Hi

#iwCLL2019

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Disclosures

Roche:TravelGrants

Abbvie: Honoraria

Treatment of CLL from 2019 onwards:

A prospective, open-label, multicenter randomized phase III trial to compare the efficacy and safety of ***fixed-duration venetoclax plus obinutuzumab*** versus chlorambucil plus obinutuzumab and in previously untreated patients with CLL and coexisting medical conditions

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CLL *14*

TABLE OF *CONTENTS*

PURPOSE CONDUCT RESULTS CONCLUSION OUTLOOK

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PURPOSE CONDUCT ***RESULTS*** CONCLUSION OUTLOOK

Unfit *or fit?*

FIRSTLINE THERAPY *Unfit*

- FIXED-DURATION CHEMOIMMUNOTHERAPY
- CONTINUOUS INDEFINITE MONOTHERAPY

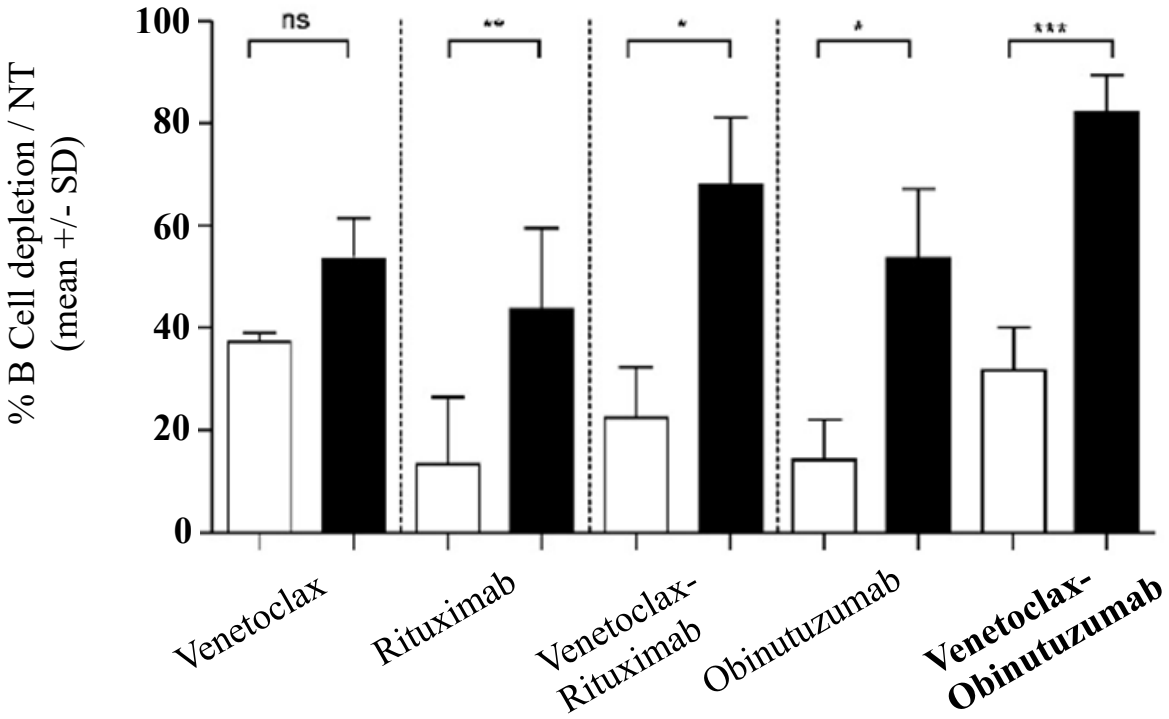
FIRSTLINE THERAPY *Unfit*

- FIXED-DURATION CHEMOIMMUNOTHERAPY
- CONTINUOUS INDEFINITE MONOTHERAPY
- ***FIXED-DURATION COMBINATION THERAPY***

Combine Venetoclax

VENETOCLAX COMBINED WITH OBINUTUZUMAB SHOWS IMPRESSIVE ADDITIVE EFFECTS IN PRE-CLINICAL MODELS

B-cell (isolated from primary CLL patient samples) depletion relative to untreated controls assessed by flow cytometry



P < .05, ** *P* < .01, *** *P* < .001,

**** *P* < .0001 by Student's t-test;

ns=not significant; NT=not treated;

