ERIC Project on TP53-Mutated Minor Clones Analysis - update

Sarka Pospisilova

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BACKGROUND

Current recommendations (*Leukemia, 2018*) - consensus of the experts in ERIC TP53 Network:
report variants ≥10% or 5-10% VAF only if stating unclear clinical impact

- Poor prognosis of all TP53-mut cases including those with low-VAF defects were described in some but not all studies.
- Lacking data from patients entering the therapy.
- Predictive impact and risk of minor clone expansion is unknown.
- Single-center data are not sufficient to show the impact in specific subgroups (esp. mut IGHV)

AIMS

- To compare NGS results among laboratories performing NGS detection of *TP53* mutations in CLL with detection limit of 1% VAF (→ methodical guide, education)

- To confirm prognostic and predictive impact of low-VAF *TP53* variants in patients entering first-line treatment, both for unmut IGHV and mut IGHV

SHOULD WE DECREASE 10% CUT-OFF FOR REPORTING TP53 MUTATIONS?

IF YES, HOW MUCH?

MAIN ACTIVITIES

- 1. **METHODICAL HARMONIZATION**

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

  Prerequisite for Data collection but not obliging participants to take part in it.

- 2. **DATA COLLECTION**

  NGS for *TP53* with detection limit at least 1%

  Consecutive samples of CLL patients entering first-line therapy before 2014 (follow-up ≥4 y)

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MAIN REQUIREMENTS FOR PARTICIPATION

- NGS methodology for *TP53* analysis with detection limit 1%
- Laboratories having consecutive samples from CLL patients entering first-line therapy and analyzed with ultra-deep NGS for *TP53* with sensitivity at least 1%
- Corresponding clinical and laboratory data („all“ data from all patients), minimal follow-up of 4 years
- Center passed the ERIC certification for *TP53* analysis

EXCLUSION CRITERIA – AVOIDING UNDESIRABLE BIAS

- The laboratory is not able to perform the NGS analysis reliably within given detection limit and to avoid significant proportion of false negatives/positives
- Non-consecutive set of samples intentionally enriched for a specific group of patients

PROJECT WORKFLOW - CURRENT STATUS

METHODICAL HARMONIZATION – phase 1 (2018-2019)

- Invitation to the study by ERIC office – autumn 2018
  36 laboratories responded + 5 organizers = **41 participants**

