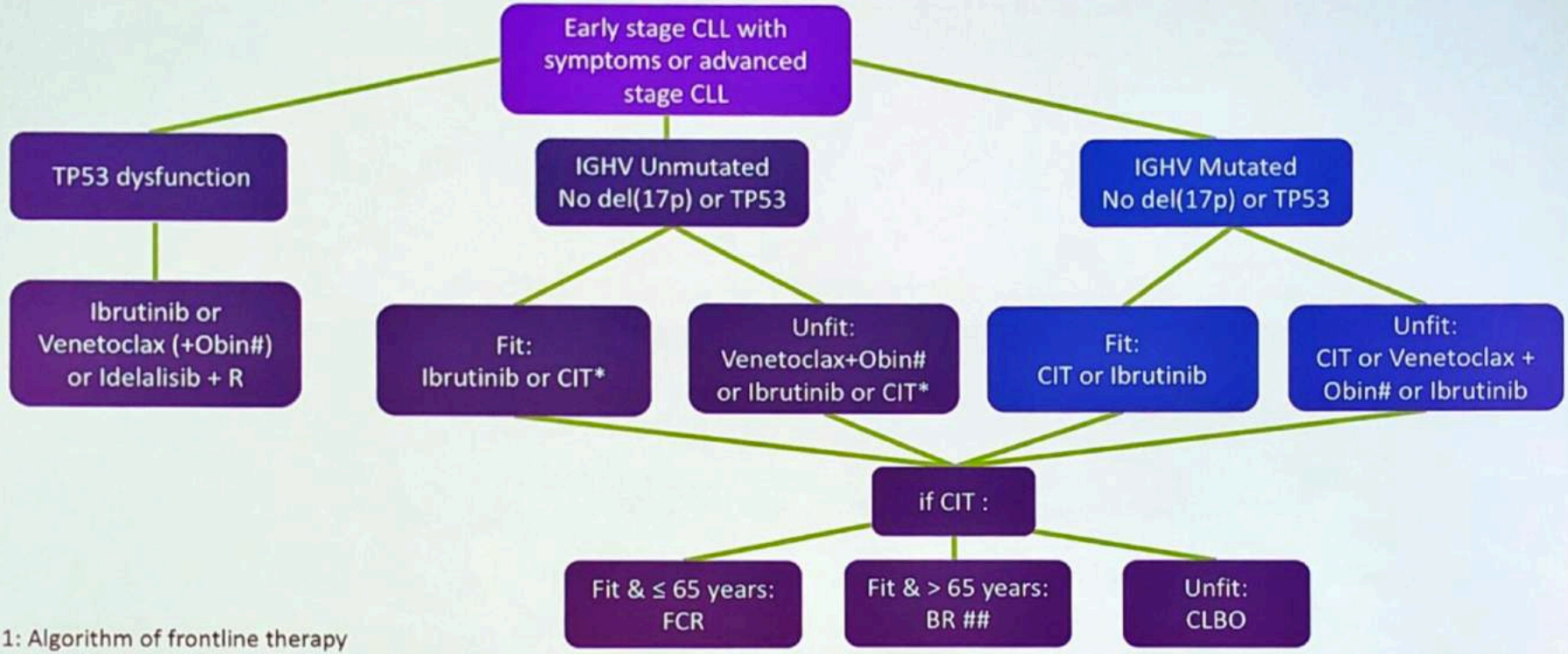
2019 EHA-ESMO guidelines for CLL treatment



igure 1: Algorithm of frontline therapy

IT: chemoimmunotherapy; Obin: obinutuzumab ; CLBO: Chlorambucil plus Obinutuzumab; R: rituximab; # if approved and available; # # CLBO might be considered as well, but no data in t patients are available; *Chemoimmunotherapy as alternative treatment only if no TP53 dysfunction and reasons against continuous treatment with ibrutinib or non-availability

Adapted from https://www.esmo.org/Guidelines/Haematological-Malignancies/Chronic-Lymphocytic-Leukaemia/eUpdate-Treatment-Recommendations