SD=standard deviation

* Flinn IW. et al., Blood 2019

CHLORAMBUCIL-
OBINUTUZUMAB

31

Months

Progression-free survival*

VENETOCLAX-
OBINUTUZUMAB

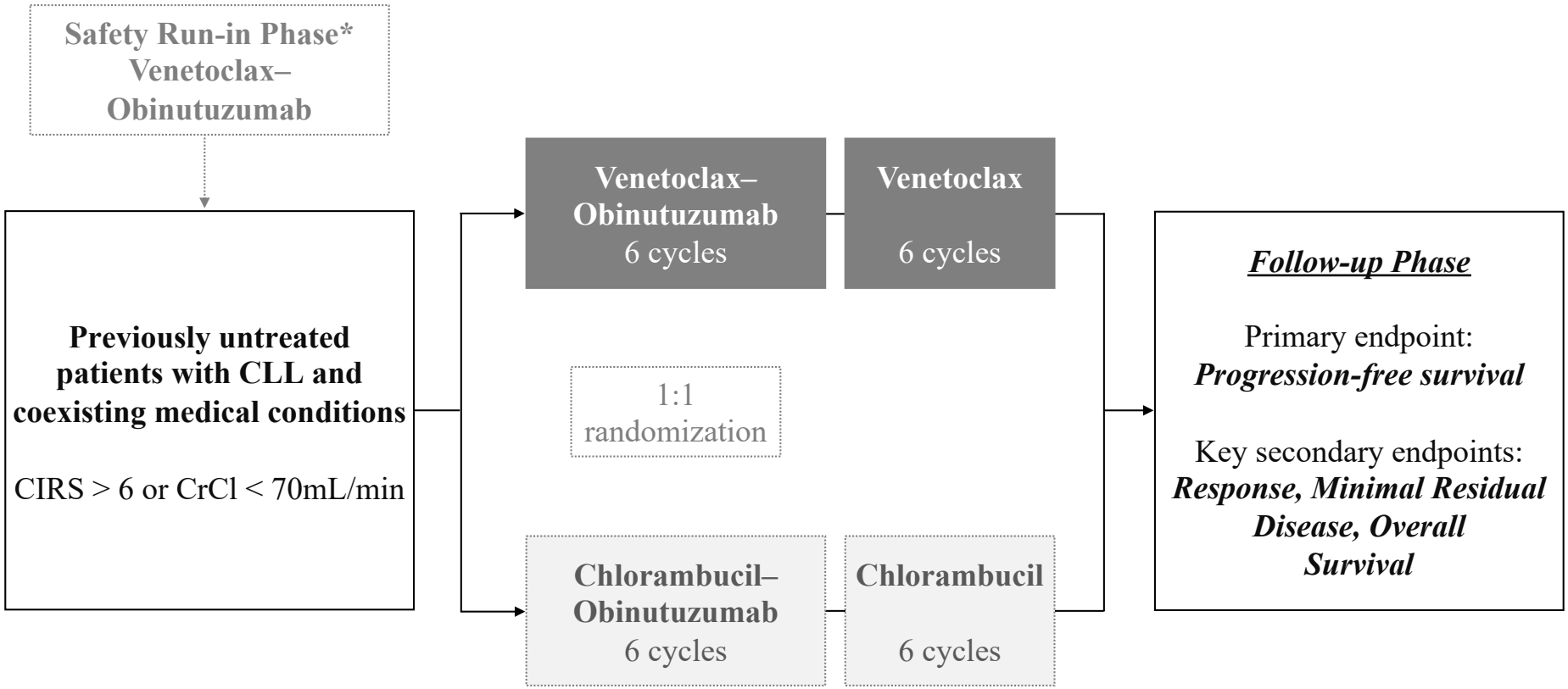
?

Months

Progression-free survival

* Goede V. et al.: NEJM 2011
Goede V. et al.: Final survival analysis of the CLL11 study, EHA 2018

Design *the trial*



* Fischer K et al. Venetoclax and Obinutuzumab in chronic lymphocytic leukemia, Blood 11 May 2017

Obinutuzumab *first,* Venetoclax *second*

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Either chlorambucil: orally, 0.5 mg/kg day 1 and day 15 ***cycle 1–12***, every 28 days

Or venetoclax: orally, 5-week ***ramp-up*** starting ***cycle 1 day 22***
[20, 50, 100, 200, 400 mg], then ***400 mg daily until end of cycle 12***

combined with obinutuzumab: IV infusion, 1000 mg ***day 1*** (or 100 mg day 1 and 900 mg day 2), 8, ***and 15 cycle 1***, 1000 mg day 1 ***cycles 2–6***, every 28 days

Patients´ *characteristics*

Patients´ characteristics I	**Venetoclax-Obinutuzumab**	**Chlorambucil-Obinutuzumab**
Number of patients, N	**216**	**216**
Median age in years	**72**	**71**
Binet stage		
A	21 %	20 %
B	36 %	37 %
C	43 %	43 %
Median total CIRS score	**9**	**8**
Median estimated CreaCl in ml/min	**65.2**	**67.5**
Risk category for TLS		
Low	13 %	12 %
Medium	64 %	68 %
High	22 %	20 %

Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

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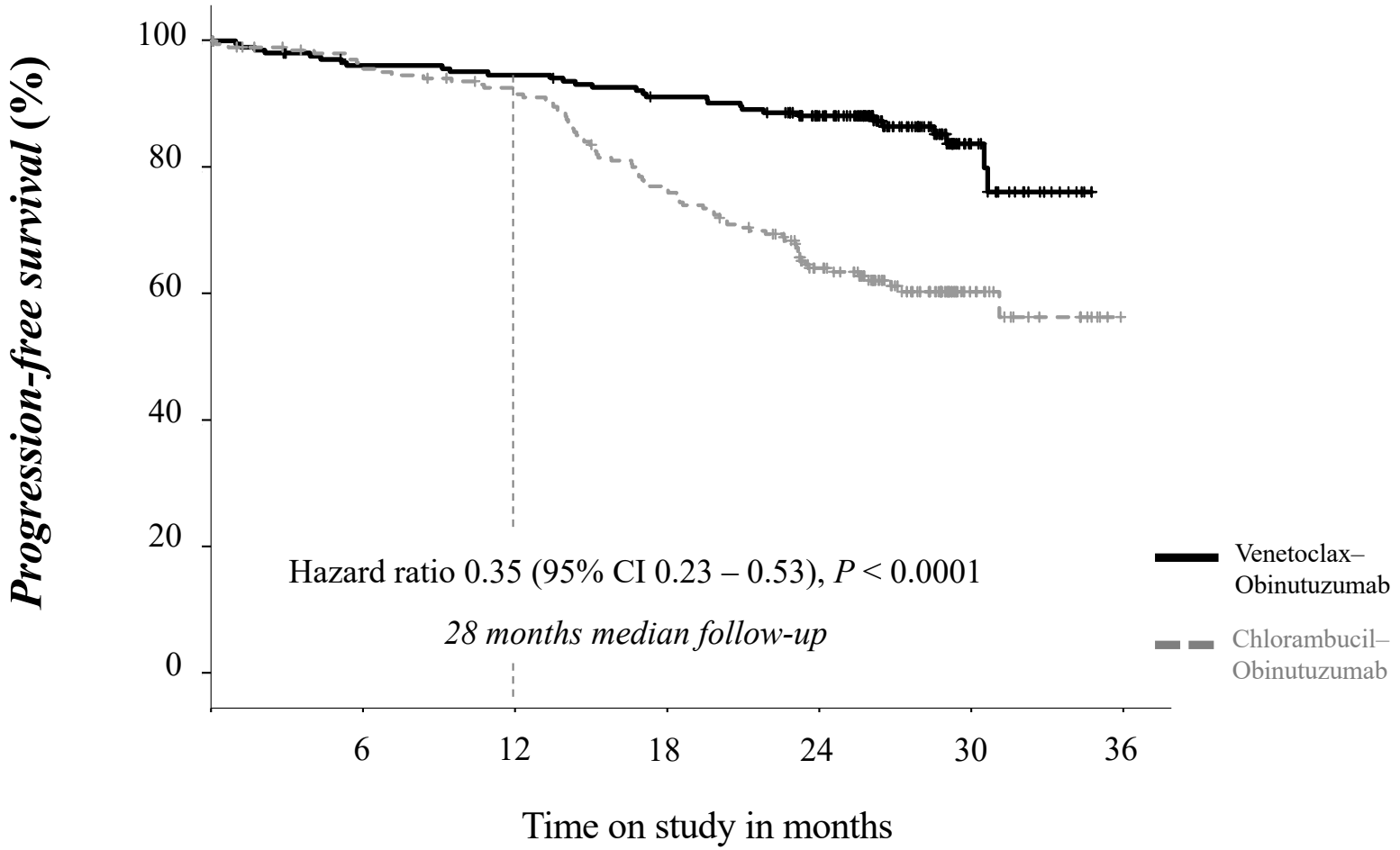
Patients´ characteristics II	**Venetoclax-Obinutuzumab**	**Chlorambucil-Obinutuzumab**
Number of patients, N	**216**	**216**
IGHV mutational status		
Unmutated	**61 %**	**59 %**
Mutated	38 %	40 %
Not evaluable	1 %	1 %
***TP53* deleted and/or mutated**	**12 %**	**12 %**
Cytogenetic subgroups*		
Deletion in 17p	**9 %**	**7 %**
Deletion in 11q	18 %	20 %
Trisomy in 12	18 %	21 %
No abnormalities	25 %	22 %
Deletion in 13q alone	31 %	31 %

