انجمن هماتولوژی و انکولوژی ایران
Iranian Society of Medical Oncology and Hematology

NOVARTIS

Disclaimer :

- The opinions expressed in this presentation and on the following slides are those of the presenter and not necessarily those of Novartis.
- The content of this slide deck is accurate to the best of the presenter’s knowledge at the time of production

SEVERE APLASTIC ANEMIA

Sahar Tavakoli.MD

Asistant Professor of Hematology and Oncology.TUMS.1400.7.2

NOVARTIS

PATIENT INTRODUCTION

- She is a 19 year-old with no significant health history
- He was more listless and less engaged over the prior few weeks
- There was no significant family history.
- No significant drug history

- **On examination:**
  - She was pale with ecchymoses throughout her lower extremities.
  - Otherwise,Physical examination was unremarkable, with appropriate stature for age and no facial or limb abnormalities

NOVARTIS

Lab tests:

- WBC = 0.7×10^9/L with 0% neutrophils
- Hgb = 7.7 g/dL
- PLT = 22×10^9/L (at presentation)

- A PBS showed a paucity of cells and no circulating malignant cells

- Urgent bone marrow evaluations showed marked hypocellularity (<5%) and no evidence of infiltrating tumor

- Karyotype was 46,XX

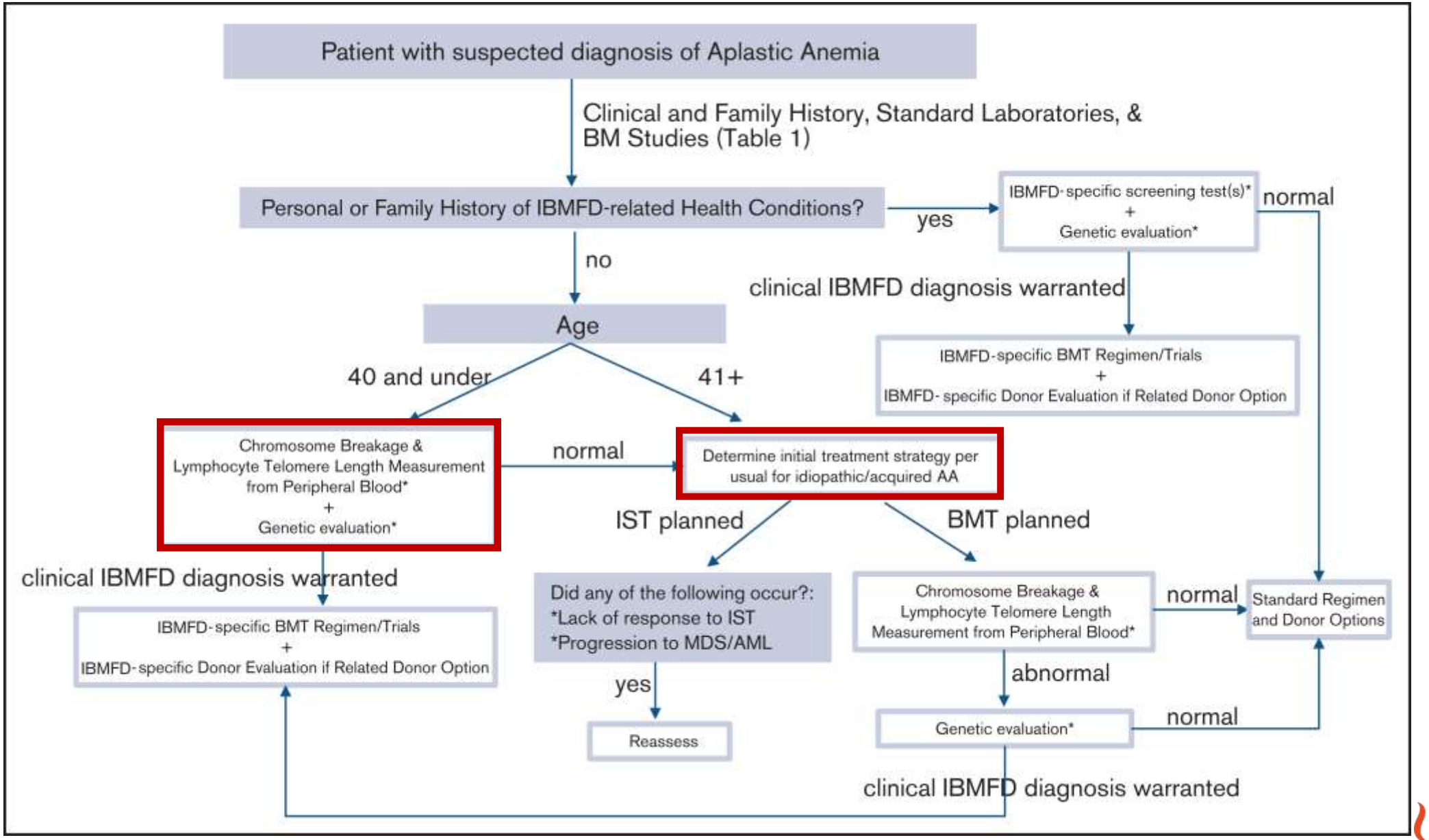
NOVARTIS

Questions?

