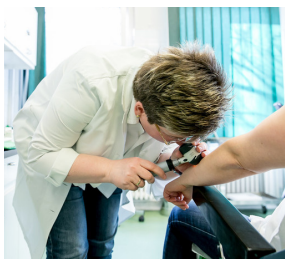




SEMMELWEIS 250 ONLINE CLINICAL CONFERENCE



PROGRAMME

9-10 NOVEMBER 2020

Semmelweis University



<http://semmelweis.hu/250/en/semmelweis-250-clinical-conference/>



09 NOV

Day 1. Monday

14:00 - 15:20 POSTER SESSIONS

14:00 - 15:25 SESSION 2: Cardiology, Hematology, Medical Imaging

RED

Chairs: Dr. Péter Lakatos, Dr. Tamás Radovits

- 14:00 - 14:05** Opening of the Session
- 14:05 - 14:10** Radiomic Analysis in Solid Tumors of the Pancreas
Dr. Veronica Frank, Semmelweis University
- 14:10 - 14:15** A different cardiac resynchronization therapy technique might be needed in some patients with nonspecific intraventricular conduction disturbance
Dr. András Vereckei, Semmelweis University
- 14:15 - 14:20** T2 „black out” phenomenon in acute stroke imaging
Dr. Nóra Nyilas, Semmelweis University
- 14:20 - 14:25** Association between gut microbial diversity and various cardiovascular imaging phenotypes
Dr. Helga Szabó, Semmelweis University
- 14:25 - 14:30** Cardiovascular Ultrasound Coexistence of Aortic Valve Stenosis and Cardiac Amyloidosis: Echocardiographic and Clinical Significance
Dr. Gergely Peskó, Semmelweis University
- 14:30 - 14:35** Challenges in the management of antiplatelet therapy in acute coronary syndrome (ACS) patients with thrombocytopenia
Dr. Ildikó Istenes, Semmelweis University
- 14:35 - 14:40** The importance of MR Imaging in stroke
Dr. Máté Magyar, Semmelweis University
- 14:40 - 14:45** Combined Upfront Immunosuppression for Elderly Patients with Acquired Hemophilia A: CyDRi is a Low Toxicity Regimen Resulting in a High Rate of Rapid Remission
Dr. Barbara Simon, Semmelweis University
- 14:45 - 14:50** Hepatitis C Virus (HCV) Infection and Malignant Lymphomas: Aspects of Care for an HCV Positive Marginal Zone Lymphoma Patient
Dr. Anikó Folfoffer, Semmelweis University
- 14:50 - 14:55** Cases of extramedullary myeloid leukemia at the 1st Department of Internal Medicine, Semmelweis University in Hungary
Dr. Ilona Tárkányi, Semmelweis University
- 14:55 - 15:00** Liquid Biopsy-Based Monitoring of Ezh2 Mutations in Follicular Lymphoma: Implications for Non-Invasive Disease Monitoring and Targeted Therapy
Dr. Bence Bátai, Semmelweis University
- 15:00 - 15:05** Tyrosine Kinase Inhibitor Therapy in Chronic Myeloid Leukemia – A Single Center Experience
Dr. Júlia Weisinger, Semmelweis University
- 15:05 - 15:10** Dissection of subclonal evolution by temporal mutation profiling in chronic lymphocytic leukemia patients treated with ibrutinib
Dr. Ambrus Gálgó, Semmelweis University
- 15:10 - 15:15** Observations in patients diagnosed with histiocytosis, a rare myeloid neoplasm
Dr. Klára Tímea Lőrincz, Semmelweis University
- 15:15 - 15:20** HLA associations of asparaginase allergy
Dr. Dániel Erdélyi, Semmelweis University
- 15:20 - 15:25** Closing Remarks

LIQUID BIOPSY-BASED MONITORING OF *EZH2* MUTATIONS IN FOLLICULAR LYMPHOMA: IMPLICATIONS FOR NON-INVASIVE DISEASE MONITORING AND TARGETED THERAPY