* By Döhner et al. NEJM 2000

Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

Progression-free *survival*



Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

VENETOCLAX-
OBINUTUZUMAB

88

Percent

24-months

Progression-free survival

CHLORAMBUCIL-
OBINUTUZUMAB

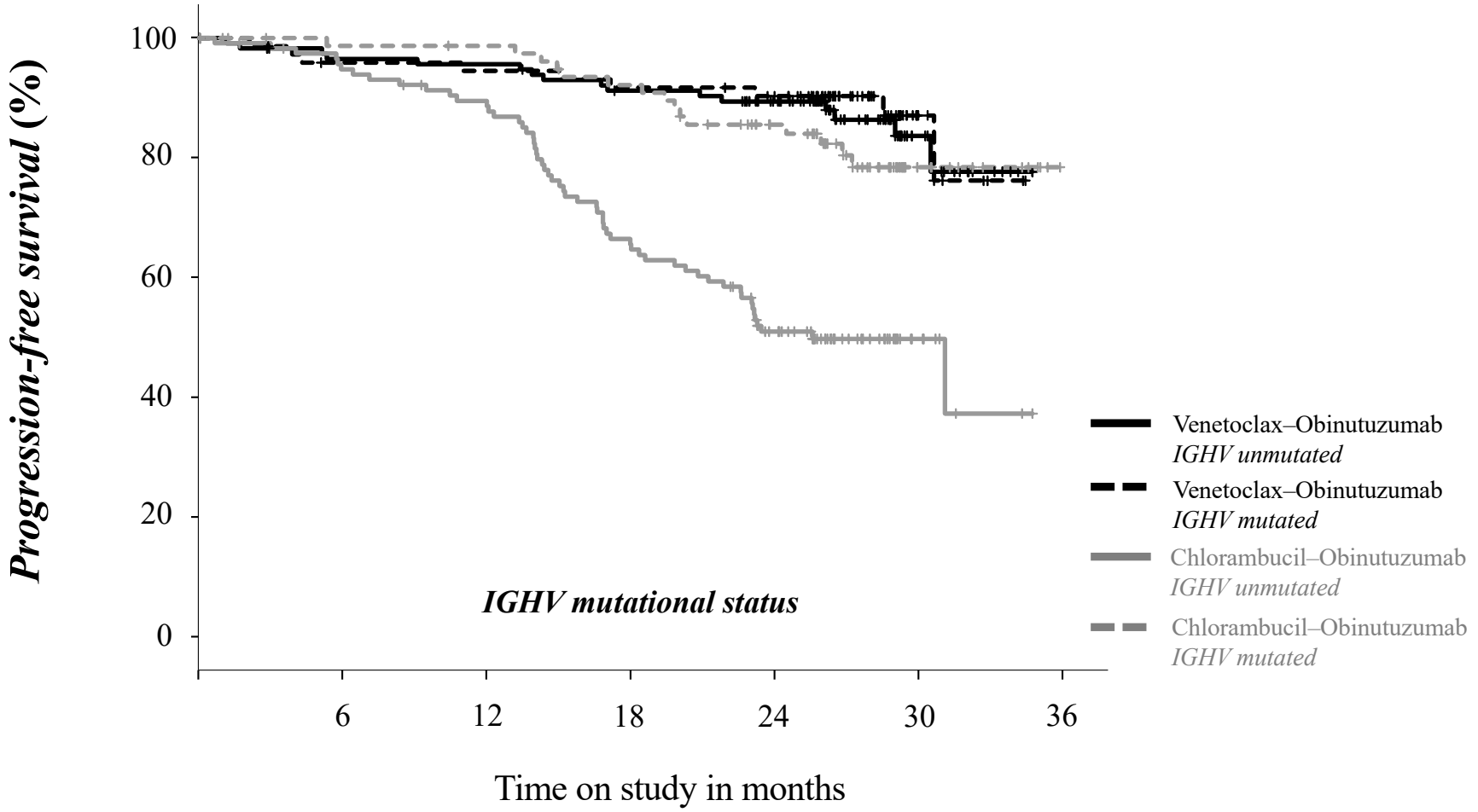
64

Percent

24-months

Progression-free survival

Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236



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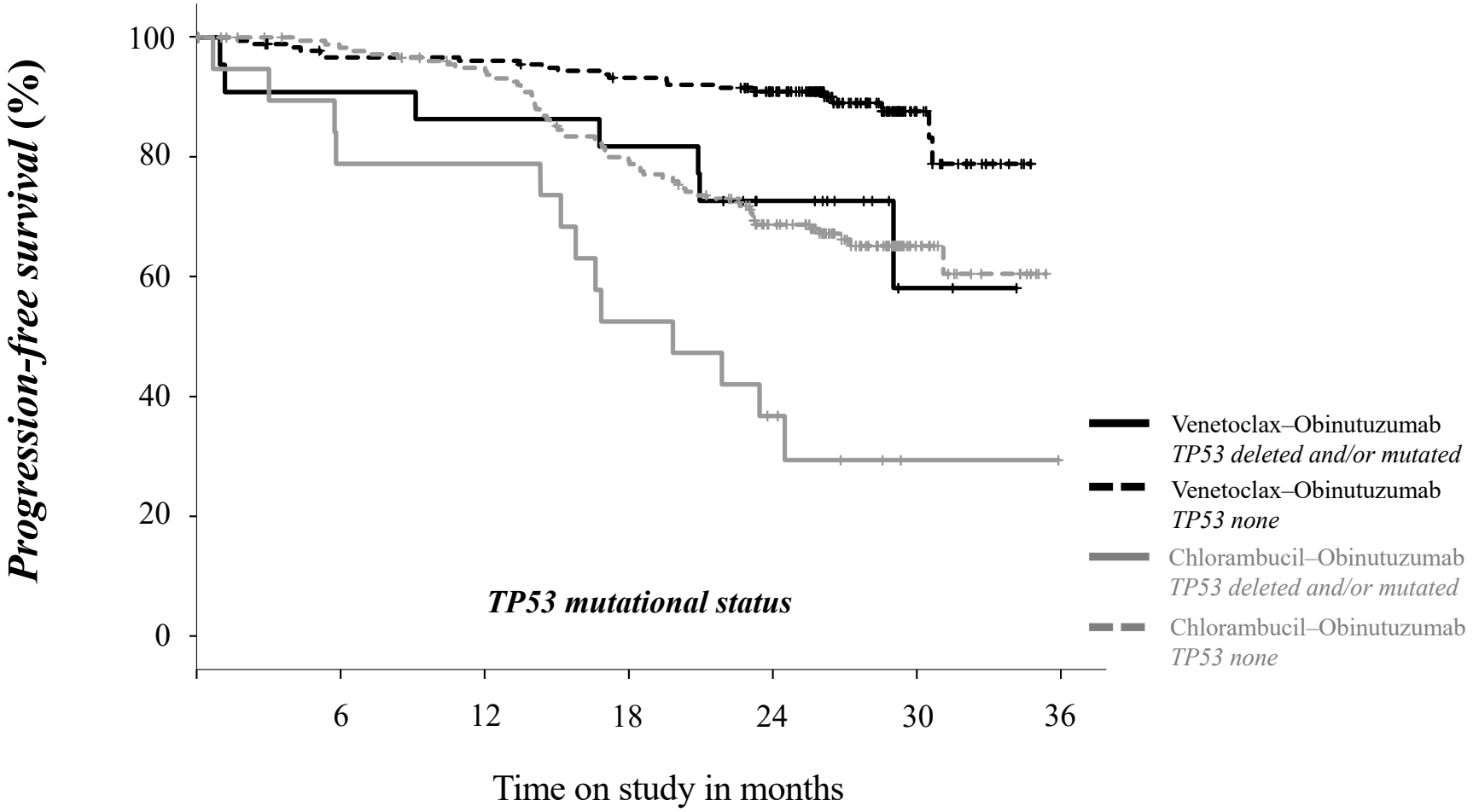

