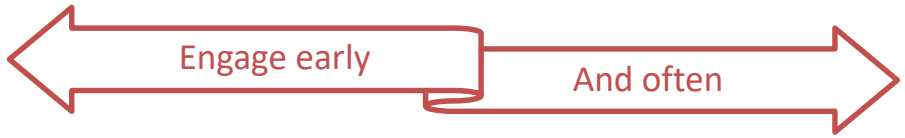
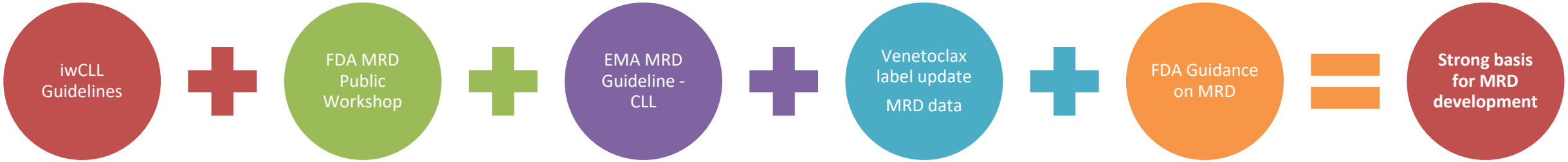
MRD in CLL: Where are we now?

MRD Towards Use as a Registrational Endpoint in CLL



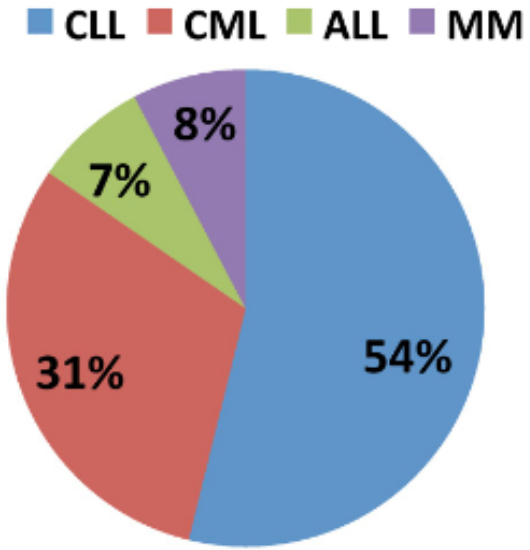


2008 2012 2014 2018 2018

FDA Analysis of MRD Data in Heme Malignancy Applications

- MRD data was included in about 40% (13 of 34) of applications between 2014 to 2016
  - 54% were CLL applications
  - For 6 of 10 applications that proposed it, MRD data was deemed adequate for inclusion in USPI

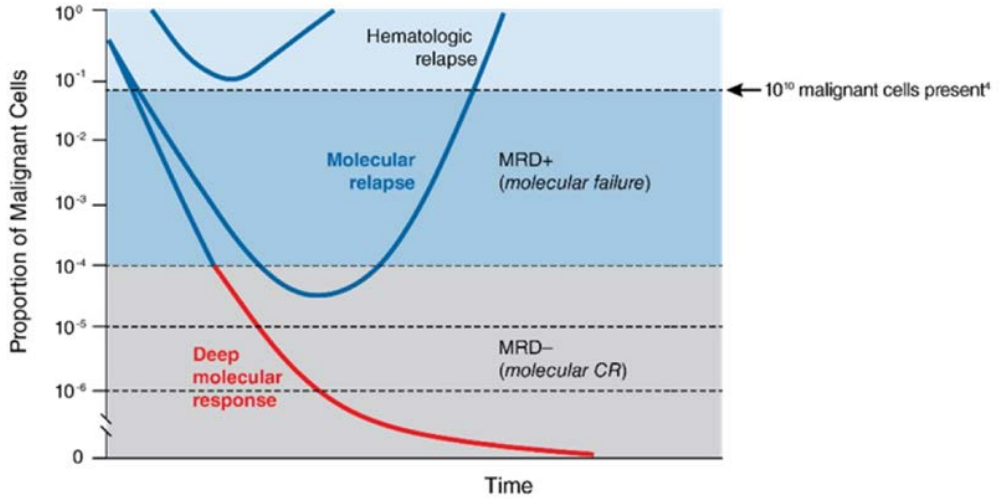
- Reasons MRD data was deemed inadequate
  - Missing data among those in CR
  - Disparate sample sources (i.e., blood vs. bone marrow)
  - High amount of test failures (i.e., inability to identify a clone)
  - Incomplete test characteristics data (i.e., limit of detection)
  - Lack of test validation in the proposed disease setting
  - Incomplete planned statistical analysis



Gormley N, et al. *ASCO*. 2017.

Challenges in Application of MRD in CLL[1]

- Standardization of detection technologies and assays
- Determination of MRD thresholds
- Optimization of measurement timepoints and sampling compartment
- Optimization of definition of patient population
- **Establishment of correlation of MRD negativity with PFS or OS**



Graphical definitions of MRD.
Adapted from Bruggemann M, et al.[2]

1.Gormley NJ, Farrell AT, Pazdur R. Minimal residual disease as a potential surrogate end point—lingering questions. *JAMA Oncol*. 2016 Sep 15. [Epub ahead of print], PMID: 27632052. 2.Bruggemann M, et al. *Blood*. 2012;120:4470-4481.