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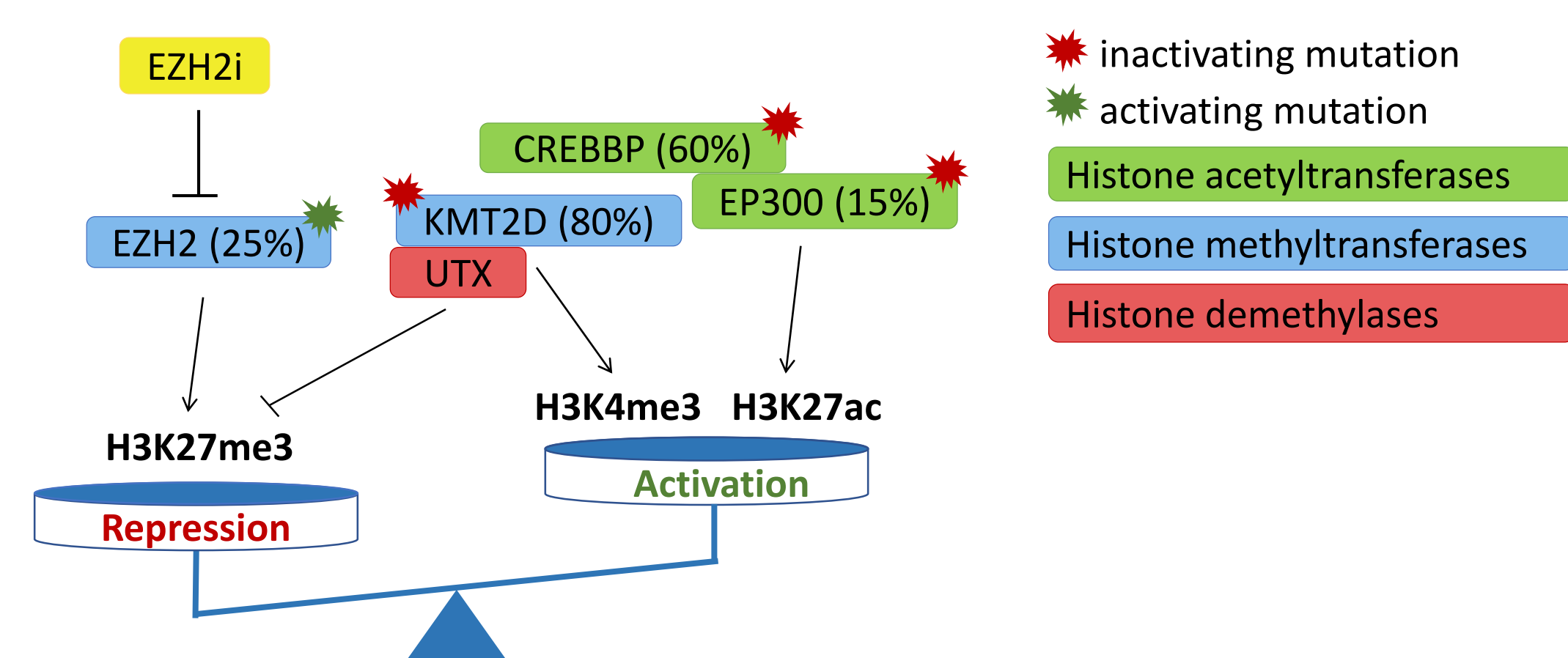
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²3rd Department of Internal Medicine, Semmelweis University, Budapest, Hungary



Introduction

- Follicular lymphoma (FL) has an **overall survival** of approximately **15 years**, characterized by a **remitting, relapsing** disease course
- Mutation analysis of **genes involved in lymphomagenesis** can be a specific target for disease monitoring in **circulating tumour DNA (ctDNA)**
- 25% of FL patients harbour ***EZH2* gain-of-function mutations**, which emerges as a target for small molecule **inhibitors (Figure 1.)**



- Routine **PET-CT** based monitoring has **limited** specificity, therefore **new approaches** are required

