Minor TP53 variants in CLL
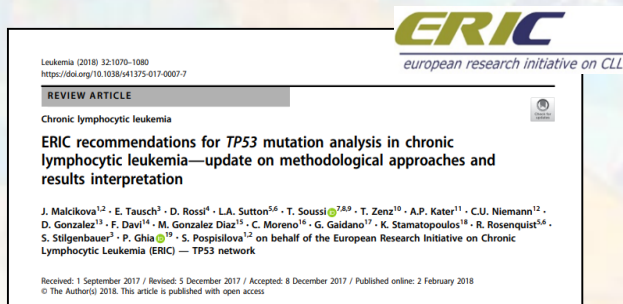
project update

50th General Assembly of ERIC Members
Wednesday, 9th of June, 2021

PROJECT TITLE:

ERIC MULTICENTER STUDY ON PROGNOSTIC AND PREDICTIVE IMPACT OF TP53 VARIANTS BELOW 10% VAF

BACKGROUND & PROJECT AIMS

ERIC recommendations for *TP53* mutation analysis in chronic lymphocytic leukemia—update on methodological approaches and results interpretation

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Should be the 10% (5%) cut-off for reporting TP53 mutations decreased?
If yes, how much?

Phase I: TECHNICAL CHALLENGES – Uncertainty regarding the reliability and reproducibility of NGS techniques
➤ To compare NGS results among laboratories performing NGS detection of TP53 mutations in CLL with detection limit of 1% VAF

Phase II: CLINICOBIOLOGICAL ASPECT – Controversial clinical impact
➤ To confirm prognostic impact of low-VAF TP53 variants in patients entering first-line treatment in with a multicenter approach
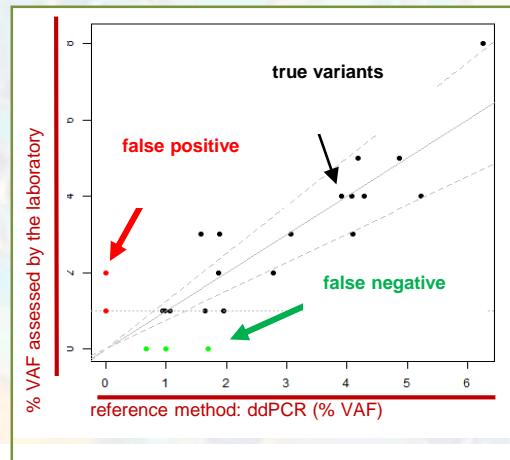
PHASE I: METHODICAL HARMONIZATION

Inter-laboratory comparison of NGS results obtained from the set of reference samples
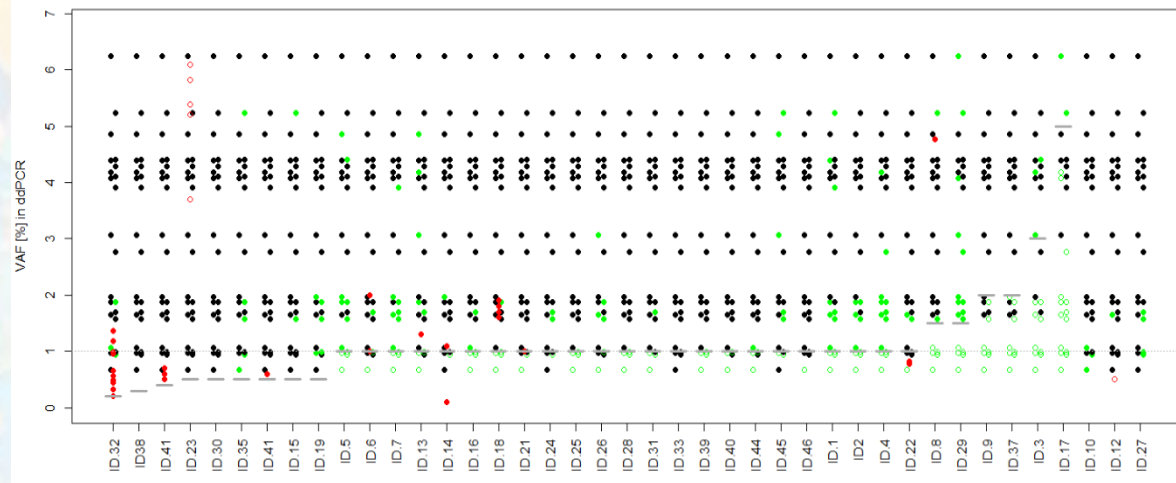
42 LABORATORIES
7 samples
23 TP53 variants 0.5-7% VAF

