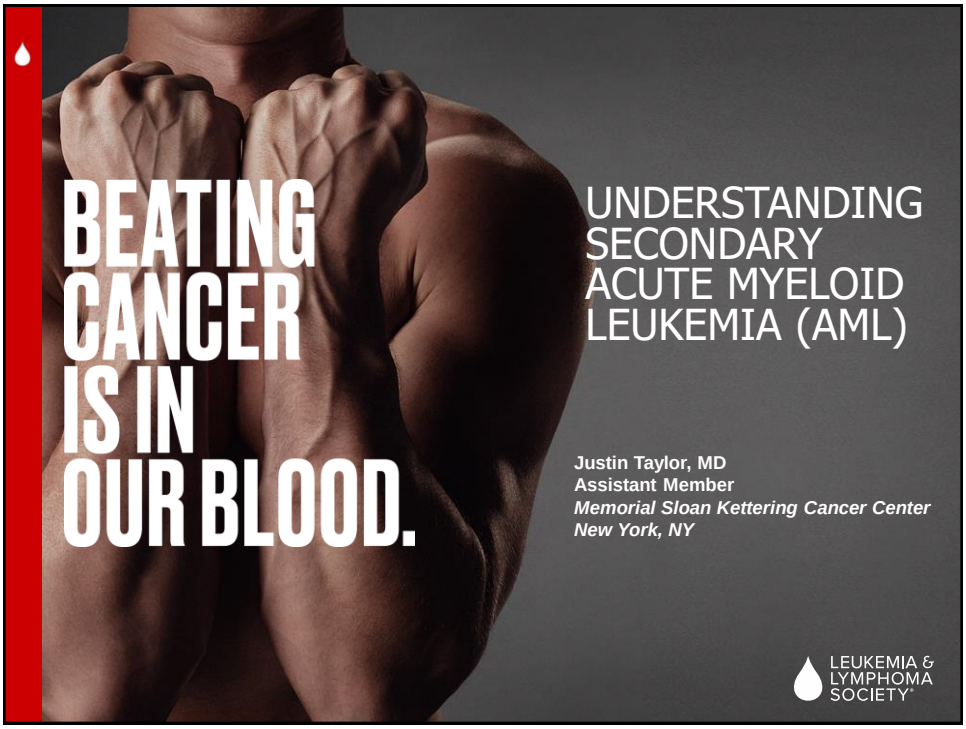

1

Secondary Acute Myeloid Leukemia

Justin Taylor, MD
Assistant Member, Leukemia Service

Memorial Sloan Kettering Cancer Center

2

Financial Relationships

No relevant financial relationship(s) exist

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3

Overview

1) What is secondary acute myeloid leukemia (AML)?

2) How is secondary AML diagnosed?

3) Current and emerging treatments for secondary AML

4) Future research directions

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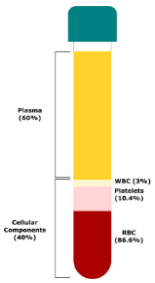
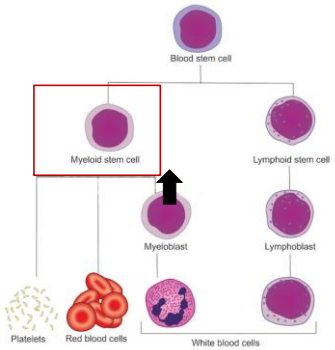
What Is Leukemia?