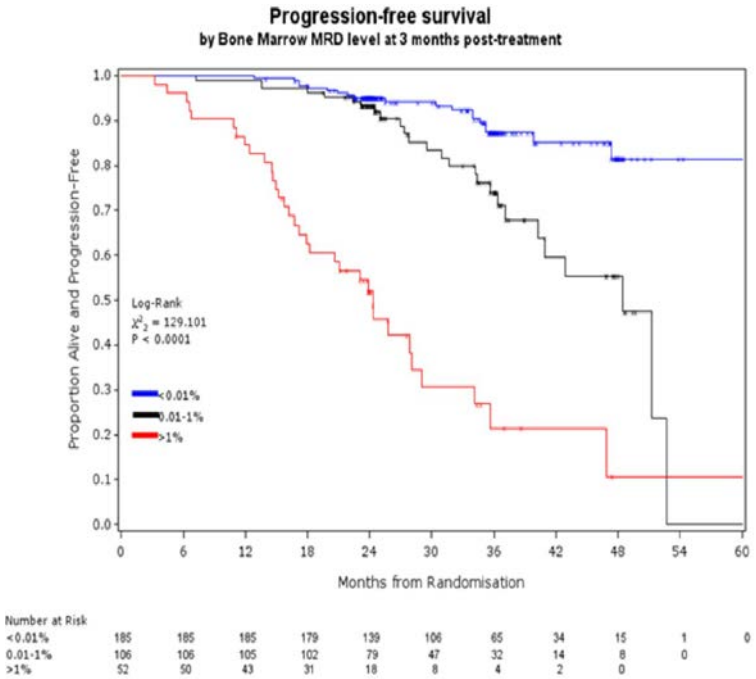
Relevant Precedents

CLL Treatment Evolution

Chemo (Chlorambucil, Fludarabine) → **Chemoimmunotherapy (FCR/BR)** → **Targeted small molecules (BTKi, BCL2i, PI3Ki)**

- ***Chemoimmunotherapy***: fixed treatment duration (6 mo) leading to **longer PFS** over time makes it more lenghty to bring new agents to patients
  - Need for a **surrogate endpoint** for PFS/OS **that can be read out earlier**
  - **MRD** negativity **shows correlation with longer PFS and survival** for chemoimmunotherapy

- ***Field moving to treating to MRD negativity especially with new targeted agents (BTKi, BCL-2) that are showing longer PFS***
  - While BTKi are effective at extending PFS, they are given to progression and are not as effective in achieving deeper responses (i.e. CRs) alone



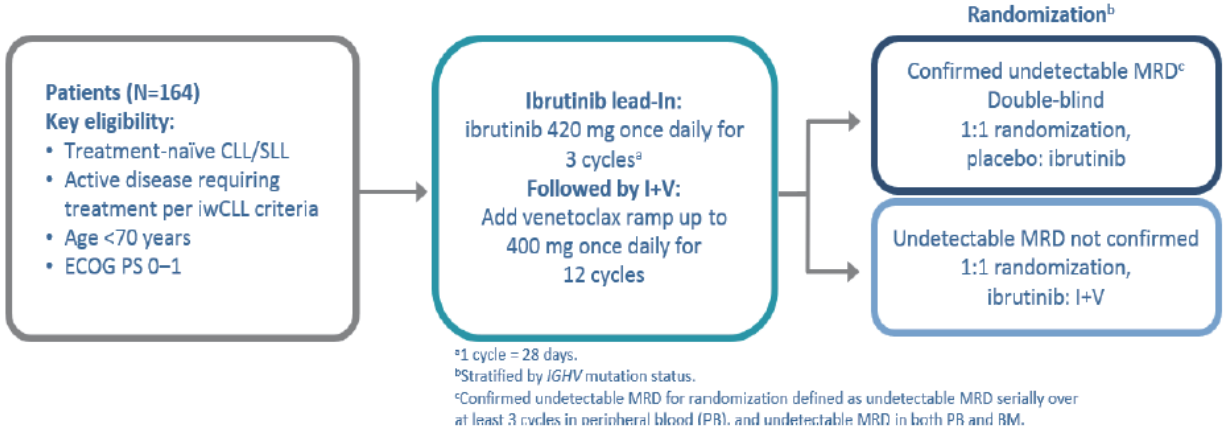
Rawstron et al, 2015

ASCO/EHA 2018 Highlights in CLL/MRD

(S806) IBRUTINIB LEAD-IN FOLLOWED BY VENETOCLAX IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: PHASE 2 CAPTIVATE EARLY SAFETY AND EFFICACY RESULTS

Presenter: Paolo Ghia, *Milano, Italy*

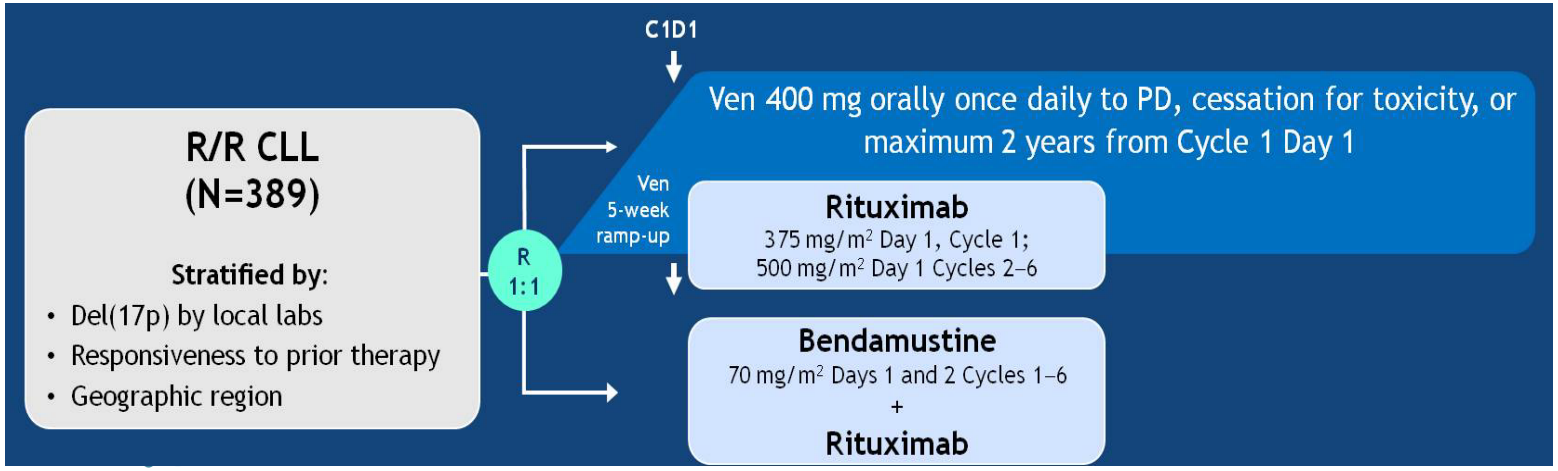
Author(s): Paolo Ghia, Constantine Tam, Tanya Siddiqi, Ian Flinn, Xavier Badoux, Thomas Kipps, John Allan, Alessandra Tedeschi, John Pagel, Bryone Kuss, Eva Gonzalez-Barca, Karl Eckert, Cathy Zhou, Joi Ninomoto, James Dean, Danelle James, William Wierda