sample	variant (c)	variant (p)	ddPCR [%]
1	c.166G>T	p.(E56*)	3.9
	c.524G>A	p.(R175H)	4.3
	c.580C>T	p.(L194F)	4.1
	c.743G>A	p.(R248Q)	2.8
	c.853G>A	p.(E285K)	4.2
2	none	none	-
3	c.166G>T	p.(E56*)	0.9
	c.524G>A	p.(R175H)	1.1
	c.580C>T	p.(L194F)	1.0
	c.743G>A	P.(R248Q)	0.7
	c.853G>A	p.(E285K)	1.0
4	c.173del	p.(P58Qfs*65)	6.3
	c.949dup	p.(Q317fs*20)	5.2
5	c.559+1G>A	p.?	1.7
6	c.173del	p.(P58fs*65)	1.9
	c.949dup	p.(Q317fs*20)	1.6
7	c.337T>G	p.(F113V)	2.0
	c.569C>T	p.(P190L)	4.4
	c.626_627del	p.(R209fs*6)	4.1
	c.672+1G>T	p.?	4.4
	c.685_689del	p.(C229fs*9)	3.1
	c.741_742delinsTT	p.(R248W)	4.9
	c.817C>T	p.(R273C)	1.9
	c.949C>T	p.(Q317*)	1.7

true variants
false positive
false negative
% VAF assessed by the laboratory
reference method: ddPCR (% VAF)