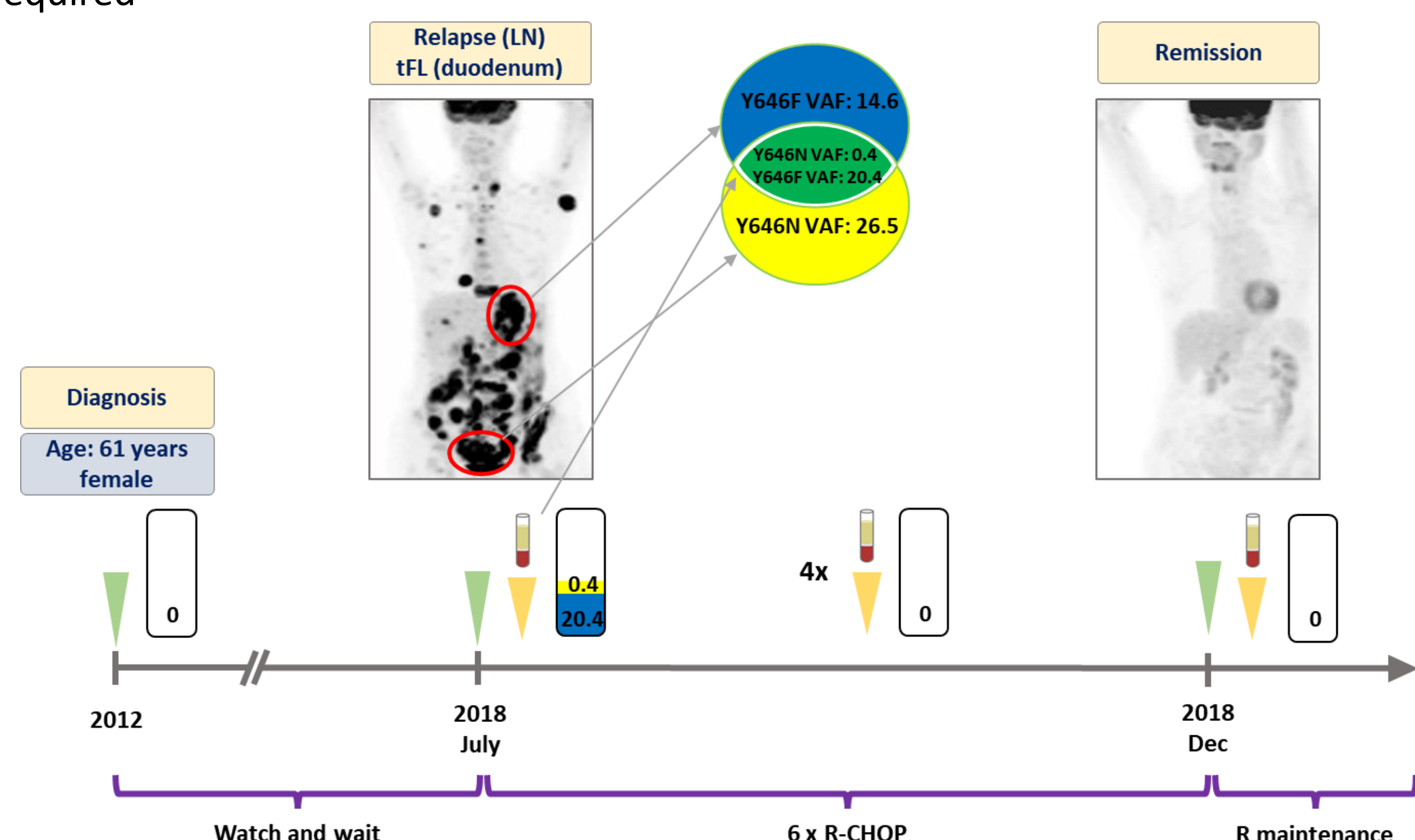


Figure 1. A 61-year-old female patient was diagnosed with grade 2 FL, which did not require treatment. At 72 months after diagnosis lymph node and duodenal biopsy showed grade 2 FL and DLBCL. ddPCR analysis identified *EZH2* Y646N mutation in the inguinal and *EZH2* Y646F mutation in the duodenal biopsy. Plasma sample was obtained prior treatment, ctDNA analysis revealed the presence of both, Y646N and Y646F mutations. In response to immunochemotherapy the patient is in remission with an undetectable *EZH2* mutation.