- To confirm your diagnosis and R/O of other diagnosis,do you need other lab tests ? what ?
- Based on which factors you choose best treatment option?
- what is your preferred option for treatment? **Transplant or IST?**
- What do you need for future decision making ?
- If the patient was febrile or had sever sepsis,do you delay your standard treatment ?
  - short-term delay to treat a serious sepsis or long term delay to clear if there is any more occult infection?

NOVARTIS

blood advances
Blood Adv (2021) 5 (12): 2660–2671.



NOVARTIS

Continue …..

- Tests for viral infection and Rhomatologic disorders was negative
- Supportive care with transfusion of PC & PLT was started
- HLA- typing was done before
- Test for PNH and FA was not done because of recent transfusion
- CsA + low dose of Prednisolon+ G-CSF +Erythropoetin + Danazole was started
- After 2 weeks there was no response to treatment

NOVARTIS

QUESTIONS?

- What is your recommendation to add **ATG** at the same time with CsA?
- Which type of ATG?

- If all of you are agree to add ATG,consider the price and the risk of prescription and hospital infra structure

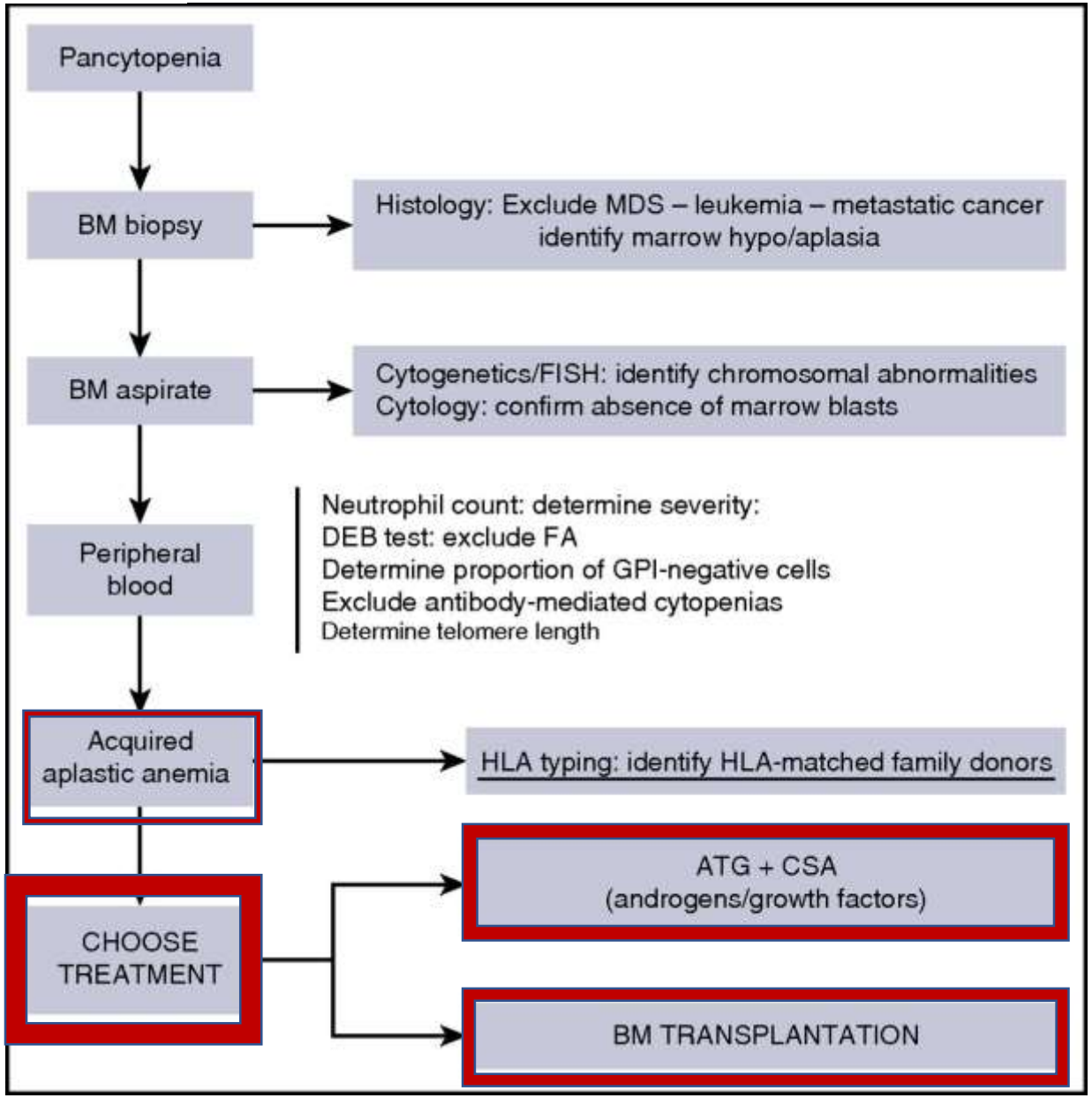
- What is your recommendation **about N-plat**(romiplostim)?
- What **about Eltrombopag**?