2018: iwCLL Updated guidelines

Additional tests prior to treatment

Additional tests prior to treatment	General practice	Clinical trial
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	Not generally indicated*	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always

FISH, fluorescence in situ hybridization.
*, conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful prior to therapy, if established methodology is available

Adapted from Hallek et al., Blood 2018;131:2745-60

PDTA 2019

LLC I linea

Stadio A e B di Binet senza segni di malattia attiva: watch and wait

Stadio A e B sintomatici o C di Binet (ricerca del17p, del1q, TP53 e IGHV mutazione)

Del 17p e/o TP53 assente

- Pazienti FIT < 65 anni FCR x 6 cicli
- Paziente > 65 anni FIT R Bendamustina x 6 cicli, Imbruvica (se IGHV non mutato e del 11)
- Pazienti 65 anni con CiRS > 6 e/o eGFR < 70 Cl Cr min/ml
  IGHV mutato +/- del 11 G- Chlorambucil, Ibrutinib
  IGHV non mutato e del 11 Ibrutinib , G- Chlorambucil
- Paziente Frail Chlorambucil + anti CD 20, Chlorambucil

Del 17p e/o TP53 presente

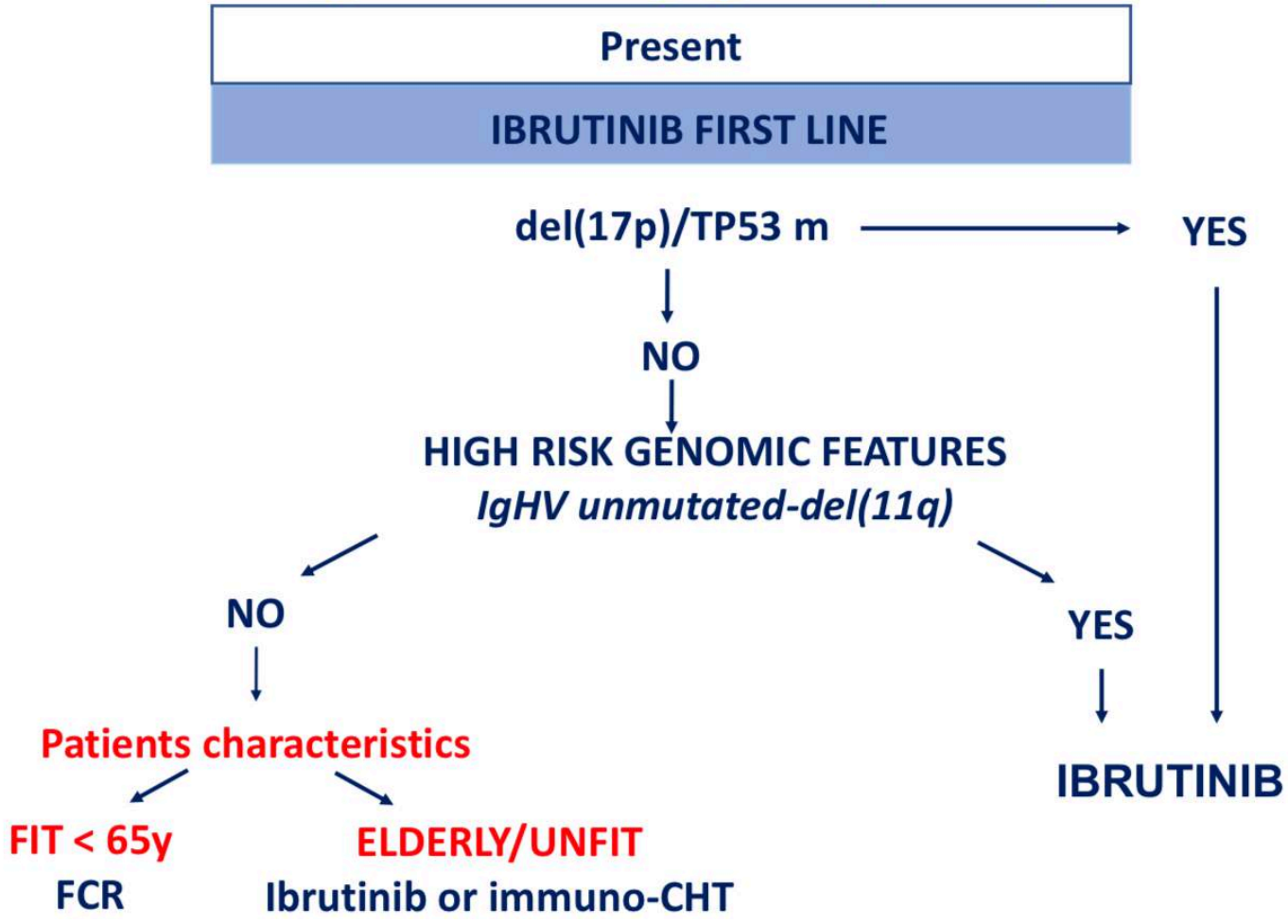
- Ibrutinib o Venetoclax nei casi in cui l'inibitore del BCRi non sia indicato