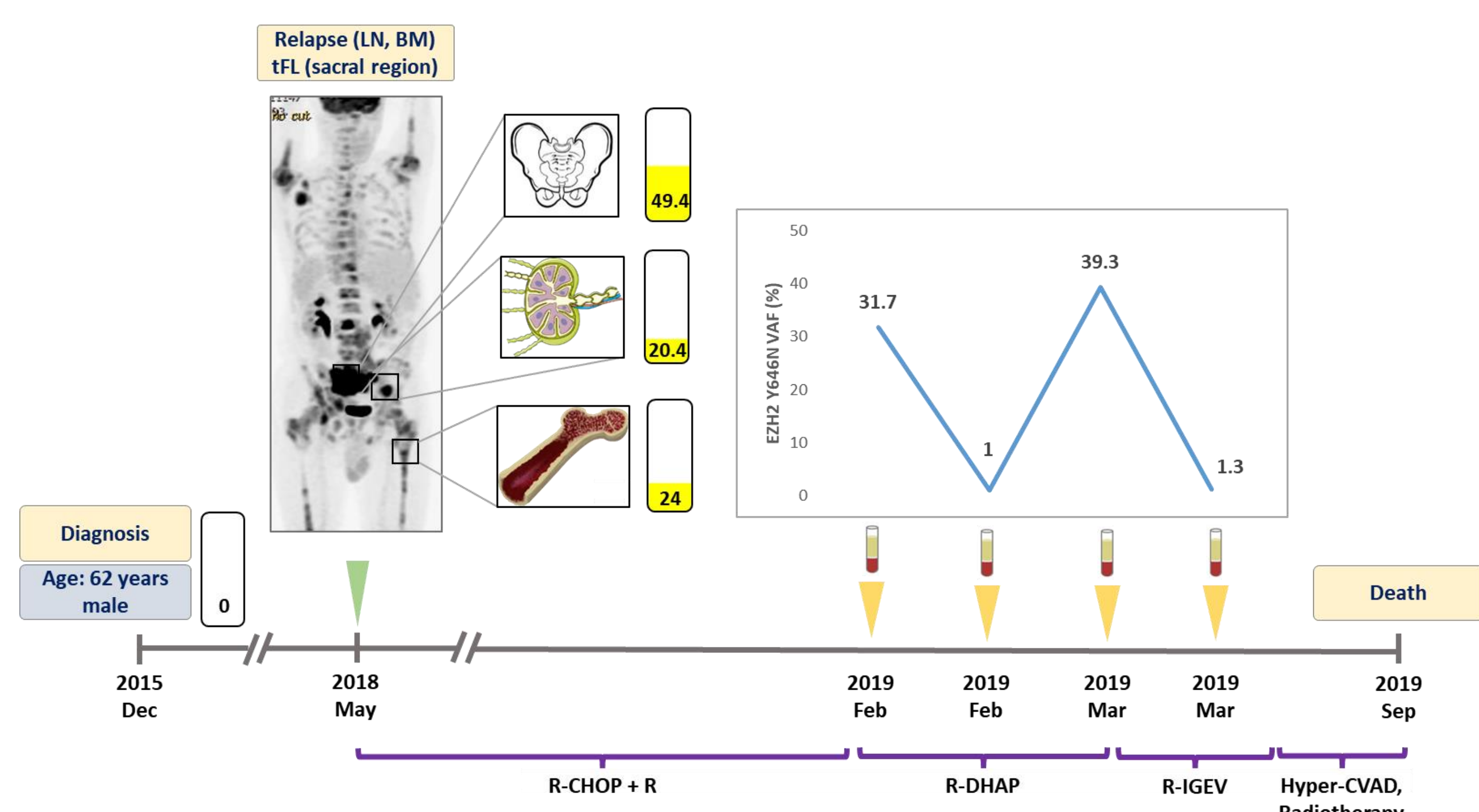


Figure 3. The patient was diagnosed with FL in December 2015. In May 2018 he relapsed, inguinal lymph node and bone marrow biopsy showed low grade FL and lymphoid infiltration of the bone marrow harbouring an *EZH2* Y646N mutation. He received R-CHOP with rituximab maintenance. In January 2019, the patient relapsed again, plasma ctDNA was positive for Y646N mutation with a VAF of 31.7 % and 1.0 % after one week of R-DHAP treatment. In March 2019 in a treatment refractory state plasma ctDNA showed elevated Y646N mutation level which was followed by a prompt decrease after one week. The patient was refractory to subsequent lines of therapy and died in September 2019.

Discussion

- ctDNA** is present in **detectable amount** in FL patients
- EZH2* mutations** can be identified in patients with **active disease**
- The variant allelic frequency of mutations can be used in the **monitoring of treatment response** and disease course
- Mutations in **transformed FL** are present with **elevated variant allelic frequencies** in the ctDNA compartment
- ctDNA analysis is a useful method for the **detection of spatial heterogeneity**, and represents a global genomic profile of the tumour

Aims of the study

- Test the feasibility of ***EZH2* mutation analysis in ctDNA** of FL patients
- Monitor the mutations** in patients receiving immunochemotherapy
- Compare** the power of detection with **PET-CT** imaging in a case series of FL patients

Patients and methods

- Plasma samples from **28 *EZH2* mutant FL patients**
- ctDNA isolation** using the QIAamp Circulating Nucleic Acid Kit (Qiagen, Germany) and **digital droplet PCR** (BioRad, USA) analysis of *EZH2* mutation hotspots previously identified in tumour tissue samples

Results

- We identified ***EZH2* mutations** in **9/28 (32%)** of the patients harbouring an *EZH2* mutation in the ctDNA compartment as well (**Figures 1-4.**)
- The ctDNA analysis returned a positive result in **9/10 (90%)** of the patients with **active disease**
- All patients (n=18) in **partial or complete remission** proved to be ***EZH2* wild-type** with ctDNA analysis