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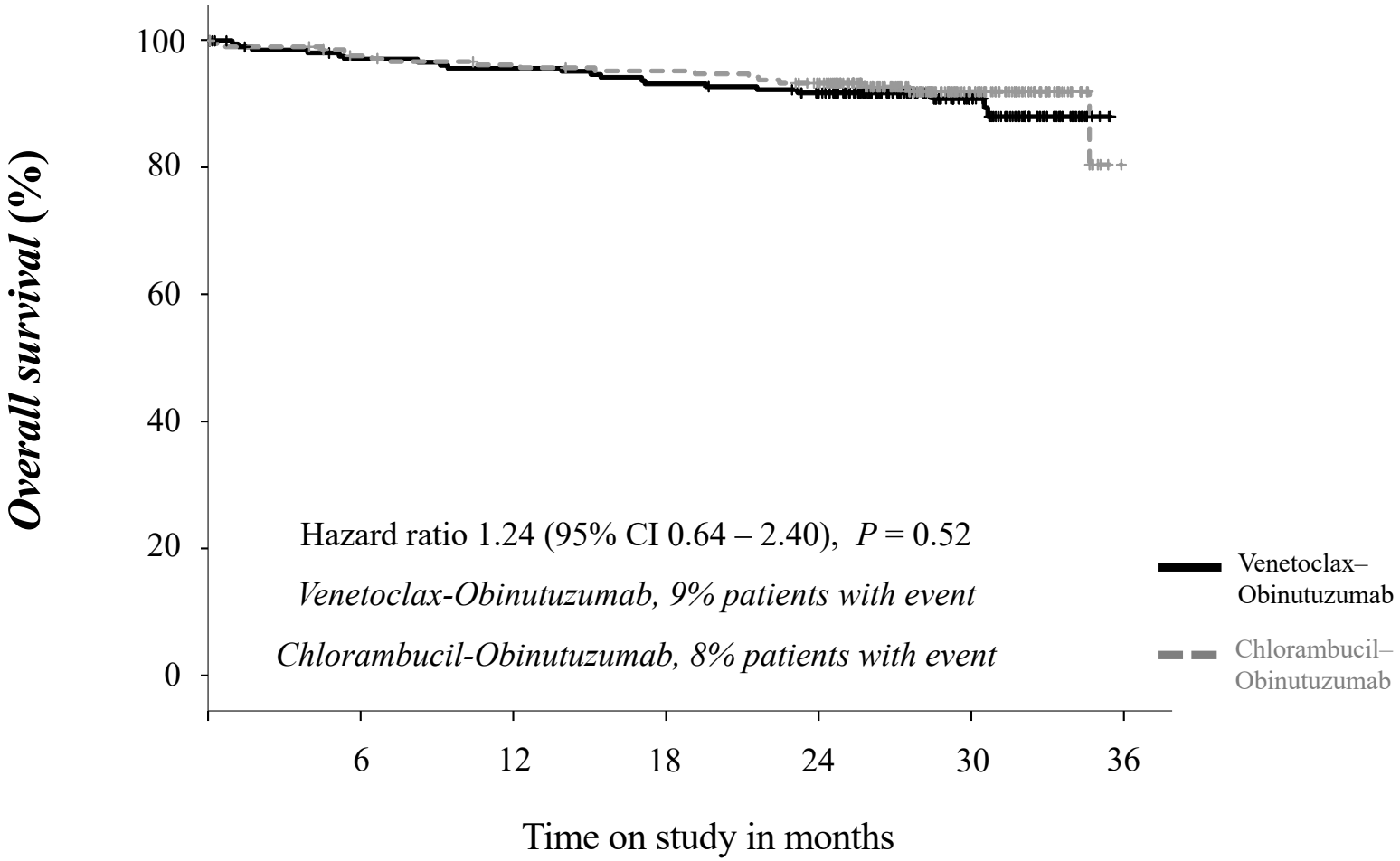