NOVARTIS

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

2017- 18

EVIDENCE BASE ANSWER:



NOVARTIS

EVIDENCE BASE ANSWER:

EHA 2021: First-Line Eltrombopag Plus Cyclosporine A Offers Benefits in Severe Aplastic Anemia

Efreen Montaño-Figueroa, MD

- —Eltrombopag in combination with cyclosporine A produced a high level of response and transfusion independence in treatment-naïve patients with severe aplastic anemia, according to results of the **SOAR trial**
- Eltrombopag, a thrombopoietin receptor agonist, is approved for patients who are refractory or have an insufficient response to immunosuppressive therapy.
- The FDA recently approved **eltrombopag as first-line therapy** when combined with standard immunosuppressive therapy.but not yet by the EMA

NOVARTIS

EVIDENCE BASE ANSWER:

Age < 40 or 50 years

- **Rapidly-available match related donor**
  - Proceeding directly to allo-HSCT rather than IST

- **DON'T have -available match related donor**
  - Initiate IST and begin a search for a suitable alternative donor
  - Matched unrelated,mismatch related,haploidentical,umbilical cord source

✓ Suggestion is triple IST

✓ based SOAR and TRACE trial

INTENSIVE IST

1. HORSE ATG
2. CYCLOSPORINE
3. ELTROMBOPAG

UPTODATE, AUG ,29 2021

EBMT 2021

NOVARTIS

QUESTIONS?

- Which kind of blood product do you recommend?
  - leukoreduced & irradiated ?
- Transfusion Treshold of PLT and PC ?
- Your recommendation about G-CSF and EPO?
- Your recommendation about prevention of infection?

NOVARTIS

EVIDENCE BASE ANSWER:

- All RBC units should be Leukoreduced to minimize risk of nonhemolytic transfusion reactions and reduced transmission of CMV to CMV neg

- Irradiation, depletes lymphocyte and reduces the risk of ta-GVHD

- Is not necessary for non eligible patients for BMT

NOVARTIS

EVIDENCE BASE ANSWER:

- G-CSF and EPO act only on late progenitors (markedly decreased in AA) and level of endogenous hematopoietic growth factors are generally high

- There is no evidence that these cytokines can correct the HSC defect or alter the course and disease response to IST or Overal Survival

- There are unproven concern that these cytokines may increase the incidence of clonal disorders : MDS,AML