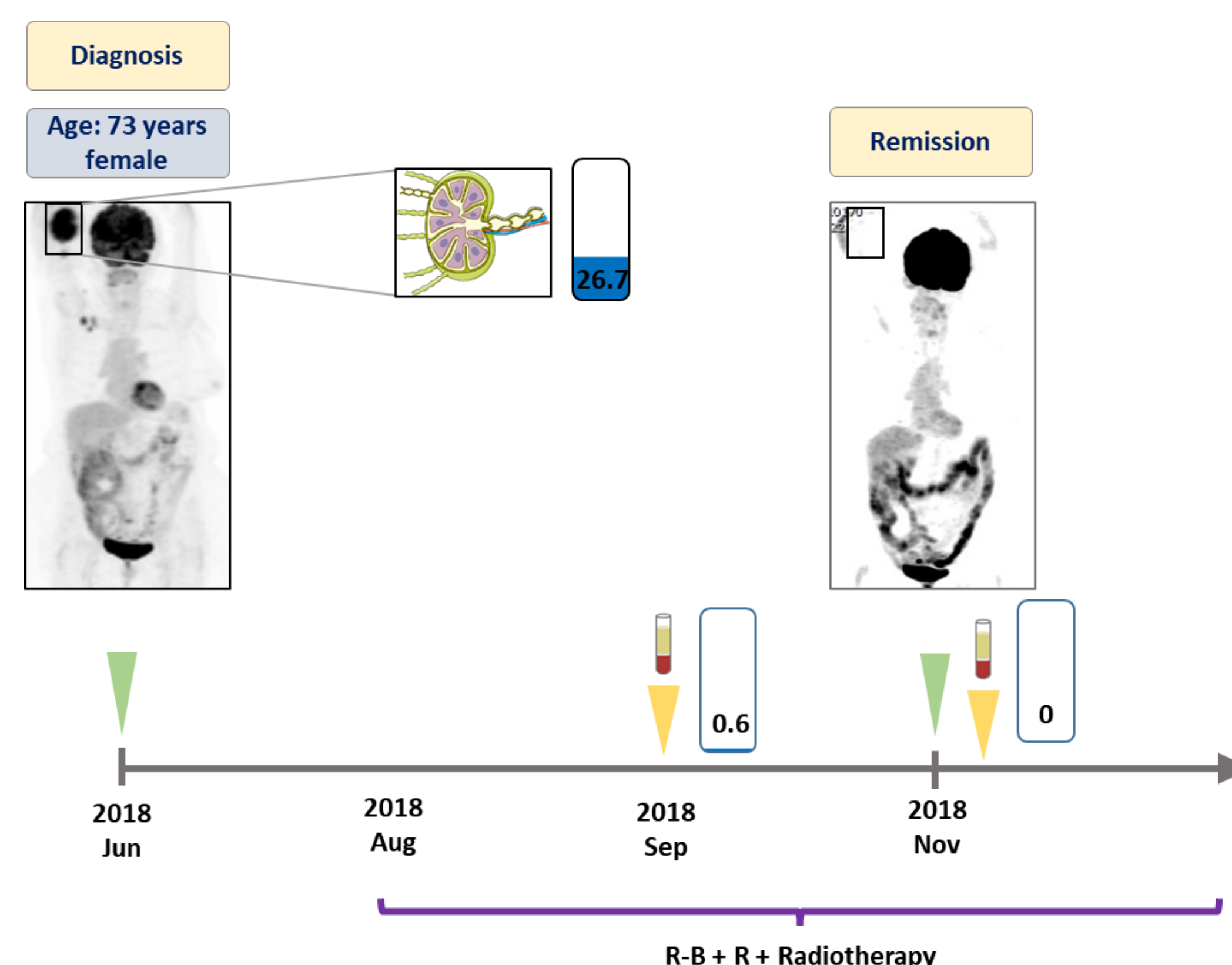


Figure 2. Diagnostic PET-CT showed increased metabolic activity in the right cubital area and in the right axillary lymph node region. The extranodal FL biopsy was found to be positive for Y646F *EZH2* mutation with ddPCR. R-B treatment was started as first line therapy. The first plasma specimen was obtained one week after treatment initiation. The Y646F *EZH2* mutation was found in the plasma sample with a VAF of 0.6 %. Control PET-CT performed after 3 months of diagnosis revealed CMR of the disease, parallelly ctDNA was found to be *EZH2* wild type.