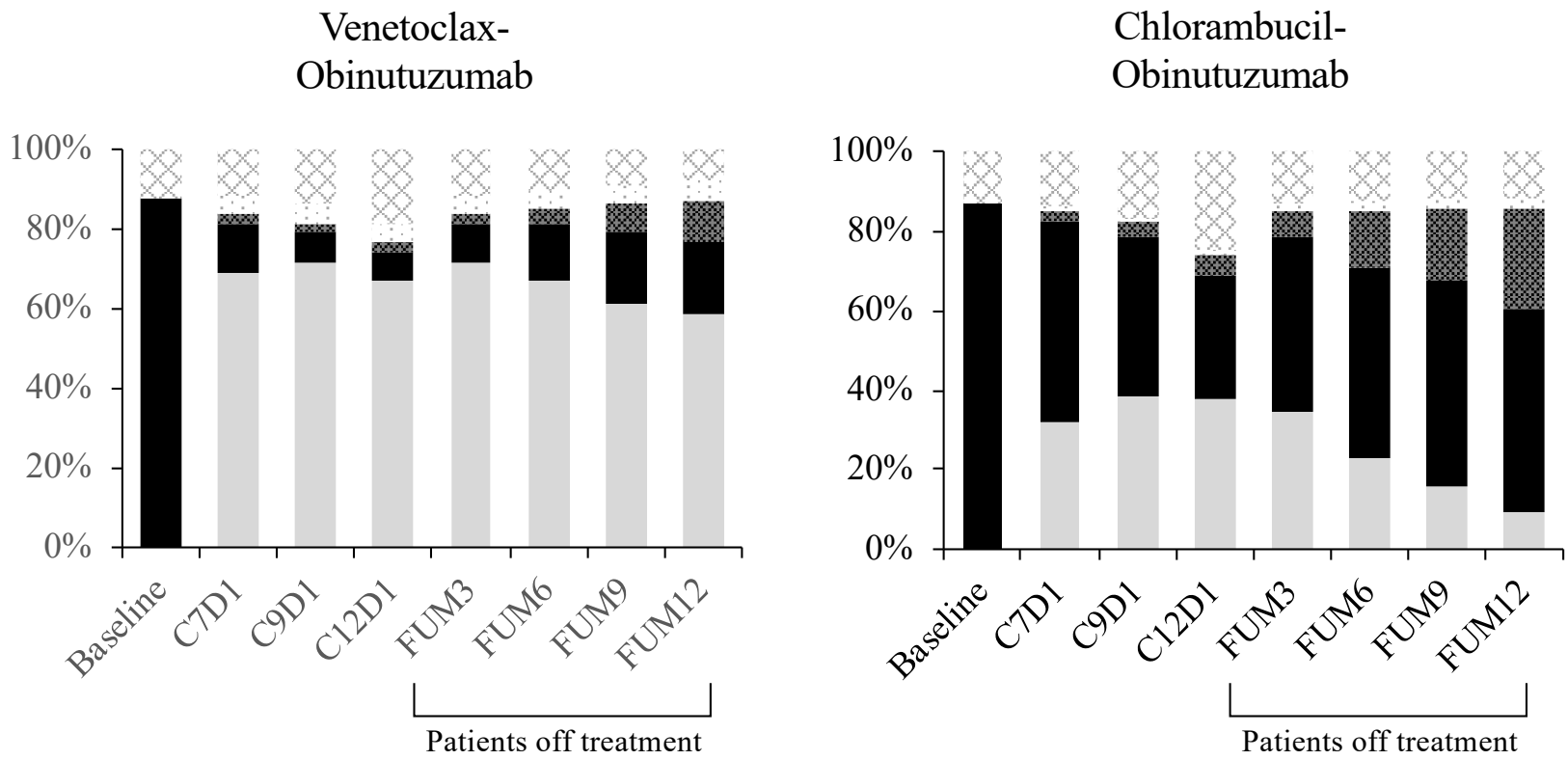
Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

MRD *in ITT*

Minimal residual disease status	**Venetoclax-Obinutuzumab**	**Chlorambucil-Obinutuzumab**	*P* value
Number of patients, N	216	216	
Peripheral blood			
Negative ($<10^{-4}$)	76 %	35 %	< 0.001
Negative ($<10^{-4}$) in complete response	42 %	14 %	< 0.001
Bone marrow			
Negative ($<10^{-4}$)	57 %	17 %	< 0.001
Negative ($<10^{-4}$) in complete response	34 %	11 %	< 0.001

By ASO-PCR 3 months after completion of treatment

Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236



Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

MRD negativity by NGS	**Venetoclax-Obinutuzumab**	**Chlorambucil-Obinutuzumab**
Number of patients, N	**216**	**216**
Minimal residual disease level		
$< 10^{-6}$	42 %	7 %
$\geq 10^{-6}$ and $<10^{-5}$	26 %	13 %
$\geq 10^{-5}$ and $<10^{-4}$	11 %	14 %
$\geq 10^{-4}$ and $<10^{-2}$	6 %	23 %
$\geq 10^{-2}$	5 %	29 %
No sample/not evaluable	12 %	14 %