NOVARTIS

EVIDENCE BASE ANSWER:

- Infections are the major cause of death in AA
- Fever + ANC < 500/microL is a medical emergency

- Tretment with Allo-BMT or intensive IST impairs T cell immunity and increases susceptibility to p.jirovecii

- **These patient should receive prophylaxis against p.jirovecii**

- **Pentamidin aerosolized 300 mg after ATG until 3 months is preferred to Co-Trimoxazol due to BM suppression and increase level of EPAG**

NOVARTIS

EVIDENCE BASE ANSWER:

- There is no consensus for porophylaxy for viruses,bacteria or fungai but some expert offers:

- **FUNGAL**: ANC persistently < 200 cells/microl
  - ✓Voriconazol or posaconazol (definitive evidence is lacking)

- **VIRAL**:
  - ✓Valacyclovir 500 mg once or twice daily for at least one month following ATG (HSV&CMV)

- **BACTERIAL**:
  - ✓Regular mouth care and food of low bacterial content

- **VACCINATION :**
  - There are some reports of relapse with both vaccin and active viral infection
  - It is better to avoid vaccination within 1 year after IST or CsA

Ash 2017

NOVARTIS

Continue…..

- Our patient has not Ralated HLA-matched donor
- She doesn’t has any HLA-matched donor in IRAN HLA-Bank
- She and her family are Economicaly poor and can`t afford search for foreign HLA-Banks
- After 1 months of IST and frequent transfusion,she was admitted for h-ATG
    - Pre med:Acetaminophen +Diphenhydramine
    - hATG: 40mg/kg /daily over 4 hours for 4 days via cv line
    - 1-2mg/kg prednisolone till 10 days with rapid taper and discontinuation by day 21
- 2 weeks after ATG she bacame independent to transfusion
- 1 month After treatment, CBC IS:
    - WBC= 4500/mL
    - Hg = 10 mg/dl
    - Plt=220000 /mL
- The CsA continued till 1 year when severe cytopenia accrued

NOVARTIS

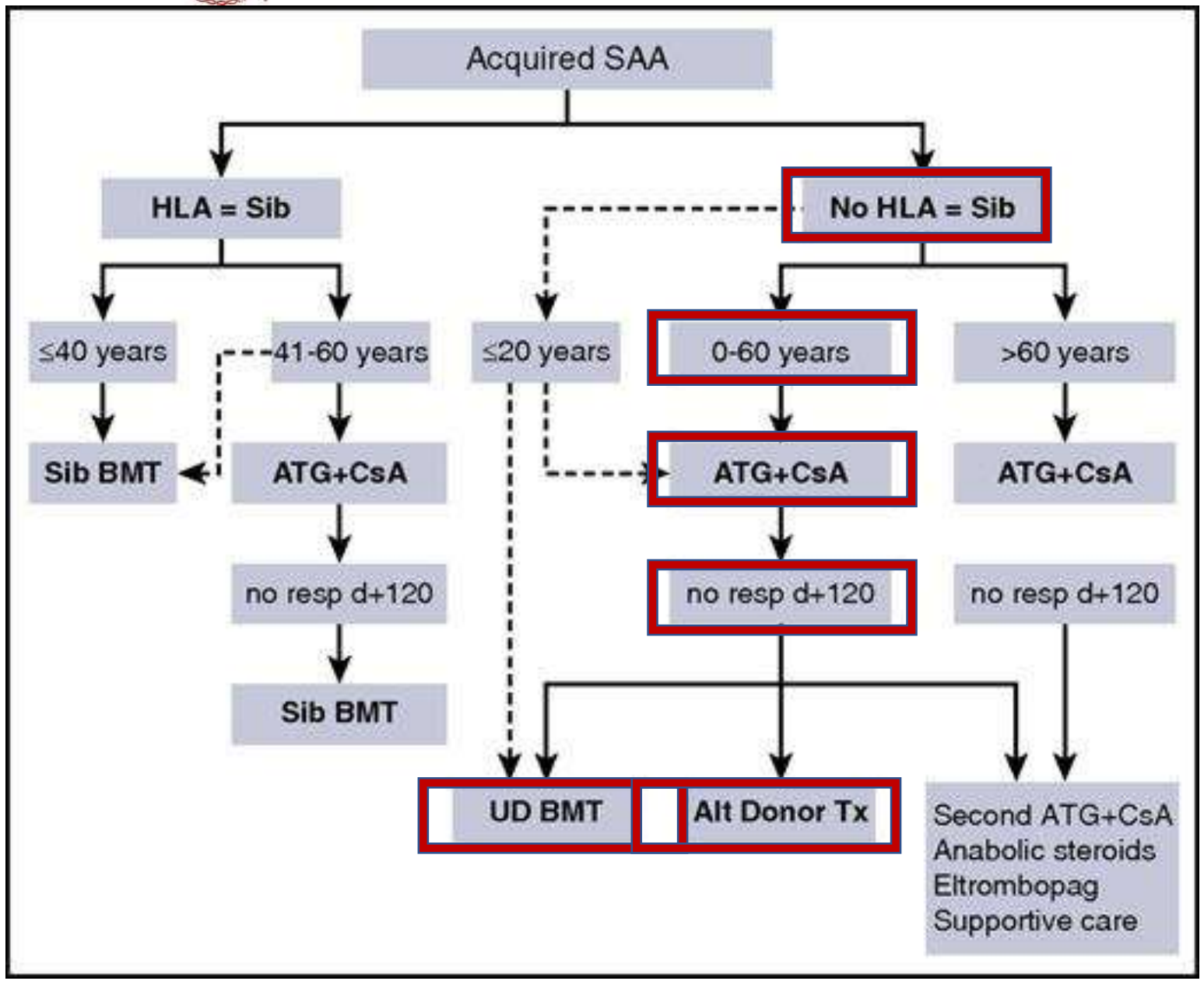
QUESTIONS?