- Literally meaning “white blood,” leukemia is a cancer of the blood-forming tissues, including the bone marrow





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Secondary Acute Myeloid Leukemia

- Definition: Secondary acute myeloid leukemia (sAML) refers to a leukemic process either:

  (A) Evolving from prior myelodysplasia (MDS), myeloproliferative disorder (MPN), or aplastic anemia with or without treatment; or

  (B) Occurring after previous exposure to radiation or chemotherapy exposure for another cancer

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Primary versus Secondary AML

- Primary AML refers to leukemia arising *de novo* (or “anew”)
- The prognosis for primary and secondary AML are different with secondary AML having worse outcomes
- Because of the worse outcomes with secondary AML the treatments have recently changed and are different from primary AML

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Changing Definitions

- Recognition that prior myelodysplastic syndromes may go undiagnosed led to development of a diagnostic classification called AML with myelodysplasia-related changes (AML-MRC)
- Chemotherapy and radiation can also induce myelodysplastic syndromes (MDS) with poor prognosis and high likelihood of transforming to AML, such that therapy-related MDS and AML are thought of similarly (t-MDS/t-AML)

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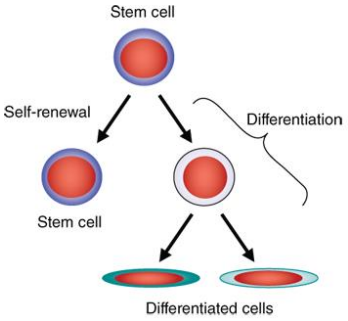
A Deeper Understanding

- The origin of AML is considered to be due to acquisition of genetic mutations over time
- Each hematopoietic (blood) stem cell divides once every 40 weeks and incurs about 11 mutations each time



- If a mutation occurs in a leukemia-related gene it leads to a condition called clonal hematopoiesis

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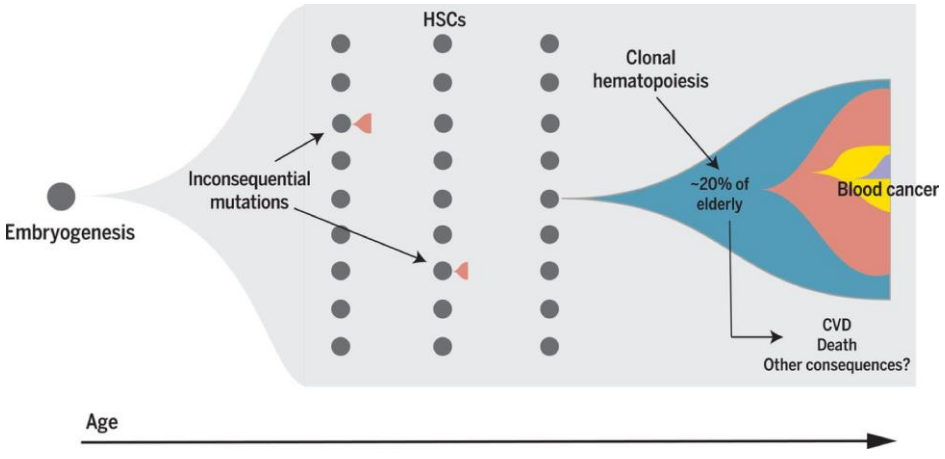
Harrison's Principles of Internal Medicine. 20th Ed.

9

Clonal Hematopoiesis Is Age-Related



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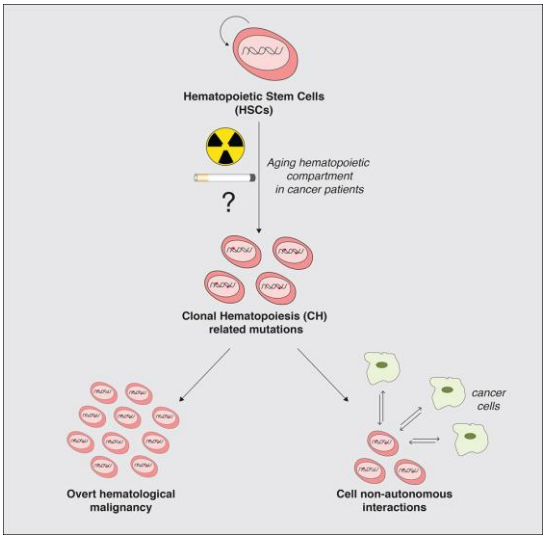
Jaiswal and Ebert. Science. 2019;366.