By NGS in peripheral blood 3 months after completion of treatment

Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

Conclusion now

FIXED-DURATION *Venetoclax and Obinutuzumab ...*

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...can be safely administered

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compared to chlorambucil and obinutuzumab regarding PFS, overall response rate, complete response rate, MRD negative responses including all relevant subgroups such as *IGVH* unmutated, *TP53* mutated and/or deleted patients

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...achieves the highest rate of MRD negative responses

observed in a randomized prospective study so far

Fischer et al. N Engl J Med. 2019 Jun 6;380(23):2225-2236

Two paradigms

TWO TREATMENT ***paradigms***

- CONTINUOUS INDEFINITE MONOTHERAPY
- FIXED-DURATION COMBINATION THERAPY

CLL17

A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, MULTICENTRE PHASE-III TRIAL OF **IBRUTINIB** VERSUS **VENETOCLAX PLUS OBINUTUZUMAB** VERSUS **IBRUTINIB PLUS VENETOCLAX** FOR PATIENTS WITH PREVIOUSLY UNTREATED CLL

Study Lead: **Dr. Othman Al-Sawaf**

HOVON

Nordic CLL Study Group

DEUTSCHE STUDIENGRUPPE CLL

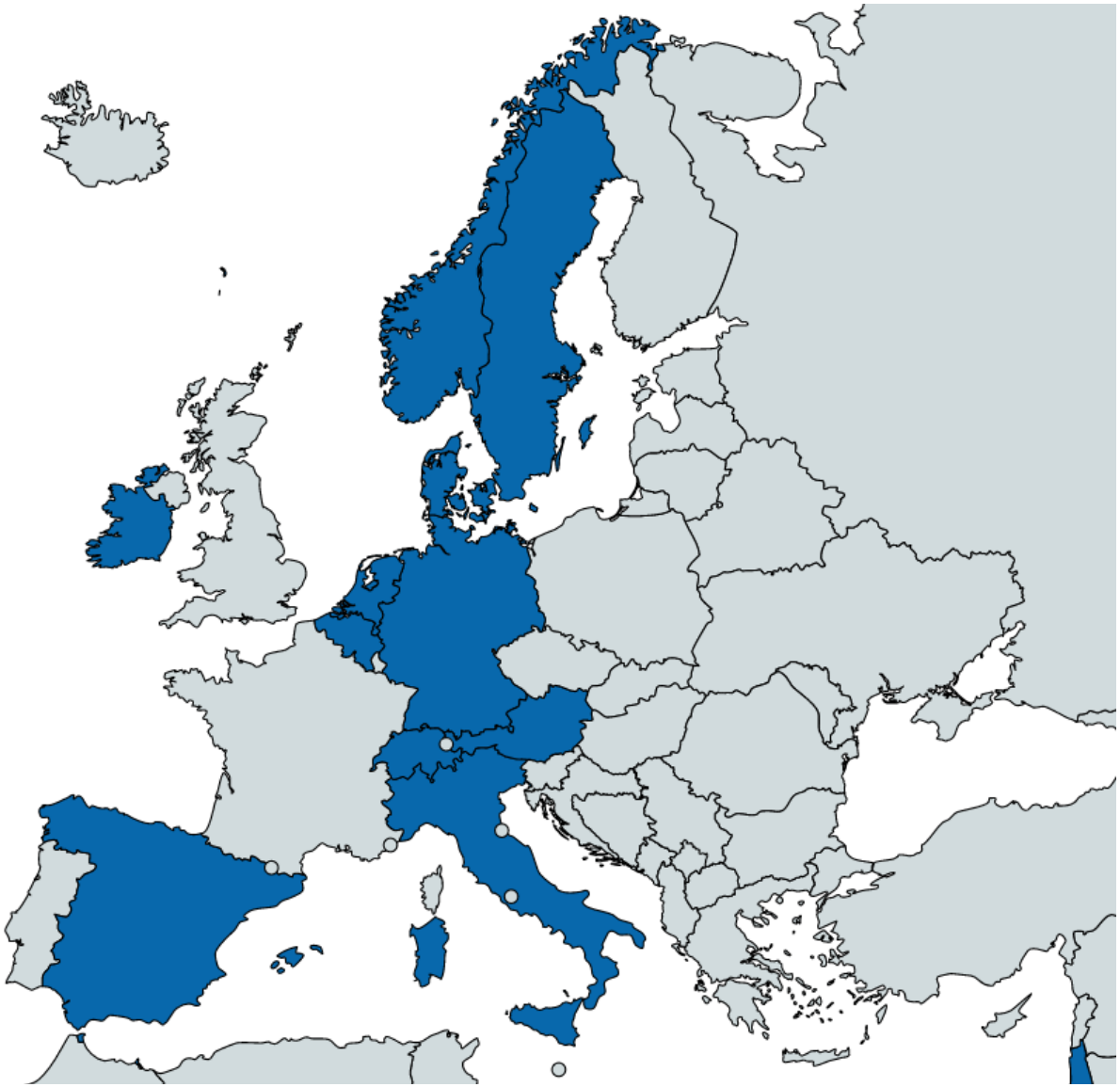
The Israeli CLL Association (ICLLA)
CLL
The Israeli CLL Study Group (ICLLSG)