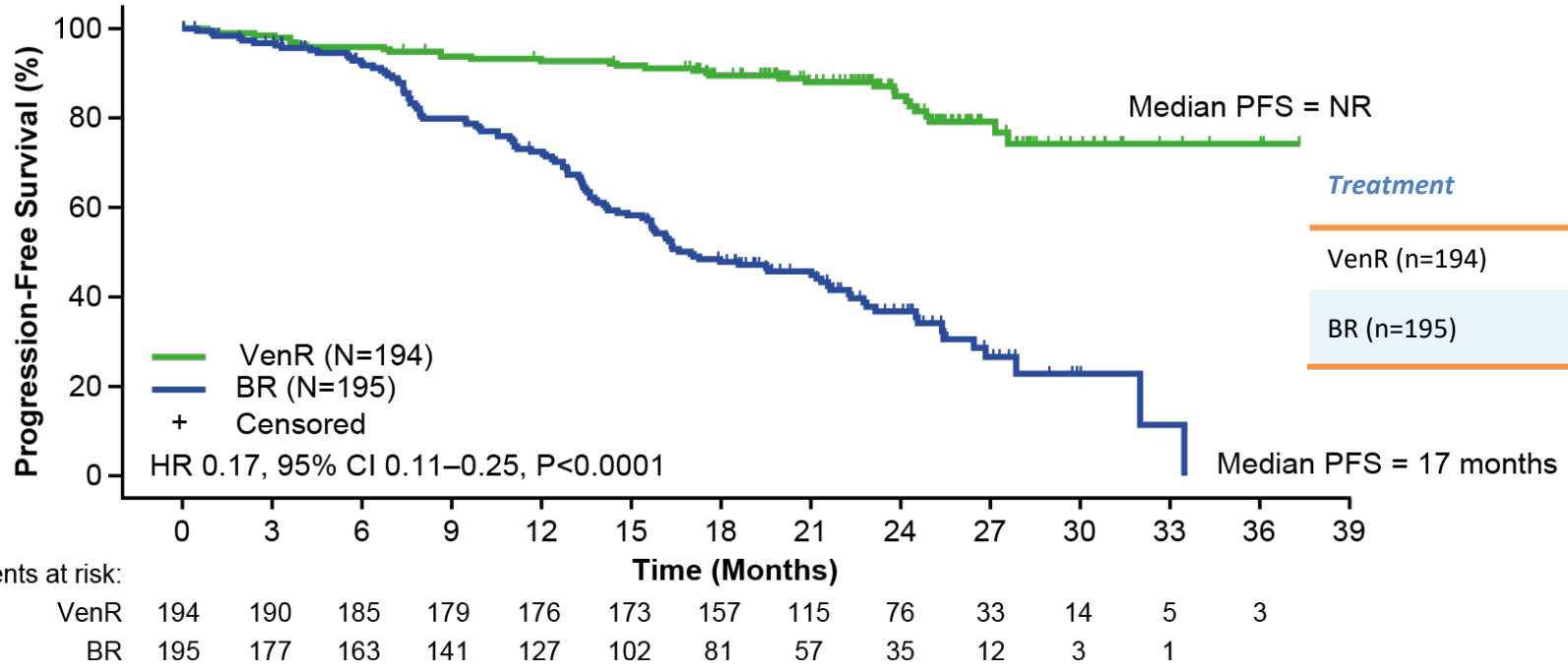
(S805) HIGH, DURABLE MINIMAL RESIDUAL DISEASE (MRD) NEGATIVITY WITH VENETOCLAX + RITUXIMAB IN RELAPSED/REFRACTORY CLL: MRD KINETICS AND RESPONSES IN CYTOGENETIC RISK GROUPS IN PTS FROM PHASE 3 MURANO STUDY

Presenter: Peter Hillmen, *Leeds, UK*

Author(s): Peter Hillmen, John F. Seymour, Anton W. Langerak, Barbara Eichhorst, Carolyn Owen, Sarit Assouline, Ann Janssens, Paula Marlton , Xavier Badoux, Rogier Mous, Brenda Chyla, Rod Humerickhouse, Michelle Boyer, Kathryn Humphrey, Elizabeth Punnoose, Jue Wang, Jenny Wu, Yanwen Jiang, Mehrdad Mobasher, Arnon P. Kater