✓ 63% laboratories
no false positivity >2% VAF
no false negativity >2% VAF

✗ 17% laboratories
false positivity above their limit of detection

VAF [%] in ddPCR
ID32 ID38 ID41 ID23 ID30 ID35 ID41 ID15 ID19 ID5 ID6 ID7 ID13 ID14 ID16 ID18 ID21 ID24 ID25 ID26 ID28 ID31 ID33 ID39 ID40 ID44 ID45 ID46 ID1 ID4 ID22 ID8 ID29 ID9 ID37 ID3 ID17 ID10 ID12 ID27
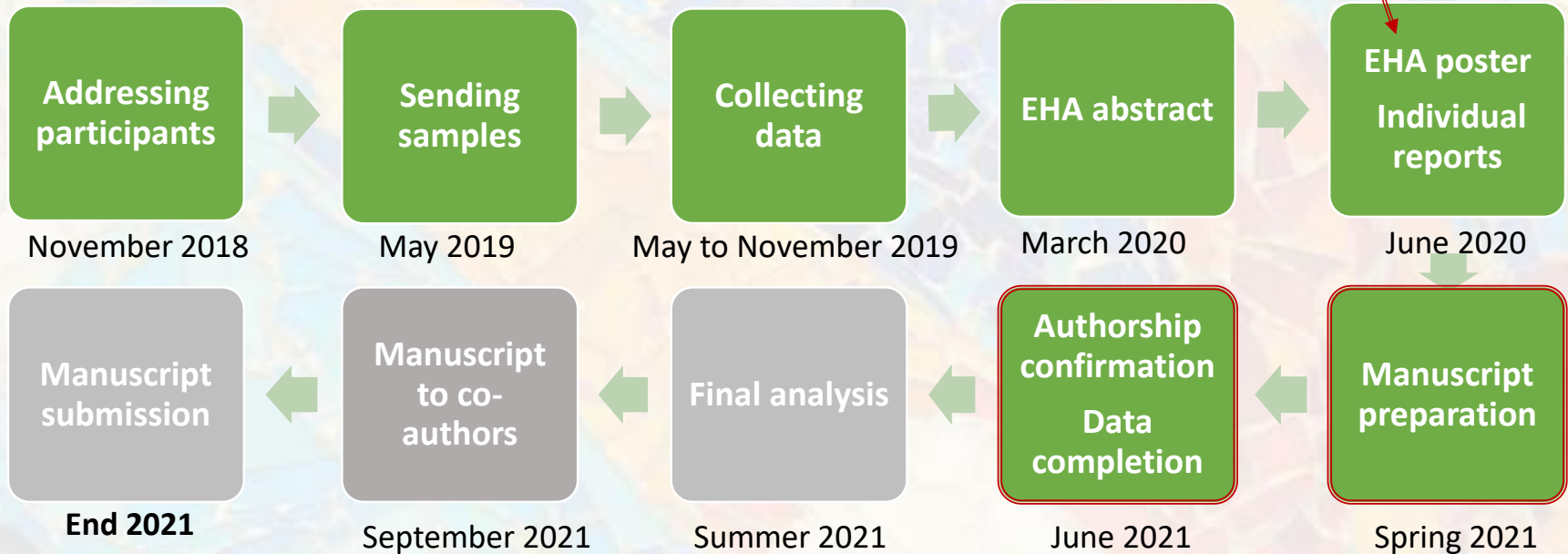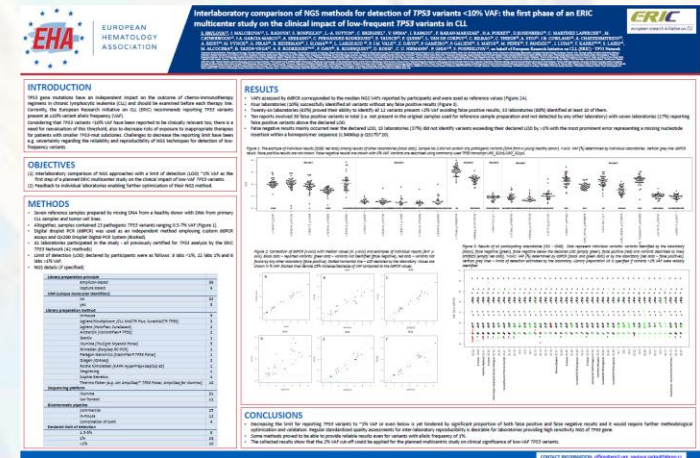
42 LABORATORIES

23 VARIANTS (0.5-7% VAF)

PHASE I: METHODICAL HARMONIZATION

Inter-laboratory comparison of NGS results obtained from the set of reference samples