10

Clonal Hematopoiesis and t-AML

- Clonal hematopoiesis is a risk-factor for therapy-related AML and is seen in a higher percentage of cancer patients compared to healthy individuals



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Clonal Hematopoiesis and AML-MRC

- Certain mutations seen in clonal hematopoiesis are associated with primary or *de novo* leukemia, but others are associated with MDS or MPN
- For example, one study showed that the presence of one of a group of mutations called spliceosome gene mutations was >95% specific for secondary AML

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How Is Secondary AML Diagnosed?

- The symptoms of secondary AML are similar to primary AML although in AML-MRC the white blood cell counts tend to be low (as compared with high in primary AML)

- Symptoms are related to the failure of the normal blood production resulting in anemia (causes fatigue or shortness of breath) and thrombocytopenia (low platelets: causes bruising or bleeding). Infections can be seen because of lowered immune system

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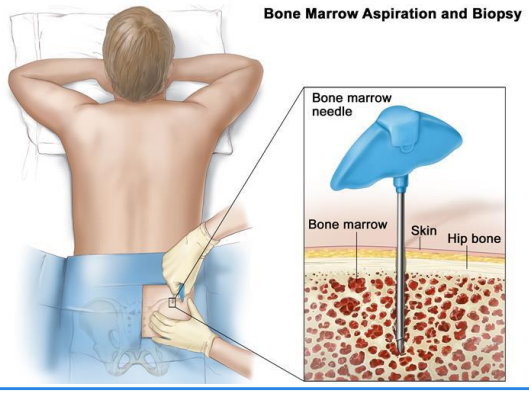
Diagnosing Secondary AML

- Even though some evidence of secondary AML can be detected from a blood draw, the diagnosis requires a biopsy of the bone marrow



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Diagnosing Secondary AML

- Your doctor knowing whether you have a history of a previous blood disorder or any radiation or chemotherapy in the past is very important because that information alone can be sufficient to make the diagnosis if AML is seen on the biopsy
- The pathologist (the doctor who makes the diagnosis by examining the bone marrow under the microscope) can also identify whether dysplasia is present and at high enough levels that it can be categorized as AML-MRC

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Genetics Are Key to Diagnosis

- If there is no known history of previous blood disorder or radiation/chemotherapy exposure and no evidence of dysplasia of the bone marrow, the diagnosis of AML-MRC can still be made
- Genetic abnormalities associated with MDS can also be used to make the diagnosis of AML-MRC

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Diagnostic Criteria for AML-MRC

- Must not have a mutation in NPM1 or biallelic CEBPA mutations
- ≥50% of dysplasia in 2 or more cell lineages
- The presence of an MDS-related cytogenetic abnormality, except for del(9q), even in the absence of dysplasia

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Prognosis of Secondary AML

- In comparison to primary AML, secondary AMLs are usually considered adverse or poor risk
- The exception is cases of therapy-related AML with inversion of chromosome 16 or a translocation of chromosomes 15 and 17, which can have the same outcomes as primary AML with those genetic abnormalities
- Complex karyotype and those with TP53 mutations may have the worst outcome overall

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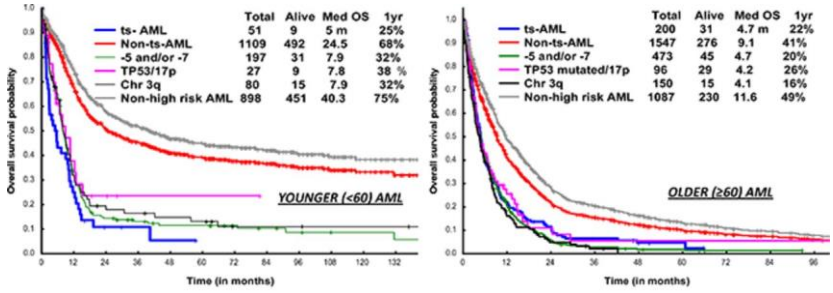
Treatment for Secondary AML

- Whether intensively treated or not, and regardless of age, patients with secondary AML have decreased survival compared to primary AML



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Boddu. Blood Advances. 2017;1312.