MURANO PFS Results – VenR vs BR



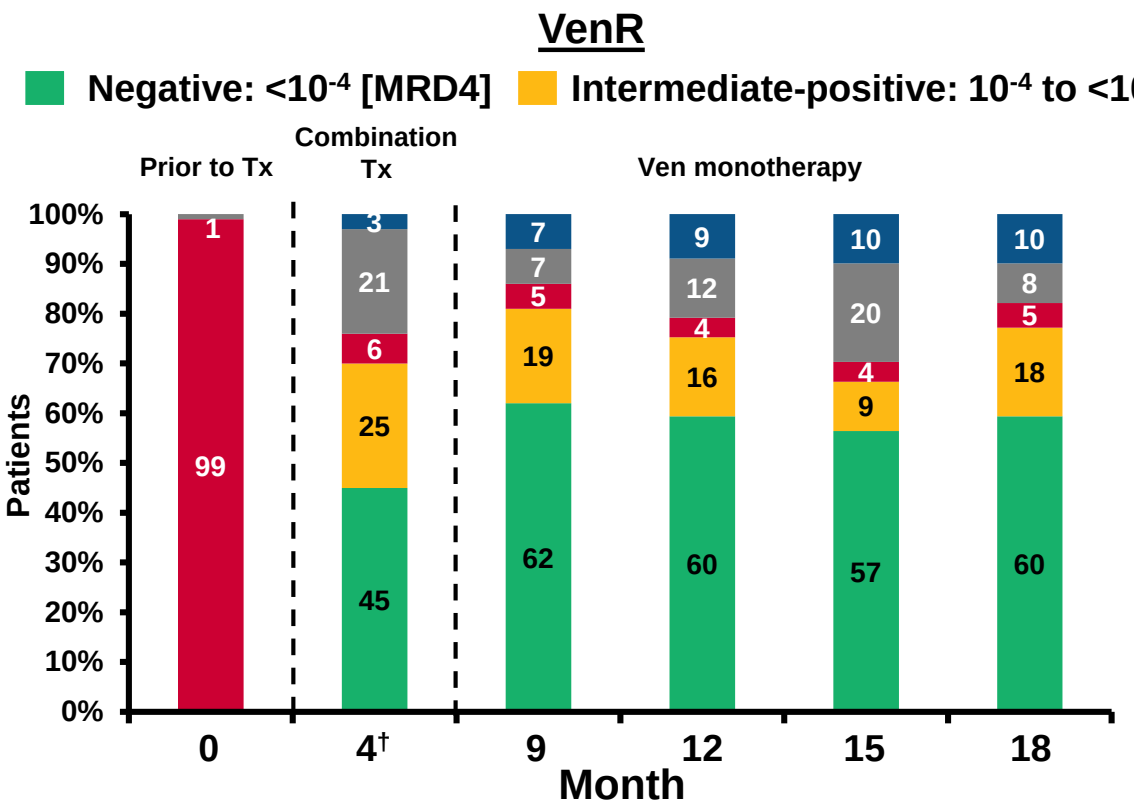
Treatment	*Patients with events, n (%)*	*1-year PFS, %*	*2-year PFS, %*
VenR (n=194)	32 (16.5%)	92.7%	84.9%
BR (n=195)	114 (58.5%)	72.5%	36.3%

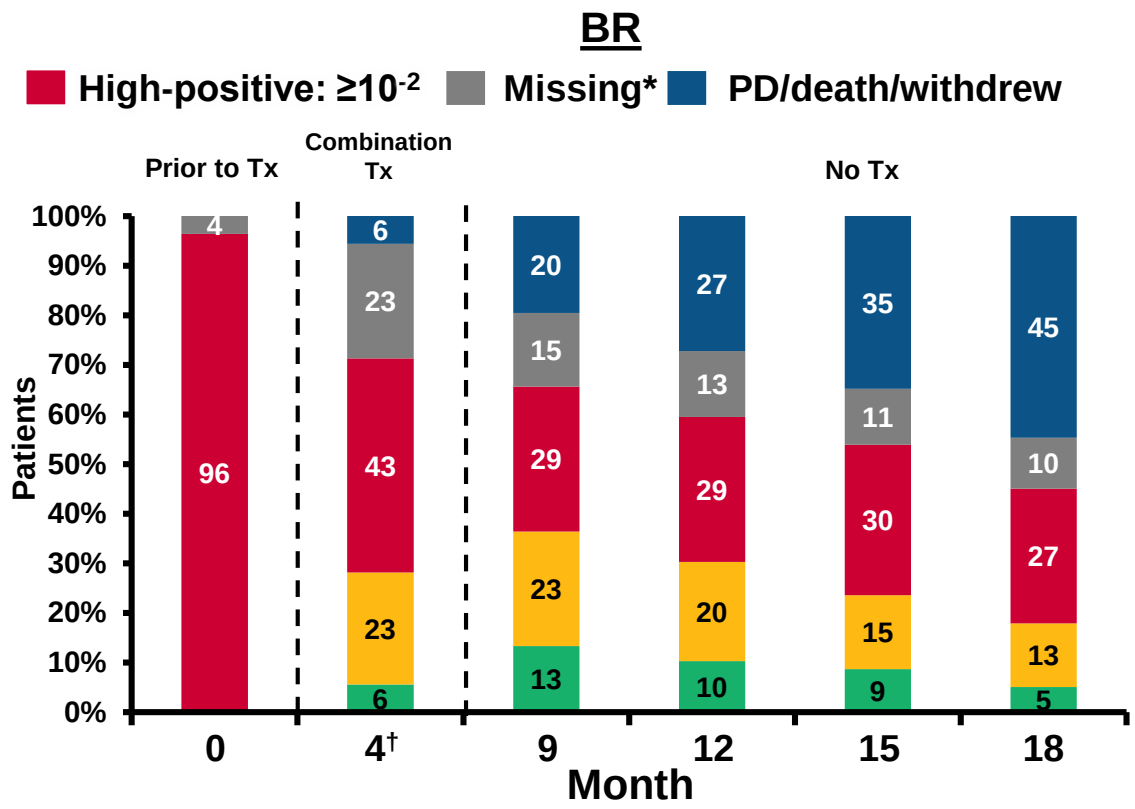
- Consistent treatment effects on PFS observed in all subgroups assessed
- The benefit of VenR over BR was confirmed by an independent review committee assessment of PFS
  - HR 0.19, 95% CI 0.13–0.28, P<0.0001
- Median (range) duration of follow-up, 23.8 (0.0–37.4) months: VenR, 24.8 months; BR, 22.1 months
  - Cutoff date for primary analysis: 8 May 2017

CI, confidence interval; HR, hazard ratio; NR, not reached

Seymour JF, et al. N Engl J Med 2018;378:1107–20.