Caratteristiche del paziente e aspetti rilevanti all'eleggibilità			
E	Età del paziente all'avvio del trattamento con ibrutinib	<65 anni	*b m*
		65-69 anni	*cl*
		≥70 anni	
E	Il paziente presenta almeno 1 delle seguenti comorbilità: clearance della creatinina <70 mL/min (secondo la formula di Cockcroft-Gault); conta piastrinica <100.000/µL o emoglobina <10 g/dL; citopenia autoimmune clinicamente manifesta (anemia emolitica autoimmune o trombocitopenia autoimmune); ECOG performance score = 1 o 2)?	Si	
		No	*s m t*

first-line* in Italy
reimbursed only for pts > 70y
or
65-70 unsuitable for chemoimmunotherapy

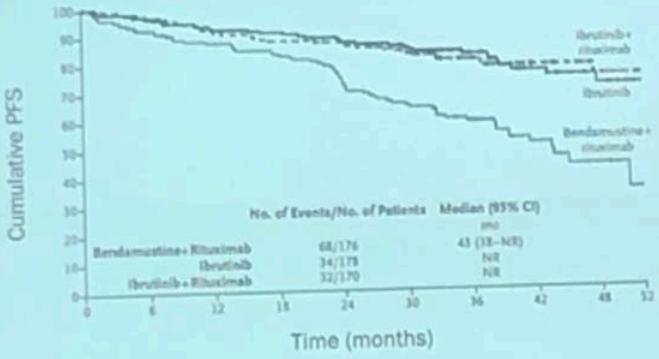
Agenzia Italiana del Farmaco
AIFA

Treatment strategies with emerging therapeutic options in first line

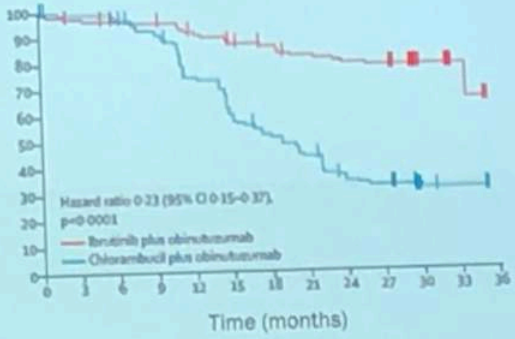


CIT vs. Inhibitors in Elderly Patients

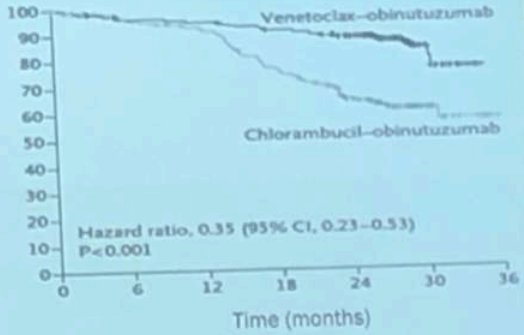
ALLIANCE A041202



ILLUMINATE



CLL14



- Treatments used in standard arms adequate for fair comparisons?