cancer trials ireland

SAKK

GELLC
Grupo Español de Leucemia Linfocítica Crónica

CLL17



Start of recruitment Q3/2020

Contact cll-17@uk-koeln.de

THANK *you!*

Allgemeines Krankenhaus der Stadt Wien Jäger Arcispedale S. Anna Cuneo Ashford Cancer Centre Research Wickham AZ. Osp. Parpado Mannina AZ. Osp. S. Maria Liberati BAG Freiberg-Richter, Jacobasch, Illmer, Wolf Jacobasch Banner MD Anderson Cancer Center Klueppelberg Bashkir State Medical University Bakirov Box Hill Hospital Schwarer Brüderkrankenhaus St. Josef Paderborn Gaska California Cancer Associates for Research and Excellence Bessudo Canterbury Health Laboratories, Christchurch Hospital Butler Centre François Baclesse Vilque Centre Henri Becquerel Lepretre Centre Jean Bernard Le Dû Centre Léon Bérard Belhabri Charité - Universitätsmedizin Berlin Pezzutto CHRU Montpellier Cartron CHU Besançon - Hôpital Jean Minjoz de Nantes - Hôtel-Dieu Mahe CHU de Rennes - Hôpital Pontchaillou De Guibert CHU Dijon - Hôpital taing Hematologie Tournilhac CHU Hôpital Henri Mondor Dupuis City Clinical Hospital No. 52 Maryin 1 Golubeva Complejo Hospitalario de Navarra Goñi Dunedin Hospital McDiarmid Fondazione Policlinico Gemeinschaftspraxis Dr. Med. Peter Schmidt/Dr. Med. Holger Klaproth Klaproth Gesundheitszentrum St. ve Roussy Ribrag Hanusch-Krankenhaus Nösslinger Heart of England NHS Foundation Trust - Heartlands nakiraman Herlev Hospital Enggard Hôpital Sainte Musse Sohn Hôpital Saint-Louis Zini Hosp Universitario Brion CHU de Grenoble Molina CHU François Mitterrand Casasnovas Chu Es- City of Hope Siddiqi Clinical MSCh No. Universitario Agostino Gemelli Laurenti Marien Fischer-Von-Weikersthal Gusta- Hospital Kishore Henry Ford Hospital Ja- Salamanca Gonzalez Hospital Clinic i Provincial Calle Delgado Hospital Clinico Universitario de Valencia Terol Hospital Das Clinicas Da FMUSP Buccheri Hospital de Clínicas de Porto Alegre Fogliatto Hospital del Mar Abella Hospital General de Culiacán Valdes-Cerda Hospital Italiano de Buenos Aires Fantl Hospital Santa Marcelina Russo Hospital Sirio Libanés da Silva Hospital Universitario 12 de Octubre De La Serna Hospital Universitario Arnau de Vilanova Lopez Hospital Universitario De Canarias Machado Hospital Universitario de la Princesa Loscertales Hospital Universitario La Paz Baltasar Hospital Universitario Ramón y Cajal Lopez Hospital Universitario Vall d'Hebron Bosch Hospital Universitario Virgen del Rocío Carrillo Hospital Virgen de la Salud Casado EP São Lucas - Instituto de Ensino e Pesquisa Santucci Alves da Silva Ingalls Memorial Hospital Kozloff Inselspital, Universitätsspital Bern Andres Institut für Versorgungsforschung in der Onkologie Van Roye Institutul Clinic Fundeni Sos Vasilica Institutul Regional de Oncologie Iaşi Burcoveanu Jewish General Hospital Assouline Joe Arrington Cancer Research and Treatment Center (JACC) Quick Klinicka Bolnica Merkur Ostojic Klinički Bolnički Centar Zagreb Aurer Kliniken Maria Hilf GmbH Graeven Klinikum der Universität München Dreyling Klinikum Esslingen Mannal Klinikum Frankfurt (Oder) Kiehl Klinikum rechts der Isar der TU München Bogner Klinikum Schwabing Wendtner Krankenhaus Barmherzige Brüder Heilmeier Lincolnshire Hospitals NHS Trust - Lincoln County Hospital Kallmeyer Liverpool Hospital Harvey Luzerner Kantonsspital Gregor Marienhospital Herne Schultheis Marienhospital Stuttgart Denzlinger Medizinische Universität Innsbruck Steurer Monash Medical Centre Opat Multiprofile Hospital for Active Treatment „Hristo Botev" Sivcheva MVZ Weiden GmbH Funck NHS Lothian - Western General Hospital Scott Nizhny Novgorod Regional Clinical Hospital Samoilova North Estonia Medical Centre Foundation Viigimaa Ospedale dell'Angelo Bassan Ospedale Molinette Coscia Palmerston North Hospital Kilfoyle Penza Regional Oncology Dispensary Chagorova Princess Alexandra Hospital Marlton Queen Elizabeth II Health Sciences Centre Robinson Republican Clinical Oncology Dispensary Kuzmin Ribrag H. 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Janusza Korczaka Homenda Wojewódzki Szpital Specjalistyczny im. M. Kopernika w Lodzi Robak

#CLL*14*