19

A New Treatment for Secondary AML

- Prior to 2017 there existed no specific treatment for secondary AML
- Vyxeos®, an intravenous drug containing two chemotherapies in an encapsulated formulation, was FDA-approved for secondary AML in August 2017
- Approval was based on a trial of patients with secondary AML receiving either Vyxeos® or the standard chemotherapies (uncombined)

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Vyxeos® for Secondary AML

- Phase 3 randomized trial of 309 patients aged 60-75 years with newly diagnosed secondary AML
- Received induction therapy with Vyxeos® or daunorubicin and cytarabine separately ("7+3")
- Primary goal of the study was to compare the overall survival based on treatment received

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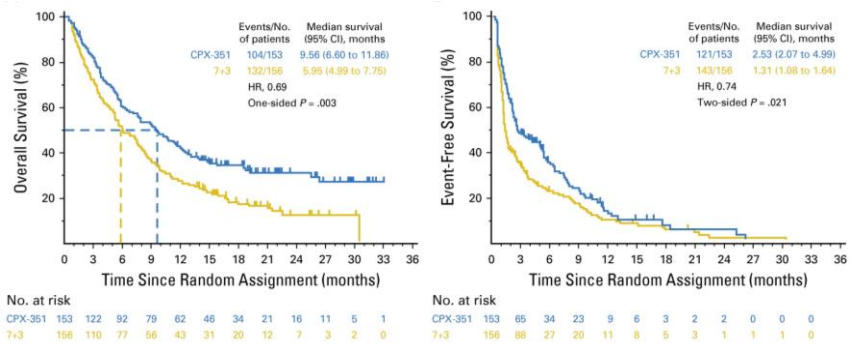
Lancet. JCO. 2018;2684.

21

Vyxeos® (CPX-351) for sAML

Overall survival was better in the Vyxeos®-treated group



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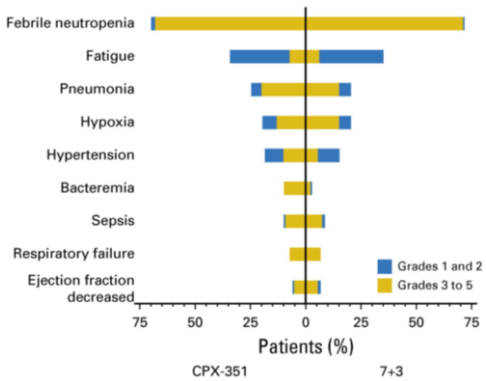
Lancet. JCO. 2018;2684.

22

Vyxeos® for sAML

- Response rates (number of complete remissions) were higher in the Vyxeos® group compared to patients who received “7+3” (47.7% vs 33.3%)
- Side effects were similar in both groups



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Lancet. JCO. 2018;2684.

23

What to Expect on Vyxeos®?

- Vyxeos® is given as a 90-minute infusion for 3 doses every other day, typically in the hospital
- Vyxeos® causes the blood counts to become very low, similarly to standard chemotherapy. The time to recovery of neutrophils and platelets is <u>1-2 weeks longer</u> than with standard chemotherapy
- Vyxeos® was also associated with self-limited rash in ~50% of patients on the trial but not with “7+3”

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What to Expect on Vyxeos®?