- Do you recommend to reevaluate the patient ? like BMB/A/cyto
- Based on evidences in Relapse, Which option is better?
  - **Haplo OR UD-BMT** or **rechalleng with ATG** or **EPAG** (only in refractory and add to CyS in relaps)
- If you recommend ATG,which kind of ATG?
- Considering patient`s economy,which option is better?
- What about Romiplostim,Alemtuzumab and high dose Cyclo?

NOVARTIS

American Society of Hematology

Helping hematologists conquer blood diseases worldwide



NOVARTIS

EVIDENCE BASE ANSWER:

- It is suggested that in the presence of a matched UD, second-line therapy should be a UD transplant, rather than a second course of ATG

- HAPLO grafts are still in the experimental stage and should be considered only after having failed at least 1 course of IST in the absence of a suitable UD

- A total of 84 patients reported BY Esteves in 2015
  - the average 1-year survival was 74%, which is very encouraging

EVIDENCE BASE ANSWER:

- For initial treatment of AA, rATG should not be substituted for hATG unless hATG is not available
  - due to the lower response rate

- Who were previously treated with hATG should be treated with rATG because of high incidence of serum sickness

EVIDENCE BASE ANSWER:

- **ROMIPLOSTIM(N-PLATE):**

- substantial activity in refractory SAA
- in 2 study, was effective and well tolerated for refractory SAA and was not with clonal evolution

  - JANG JH,et al. IN BR J HAEMATOL,2021
  - LEE JW ,et al. LANCET .2019

NOVARTIS

EVIDENCE BASE ANSWER:

- **ALEMTUZUMAB**

- Is a monoclonal Ab against anti-CD52 on lymphocyte and other HSC

- The largest trial rendomized 54 patients refractory AA to Alem v.s ATG/CsA with similar RR(37 v.s 33%)

NOVARTIS

PREGNANCY AND AA

- It is unclear if pregnancy increase the risk for AA
- AA can present during pregnancy
- Pregnancy appears to increase the risk of **relapse of AA**
- **Supportive care is the mainstay of treatment of AA in pregnancy**
- **Delay definitive therapy with IST or Transplant**
- **Save PLT**> 20000/microL
- **CsA** can be given during pregnancy if necessary

NOVARTIS

- Pregnancy and a good obstetrical outcome are possible for women previously treated with IST

- 36 women who had received IST and subsequently became pregnant
  - ✓relaps of AA occurred in 7 and more likely in women who initially had only a partial response to IST

NOVARTIS