Deep MRD Response with VenR vs BR





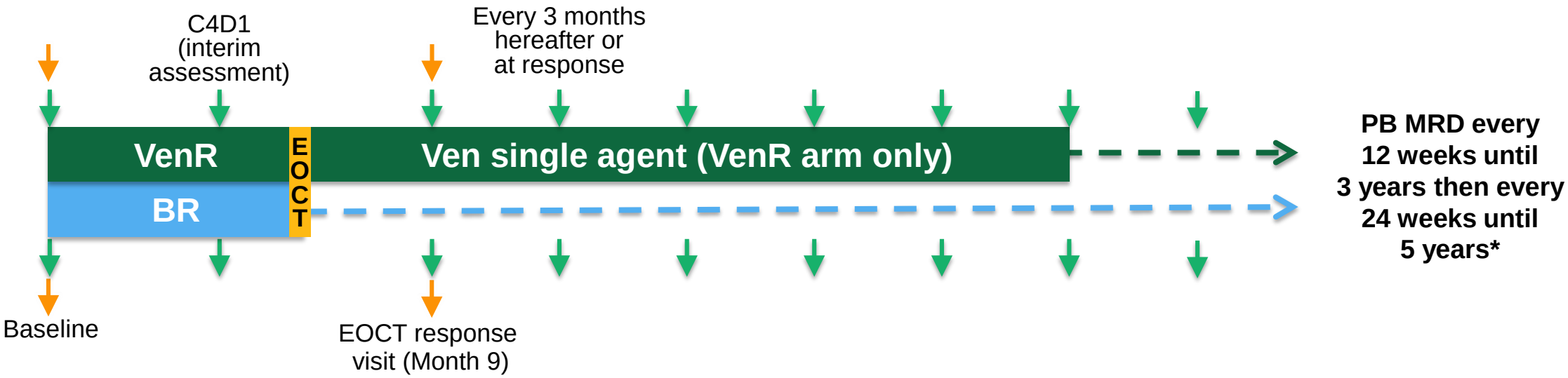
- Most MRD assay positive patients in the VenR arm were intermediate-positive (10^{-4} to $<10^{-2}$)
- 17 VenR patients achieved MRD– status after 9 months

- Most MRD assay positive patients in the BR arm were high-positive: $\geq 10^{-2}$
- Two BR patients achieved MRD– status after 9 months

*Includes patients who have reached a specific time point but did not have MRD sample collected or had an undetermined MRD result, and patients who have not reached that particular time point due to reasons other than PD/death. †First assessment. Tx, treatment

Assessment of MRD in MURANO

- MRD negativity: <1 CLL cell per 10 000 leukocytes (10^{-4})[1]
- Sample collection times for PB (↓) and BM (↓) identical in both arms



- MRD was centrally assessed by ASO-PCR[1] and/or multicolour flow cytometry[2] and highly concordant (85%)
- MRD status reported as follows:
  - MRD+ if **either** ASO-PCR or by flow cytometry is reported as positive
  - Analysis is by ITT population. Missing MRD data or assay failure is reported as MRD+

*BM MRD assessment performed on responding patients but not required, as determined by the INV

ASO-PCR, allele-specific-oligonucleotide polymerase chain reaction; INV, investigator; ITT, intent-to-treat

[1]Van der Velden VH, et al. Leukemia 2007;1:604–11;
[2]Rawstron AC, et al. Leukemia 2013;27:142–9.

Gaps and Next Steps for CLL in MRD

MRD Neg

- Methods and definition
- Does MRD + mean progression?
- MRD as response criterion

Depth

- What's the threshold for progression?
- Is deeper MRD negativity clinically relevant?

Verified Correlation

- Statistically verified correlation with PFS/OS (long term data)
- Prospective correlation plans agreed w HAs

Consortium!

Principles of Success

Consolidate	• 60 ongoing studies on ClinicalTrials.gov are examining MRD outcomes in CLL patients
Confirm	• Remarkable responses, but haven't demonstrated long-term survival advantage → Interest of regulators and payers
Align	• Collectively balance cost of the experiment with the relevance of the scientific questions
Healthy Competition	• Address the challenge of converting competition to healthy collaborations
Regulatory Partnership	• Leverage recent guidelines and start a dialogue to ensure appropriateness of the plans

Achieving Successful Application of MRD in CLL Requires Collaboration of All Stakeholders

- Understanding and inclusion of MRD in clinical trials
- Harmonize on MRD outputs (compartment, cut off and timepoint/event driven)

Industry

Consortia, WGs

- Platform for collaboration
- Venue for assessing progress and future directions

Consortium!