Woyach et al., N Engl J Med 2018; 379:2517-28
Moreno et al., Lancet Oncol 2019; 20:43-56
Fischer et al., New Engl J Med 2019; 380:2225-36

II LINEA

RECIDIVA > 24-36 MESI DALLA I LINEA

- **Del 17p e/o TP53 assente**
  Possibile ripetere la terapia di I linea, R-Bendamustina oppure inibitori del BCR

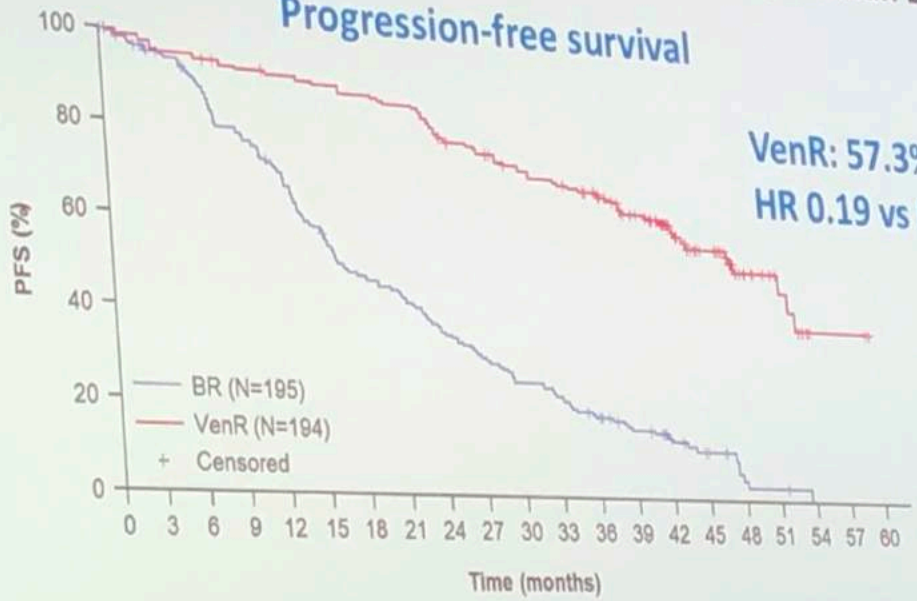
- **Del 17p e/o TP53 presente**
  Ibrutinib, R-Idelalisib, Venetoclax (se già trattato o controindicazioni a Ibrutinib/Idelalisib)

MALATTIA REFRATTARIA O RECIDIVA (entro 24-36 mesi dalla I linea)

- Considerare l'inserimento in studi clinici, Ibrutinib, R-Idelalisib, Venetoclax (se già trattato o controindicazioni a Ibrutinib/Idelalisb)
- Se età < 65 anni valutare allotrapianto in caso di risposta

MURANO: Ven-R vs BR in relapsed CLL

Ven-R PB uMRD rates: 62% @ EoCT, 84% uMRD at any time on treatment
Median follow-up 48 months; 130 pts completed 24 Mo Ven, median 22 Mo off drug