- After recovery of blood counts, a bone marrow biopsy is performed to assess for remission
- If in remission, patients on the trial received up to 2 cycles of consolidation (lower dose of Vyxeos® for just 2 doses) or could receive an allogeneic hematopoietic stem cell ("bone marrow") transplant

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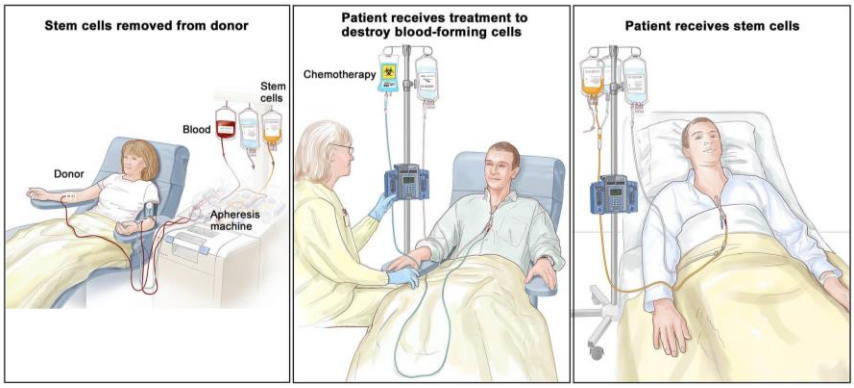
Hematopoietic Stem Cell Transplant

- Allogeneic means received from a donor. This typically is a sibling or unrelated individual who is found to have matching immune system markers



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www.cancer.gov.

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HSCT for Secondary AML

- A Swedish population registry trial showed that after 5 years there was <5% of intensively treated sAML patients alive who had not received an allogeneic HSCT
- Comparatively, receiving an allo-HSCT was associated with 20-30% being alive at 5 years
- This data could be confounded because patients who are sicker might not get HSCT

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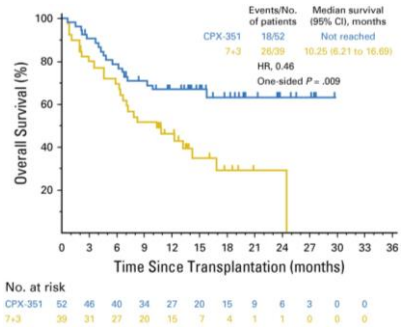
Nilsson. BBMT. 2019;1770.

27

HSCT After Vyxeos®

- More patients treated with Vyxeos® received HSCT compared to standard chemotherapy (34% vs 25%) and had better outcomes after transplant



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Lancet. JCO. 2018;2684.

28

Less Intensive Treatment Options

- Deaths after either Vyxeos® or chemotherapy within the first 60 days was 14% and 21%, respectively
- In some patients it might be better or the patient may decide to use a less intensive treatment
- The hypomethylating agents azacitidine and decitabine are a class of agents typically used in MDS and therefore have a rationale in sAML, though neither are FDA-approved for sAML

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Hypomethylating Agents (HMA) for sAML

- Compared to intensive chemotherapy, HMA therapy can take a longer time to induce remission
- Both azacitidine and decitabine are intravenous, though azacitidine can also be given subcutaneously
- Both HMAs cause the blood counts to fall, though not to the same degree as intensive chemotherapy

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HMA Plus Venetoclax for sAML

- Venetoclax is an oral BCL2-targeted therapy recently approved for AML in older patients in combination with HMA or low-dose chemotherapy
- In the largest study of venetoclax with HMA (either azacitidine or decitabine), 25% of patients had secondary AML
- Similar to the entire cohort, 67% of patients with sAML had a complete remission with the median overall survival not reached at 15 months

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HMA+Ven versus Vyxeos®

- Cannot truly compare the two because the trials were very different. The Vyxeos® trial had 300 sAML patients and was randomized while the HMA+Ven trial had a subgroup of only 25 sAML patients
- Patients getting HMA+Ven were not allowed to have had prior therapy for MDS/MPN but that was allowed on the Vyxeos® trial.
- 60-day mortality was lower (8%) for HMA+Ven

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DiNardo. Blood. 2019;7-17.