- Regulatory guidance and precedence
- Pathways to surrogacy

Regulators

Academia

- Generation and interpretation of data
- Long term collaboration

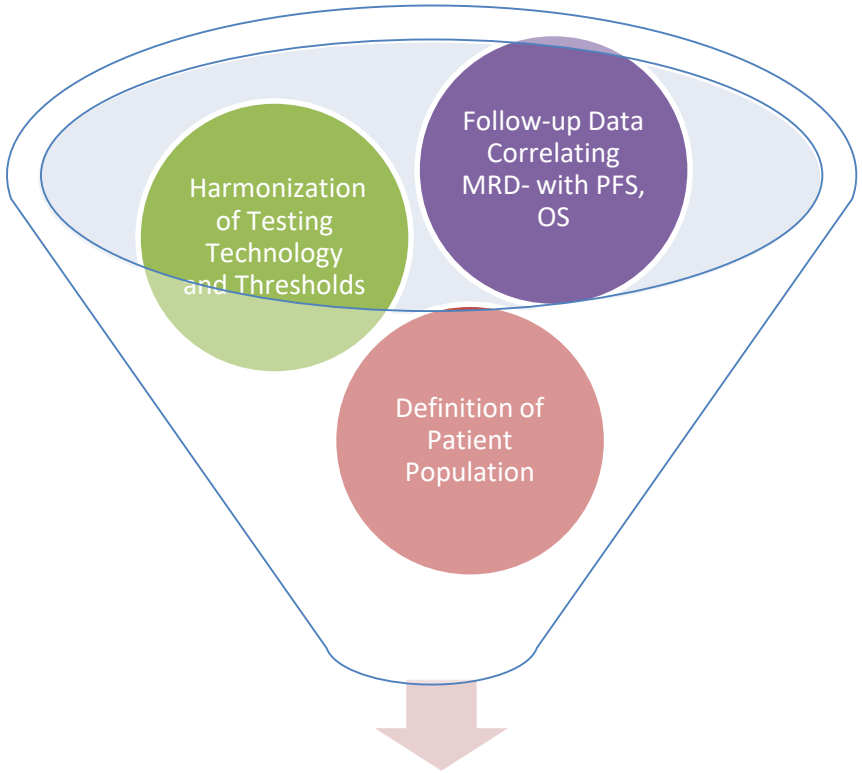
U.S. FOOD & DRUG ADMINISTRATION

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

THANK
YOU !

Back-Up Slides

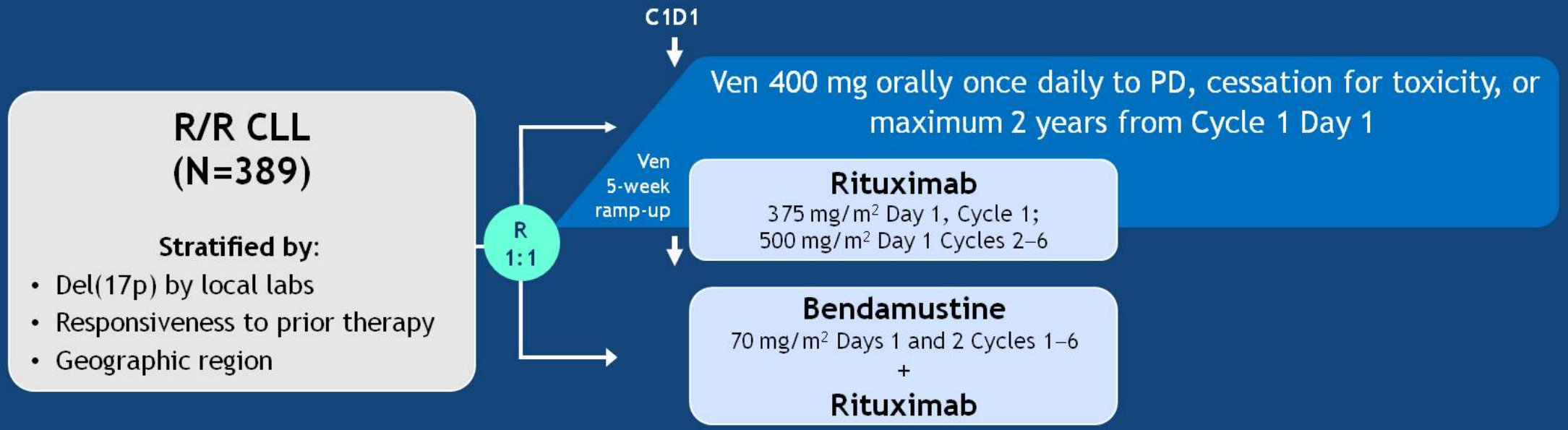
Future Progression of MRD for CLL Indications



Progress Towards:

1) MRD in a CLL indication statement
2) MRD as a surrogate endpoint for PFS and or OS to gain accelerated approval
3) Incorporation of MRD status for treatment decision

MURANO Study Design and Endpoints



Primary Endpoint	Investigator-assessed PFS
Secondary MRD Endpoint	MRD– in peripheral blood (PB) at the end of combination treatment (EOCT) visit
Exploratory MRD Endpoints	MRD– in bone marrow (BM) at the EOCT visit MRD– in PB over time

C1D1, Cycle 1 Day 1; PD, progressive disease

Seymour JF, et al. New Engl J Med 2018;378:1107-20.

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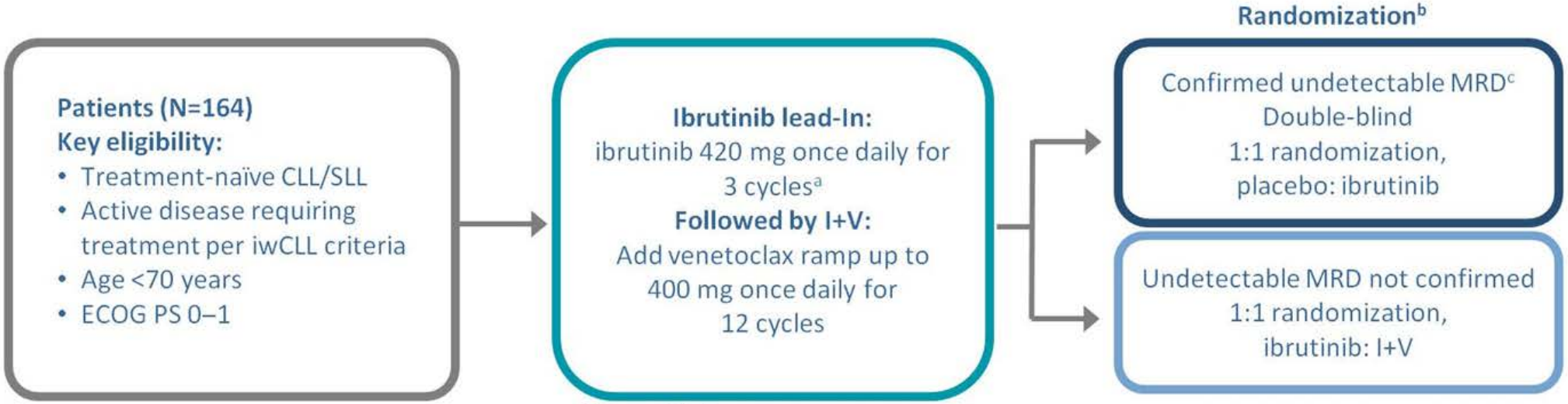
Presented By Peter Hillmen at 2018 ASCO Annual Meeting

Phase 2 CAPTIVATE Study Design (NCT02910583)



[a]1 cycle = 28 days.
[b]Stratified by *IGHV* mutation status.
[c]Confirmed undetectable MRD for randomization defined as undetectable MRD serially over at least 3 cycles in peripheral blood (PB), and undetectable MRD in both PB and BM.