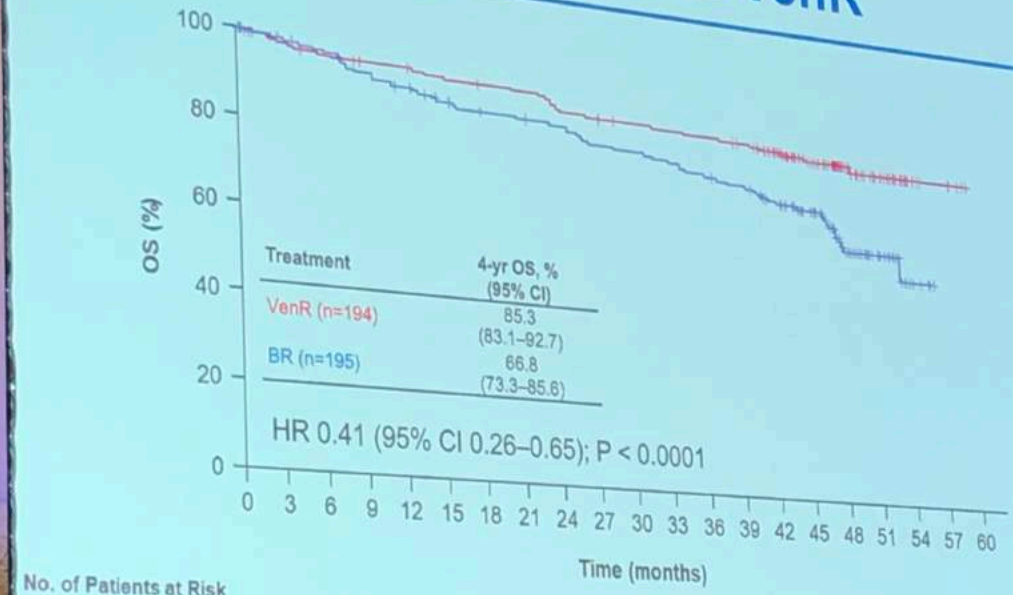


No. of Patients at Risk

BR	195	178	165	143	129	104	85	80	66	56	45	40	32	23	14	9	3	2
VenR	194	190	185	179	176	174	170	167	161	150	141	134	130	118	101	55	40	14	7	2

Seymour JF, *et al*. iwCLL 2019 (Abstr)

Improvement in OS with VenR



No. of Patients at Risk

BR	195	181	175	167	162	155	152	150	147	141	140	138	134	130	116	94	58	29	7
VenR	194	190	185	183	182	179	178	176	173	168	166	165	164	163	154	110	84	34	15	6	1

Seymour JF, *et al.* iwCLL 2019 (Abstr)

Treatment options for relapsed/refractory CLL (ESMO Guidelines 2019)