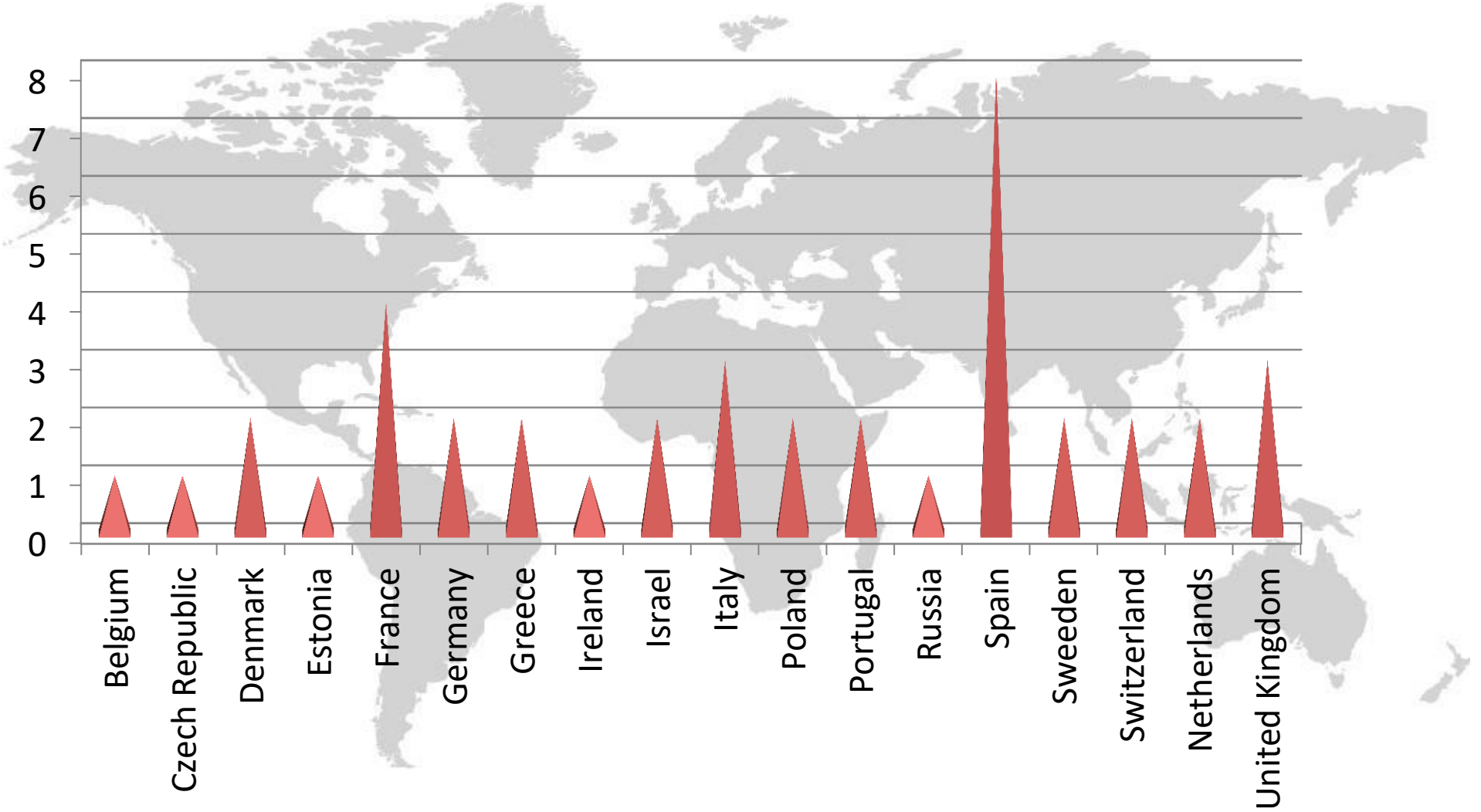
- 7 samples with variants <10% VAF prepared in Brno and Milan,
  sent 7/5/2019 by ERIC office (deadline 3 months from sample delivery)

- **Inter-laboratory comparison of NGS results obtained from the set of reference samples** – comparision of individual results with results of other groups – statistical analysis, individual feedback and summary report (Q3-Q4/2019)

DATA COLLECTION AND ANALYSIS – phase 2 (2020 – 2021)

- **Patient data collection**
- **Statistical analysis**
- **Publication of the results**

Participating Laboratories



41
Laboratories (incl. Organizers)

7
Methodical harmonization only

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PATIENT DATA COLLECTION AND STATISTICAL ANALYSIS

REQUIRED DATA

- **Info on analysed sample** (PB count, separation method)
- **All exonic and splice site variants in TP53 gene** in the sample - correct description, VAF,
- NGS **method** (coverage, DNA input..) and detection limit
- **Disease course** data - date of diagnosis, first therapy, progression and second therapy date, follow up (OS)
- Date of **swich to targeted therapy**
- **Therapy** information - type of therapy administered, number of cycles, response
- **IGHV status**
- **FISH result** from date corresponding to TP53 analysis
- Clinical trial or not

Optional: Information on TP53 cnLOH and karyotype complexity, if available

ERIC
european research initiative on CLL

PATIENT DATA COLLECTION AND STATISTICAL ANALYSIS

PLANNED ANALYSES:

→ PFS after the first-line therapy and time to second therapy line

→ therapy response in defined therapy groups (e.g. FCR)

→ OS from from therapy initiation (and dg)

→ search for clinically relevant cut-offs in group with mutations ≤10% VAF

→ analysis stratified according the IGHV mutation status

european research initiative on CLL

THANK YOU VERY MUCH FOR YOUR ATTENTION !

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