Study Populations:

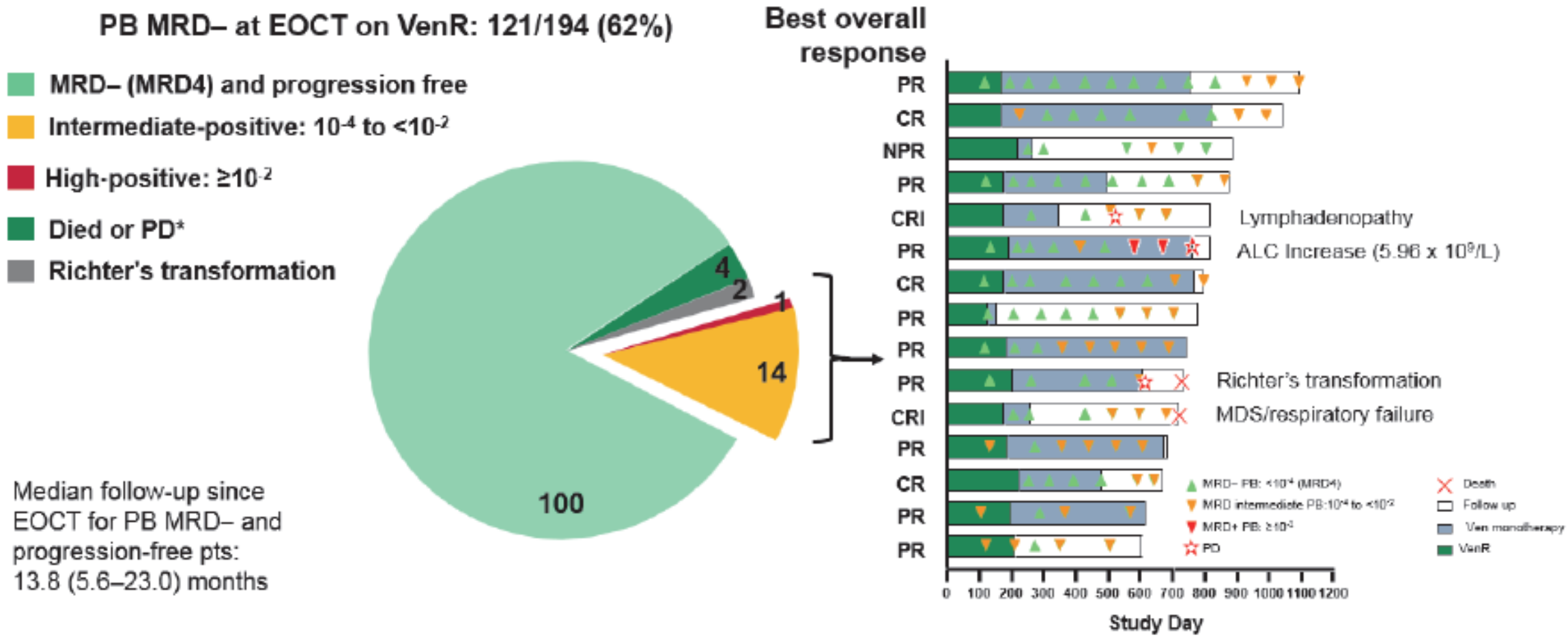
- MRD cohort (N=164): exposure and safety analysis
  - Safety Run-in: first 14 patients completed C15 treatment (12 cycles of I+V); no dose-limiting toxicities (DLT) or clinical TLS during first 6 weeks of I+V combination
  - Prespecified analysis of the first 30 patients who completed C9 treatment (6 cycles of I+V) for MRD evaluation
- Fixed Duration cohort (N=159): separate cohort; analysis not shown

3

ASCO 2018, 1142 Wierda et al.

CDDF Cancer Drug Development Forum

Most Patients Who Achieved PB MRD– on VenR Remained MRD– and Progression Free



P. Hillmen, A. Janssens, A. Langerak et al., Abstract S 805

FDA Approved Venetoclax Label

- April 2016: M13-982 MRD data in approved label
  - 14.2 R/R Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Monotherapy

> MRD was evaluated in peripheral blood and bone marrow for patients who achieved CR or CRi, following treatment with VENCLEXTA. Three percent (3/106) achieved MRD negativity in the peripheral blood and bone marrow (less than one CLL cell per 10^4 leukocytes).

- September 2018: MURANO MRD data added to venetoclax label
  - 14.1 R/R Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Combination Therapy

> Minimal residual disease (MRD) was evaluated using allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). The definition of negative status was less than one CLL cell per 10^4 leukocytes. At 3 months after the last dose of rituximab, the MRD negativity rate in peripheral blood in patients who achieved PR or better was 53% (103/194) in the VEN+R arm and 12% (23/195) in the B+R arm. The MRD-negative CR/CRi rate at this timepoint was 3% (6/194) in the VEN+R arm and 2% (3/195) in the B+R arm.