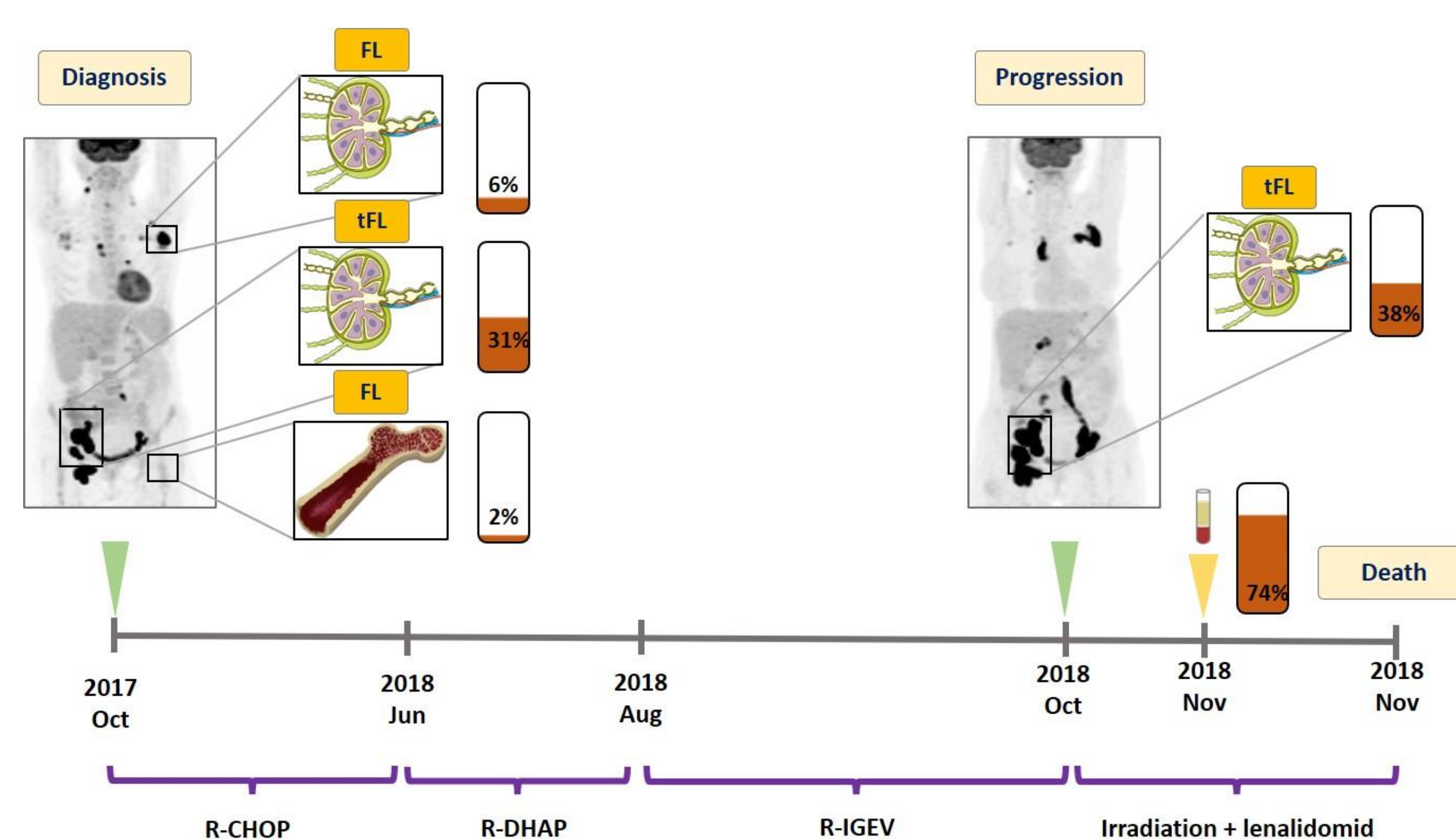


Figure 4. The patient was diagnosed with FL in October 2017 and was initially treated with R-CHOP and R-DHAP regimens. In June 2018, tissue biopsy of inguinal lymph node and bone marrow biopsy confirmed tFL and lymphoid infiltration. *EZH2* A682G mutation was found in both specimens. The patient had no response to subsequent therapeutic lines (R-IGEV, irradiation, lenalidomid). In November 2018 blood plasma specimen was collected which revealed *EZH2* A682G mutation in ctDNA with a high variant allelic frequency. The patient deceased in November 2018.

Acknowledgements

This study was funded by the Hungarian National Research, Development and Innovation Office (NKFIH) (KH17-126718, NVKP_16-1-2016-0004, K_16 #119950 grants and FK_134253), as well as by the Momentum grant (LP-95021) and János Bolyai Research Scholarship (BO/00320/18/5) of the Hungarian Academy of Sciences. The study was also supported by the ÚNKP-19-4-SE-77, ÚNKP-19-2-I-SE-47 and ÚNKP-20-5-SE-22 grants of the New National Excellence Program of the Ministry for Innovation and Technology as well as by the Complementary Research Excellence Program and Kerpel Talent Award of Semmelweis University (EFOP-3.6.3-VEKOP-16-2017-00009), and the Higher Education Institutional Excellence Program of the Ministry of Human Capacities in Hungary and the ELIXIR Hungary