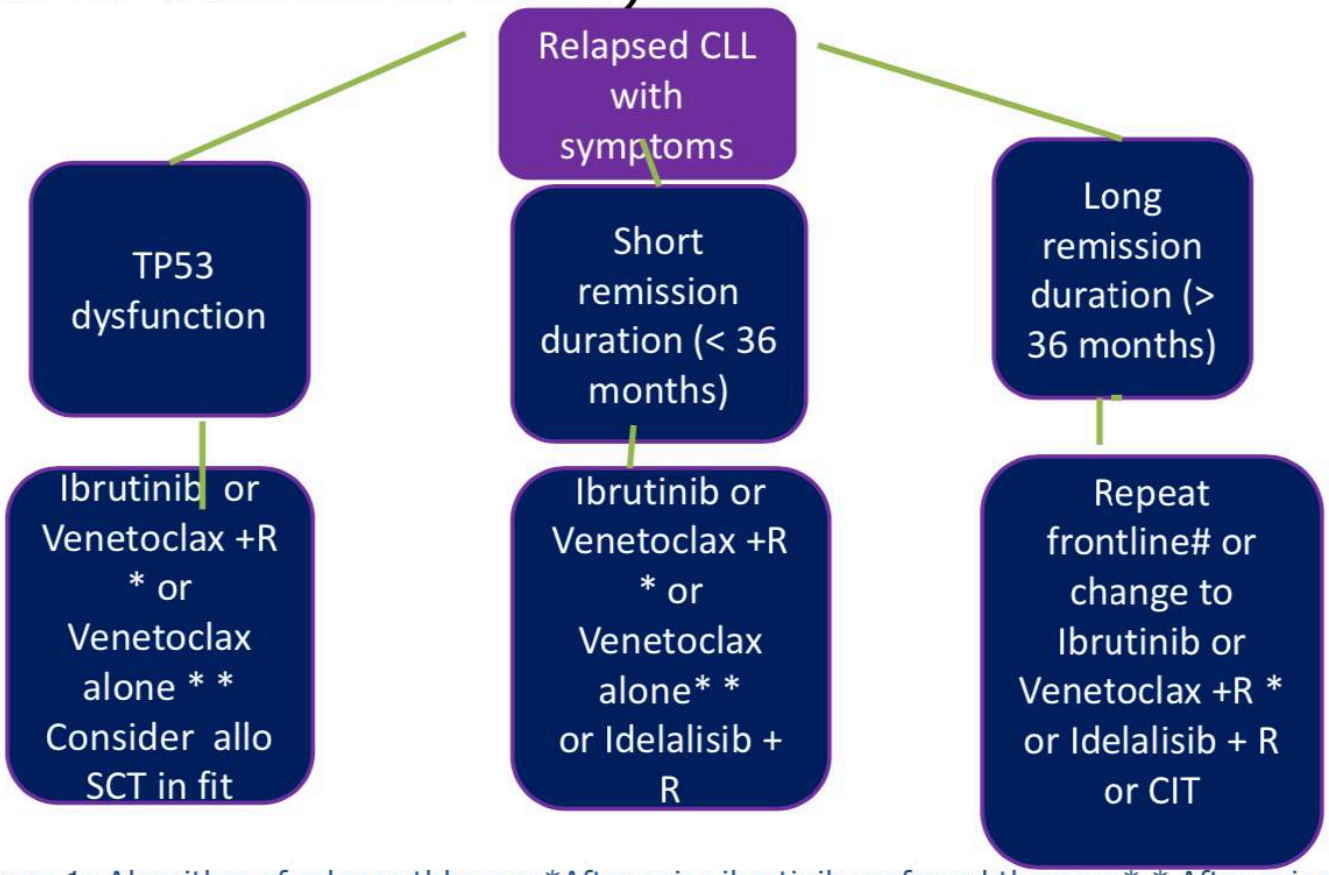


Figure 1: Algorithm of relapse thherapy*After prior ibrutinib preferred therapy;* * After prior chemoimmunotherapy and BCRi; # Repetition of FCR not recommended Eichhorst et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines Ann Oncol 2019

Treatment of relapse and refractory disease
ESMO reccomendations - 2019

- As in first-line therapy, treatment at relapse should only be started in symptomatic patients and not simply at the time of reappearance of the disease

- Symptomatic relapse within 3 years after fixed-duration therapy or non-response to therapy, the therapeutic regimen should be changed regardless the type of first-line therapy (CIT or novel therapies):
  - Venetoclax + rituximab for 24 months
  - Ibrutinib as continuous therapy
  - PI3K inhibitor idelalisib + rituximab
  - CIT if no *TP53* dysfunction and no other treatment options with inhibitors are available

  (response to prior BR should have lasted at least 3 ys ; **repeated administration of FCR not recommended)**

Eichhorst et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines Ann Oncol 2019

Role of haematopoietic stem cell transplantation

- ESMO 2019 guidelines:Allogeneic stem cell transplantation (alloSCT) should be considered in:

- Patients refractory to CIT with *TP53* dysfunction, but fully responsive to novel inhibitor therapy.

- Patients refractory to CIT and to novel inhibitor therapy, even for patients with a higher risk of non-relapse mortality

- Patients with Richter's transformation in remission after therapy and clonally related to CLL

- Practice guidelines by the American Society of Blood and Marrow Transplantation (ASBMT), iwCLL , ERIC and EBMT recommend allo-HCT for:

- High-risk CLL patients with refractory disease to at least one of the novel agents while still responding to either BCR inhibitors or venetoclax

Eichhorst et al. Ann Oncol (subm);Hallek et al. Blood. 2018;131(25):2745–60.; Kharfan-Dabaja Biol BloodMarrow Transplant. 2016;22(12):2117–25; Dreger et al. Blood 2018;132(9):892–902.