42 LABORATORIES
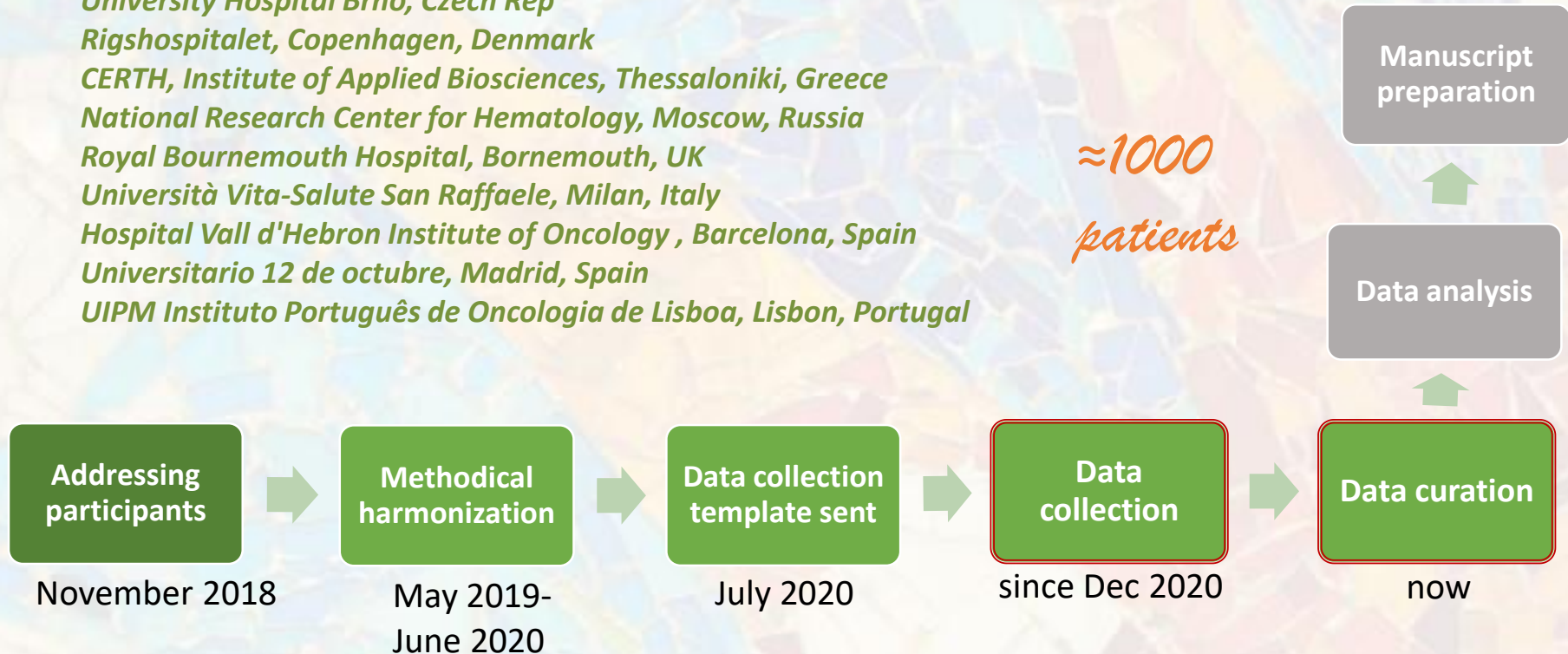*7 samples*
23 TP53 variants 0.5-7% VAF

Addressing participants	Sending samples	Collecting data	EHA abstract	EHA poster Individual reports
November 2018	May 2019	May to November 2019	March 2020	June 2020

Manuscript submission	Manuscript to co-authors	Final analysis	Authorship confirmation Data completion	Manuscript preparation
End 2021	September 2021	Summer 2021	June 2021	Spring 2021

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PHASE II: DATA COLLECTION

Results of TP53 analysis performed before 1st therapy using NGS with detection limit ≤1% VAF

2%

A consecutive cohort of patients (including both wt-TP53 and mut-TP53 CLL) entering 1st line therapy before 12/2017.
Corresponding clinical and laboratory data.

University Hospital Brno, Czech Rep
Rigshospitalet, Copenhagen, Denmark
CERTH, Institute of Applied Biosciences, Thessaloniki, Greece
National Research Center for Hematology, Moscow, Russia
Royal Bournemouth Hospital, Bornemouth, UK
Università Vita-Salute San Raffaele, Milan, Italy
Hospital Vall d'Hebron Institute of Oncology , Barcelona, Spain
Universitario 12 de octubre, Madrid, Spain
UIPM Instituto Português de Oncologia de Lisboa, Lisbon, Portugal

≈1000 patients

| Manuscript preparation |
| Data analysis |

| Addressing participants | → | Methodical harmonization | → | Data collection template sent | → | Data collection | → | Data curation |

November 2018   May 2019- June 2020   July 2020   since Dec 2020   now

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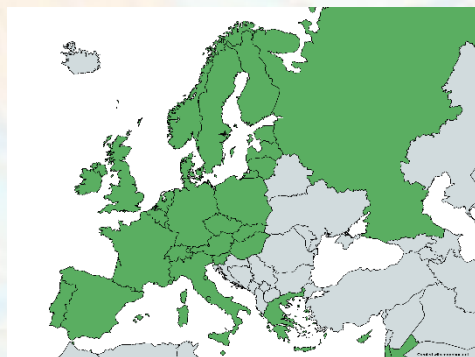
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Hospital Universitario Puerta de Hierro-Majadahonda; Madrid; Spain
Hospital clinico universiario; Valencia; Spain
Hospital del Mar-IMIM; Barcelona; Spain
Ulm University; Ulm; Germany
Karolinska Intitutet; Stockholm; Sweden
St. James's Hospital; Dublin; Ireland
University Medical Center ; Utrecht; The Netherlands
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