EMA Approved Venetoclax SmPC

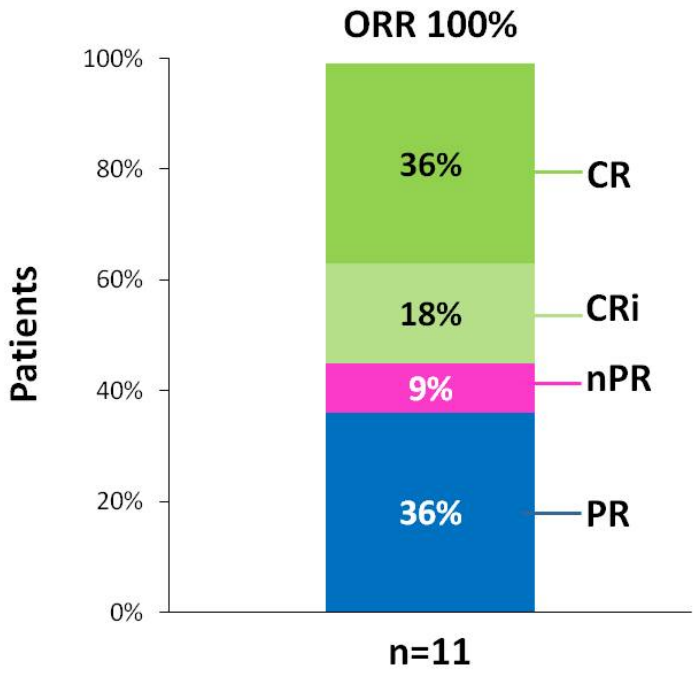
- MRD in venetoclax label for R/R CLL with 17p deletion or TP53 mutation (Study M13-982)

Minimal residual disease (MRD) was evaluated using flow cytometry in 93 of 158 patients who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), or partial remission (PR) with limited remaining disease with venetoclax treatment. MRD negativity was defined as a result below 0.0001 (<1 CLL cell per 10^4 leukocytes in the sample). Twenty-seven percent (42/158) of patients were MRD negative in the peripheral blood, including 16 patients who were also MRD negative in the bone marrow.

- MRD in CLL patients who were previously treated with and failed ibrutinib or idelalisib therapy (Study M14-032)

Twenty five percent (16/64) of patients were MRD negative in the peripheral blood, including 1 patient who was also MRD negative in bone marrow.

Deep Responses Achieved With 12 Cycles I+V With Undetectable MRD in PB and BM



MRD and Full ORR Assessments to Date (n=11)	CR/CRi (n=6)	PR/nPR (n=5)[a]
Confirmed undetectable MRD (n=9)	6/6[b]	3/5
Detectable MRD (n=2)[c]	0/6	2/5

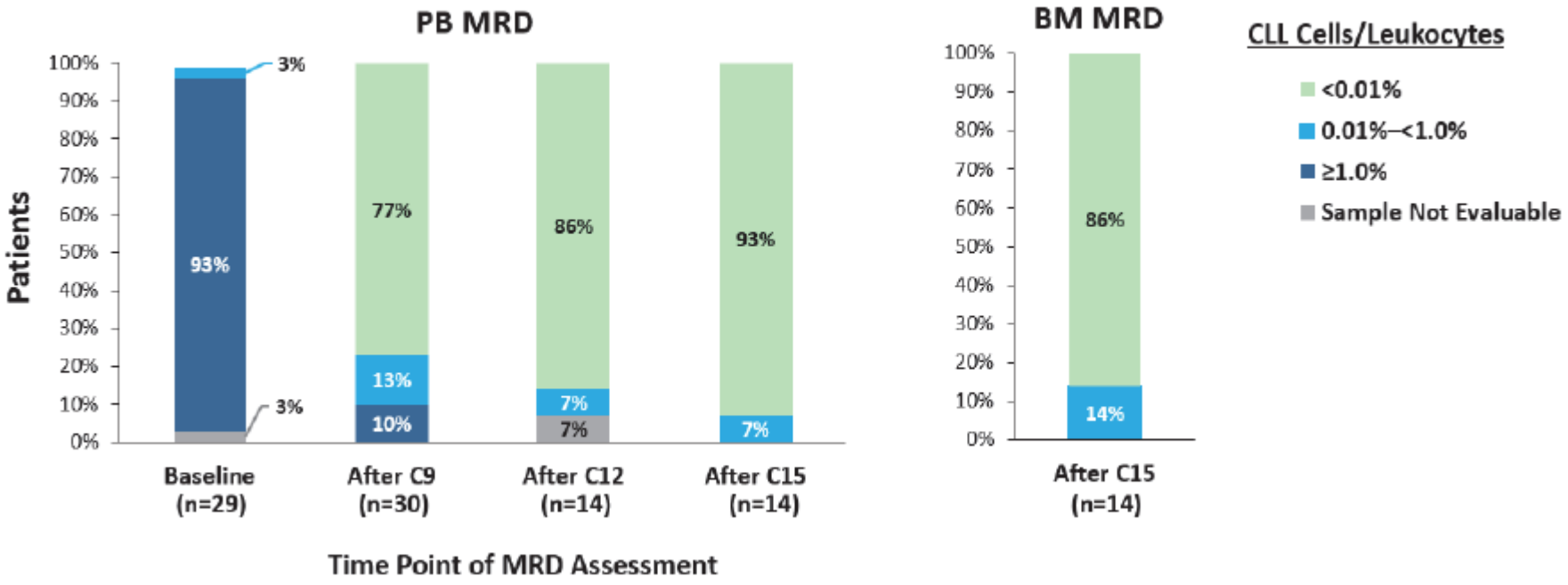
[a]4/5 patients had LN 1.6 to 2.5 cm.
[b]Includes 1 patient with variant CLL.
[c]CLL cells <1% in these 2 patients.

- Clinical response assessment in 11/14 patients who completed 12 cycles of I+V
  - 6/11 (55%) CR/CRi and 5/11 (45%) nPR/PR
- Confirmed undetectable MRD ($<10^{-4}$) in all patients with CR/CRi
- CR/CRi in 2/2 patients with del17p and 4/9 patients without del17p

ASCO 2018, 1142 Wierda et al.

Presented By William Wierda at 2018 ASCO Annual Meeting

CAPTIVATE Study MRD Outcomes



P. Ghia, A. Tedeschi, B. Kuss et al., Abstract S806