32

Targeted Therapies for sAML

- Recent drugs approved to target specific mutations in MDS or AML can also be used for sAML with those mutations
- IDH1 and IDH2 mutations are found in 5% and 20% of patients with sAML, respectively. Specific inhibitors called ivosidenib and enasidenib can selectively target the mutant proteins
- IDH inhibitor drugs are very well tolerated but can also take several months to have maximal effect

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Emerging Therapies for sAML

- TP53 mutations are common and predict poor response to chemotherapy in sAML
- APR-246 is a first-in-class mutant TP53 stabilizing drug that is being developed in combination with azacitidine in MDS and AML with low blast count
- Of 45 patients, 53% had a complete response and the median survival was 11.6 months in preliminary findings

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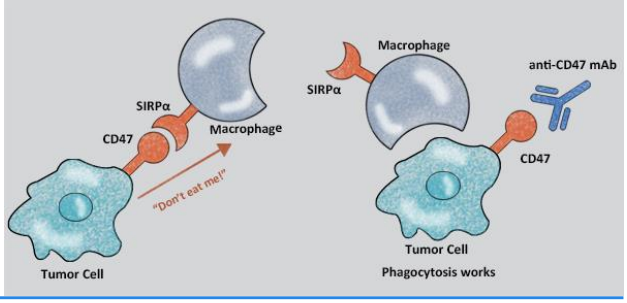
Sallman. ASH abstract. 2019.

34

Emerging Therapies for sAML (cont'd)

- Magrolimab is a CD47-blocking antibody. CD47 is a defense co-opted by cancer cells to tell the immune system "don't eat me"

- 7 out of 9 patients with TP53 mutant AML responded in a phase 1 study



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Sallman. ASH abstract. 2019.

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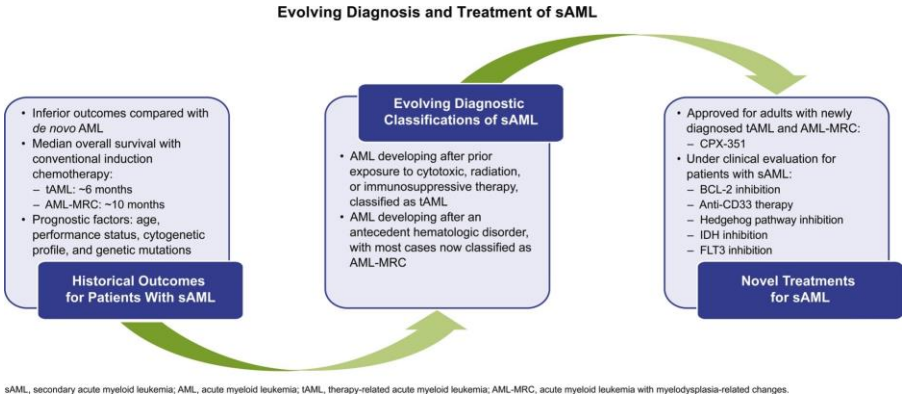
Summary



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Ossenkoppele. Crit Rev in Oncol/Hematol. 2019.

36

Questions?

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Q&A SESSION

Understanding Secondary Acute Myeloid Leukemia (AML)

Q&A Session

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- **Information Specialists**

  Master's level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.

  - **EMAIL: infocenter@LLS.org**
  - **TOLL-FREE PHONE: 1-800-955-4572**

- **Additional Information about Leukemia:**
  - **www.LLS.org/leukemia**
- **Education Booklets about AML:**
  - **www.LLS.org/booklets**
- **Telephone/Web Programs:**
  - **www.LLS.org/programs**
- **Weekly Acute Leukemia Online Chat:**
  - **www.LLS.org/chat**

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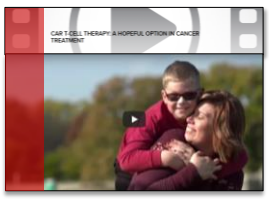
FREE LLS EDUCATION & SUPPORT RESOURCES



- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: **www.thebloodline.org**

- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: **www.LLS.org/educationvideos**

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: **www.LLS.org/firstconnection**

- **Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: **www.LLS.org/nutrition**

- **What to Ask**

  Questions to ask your treatment team: **www.LLS.org/whattoask**

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: **www.LLS.org/support**

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THANK YOU
We have one goal: A world without blood cancers
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