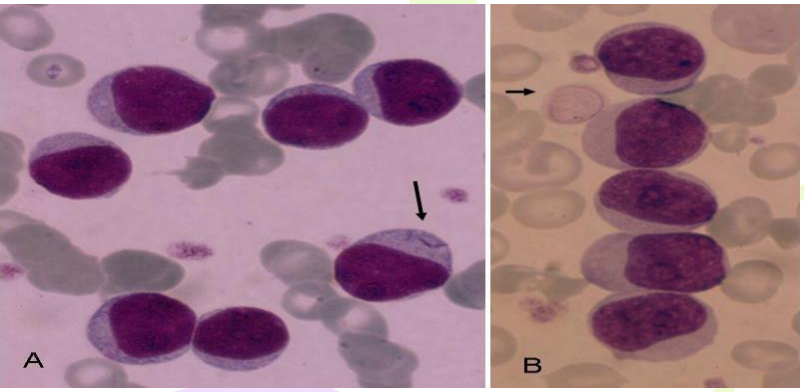
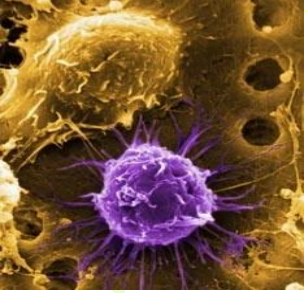


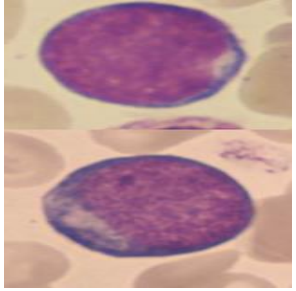
YAŞLI AML'DE
STANDART İNDÜKSİYON
VS
EPİGENETİK TEDAVİ

Dr. Mine MİSKİOĞLU

İç Hastalıkları AD, Hematoloji BD,
CBÜTF, Manisa



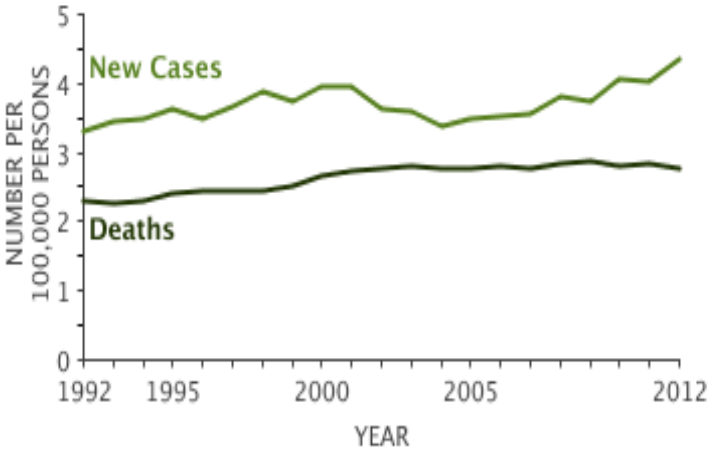
AML



- Myeloid öncüllerin klonal proliferasyonundan kaynaklanan, fatal bir hematopoietik kök hücre hastalığı
- KLL'den sonra 2. sıklıkta görülen lösemi (yılda 4/100 000)
- Her yaşta görülür, ancak ileri yaşla sıklık artar (medyan tanı yaşı 67) → YAŞLILIK HASTALIĞI

AML

Estimated New Cases in 2015	20,830
% of All New Cancer Cases	1.3%
Estimated Deaths in 2015	10,460
% of All Cancer Deaths	1.8%



Percent Surviving 5 Years
25.9%
2005–2011

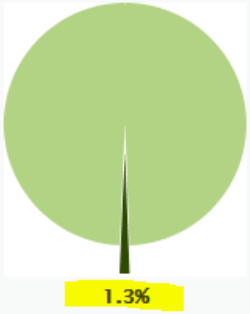
Number of New Cases and Deaths per 100,000: The number of new cases of acute myeloid leukemia was 4.0 per 100,000 men and women per year. The number of deaths was 2.8 per 100,000 men and women per year. These rates are age-adjusted and based on 2008–2012 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 0.5 percent of men and women will be diagnosed with acute myeloid leukemia at some point during their lifetime, based on 2010–2012 data.

- Kanserlerin %1.3’ünü oluşturur

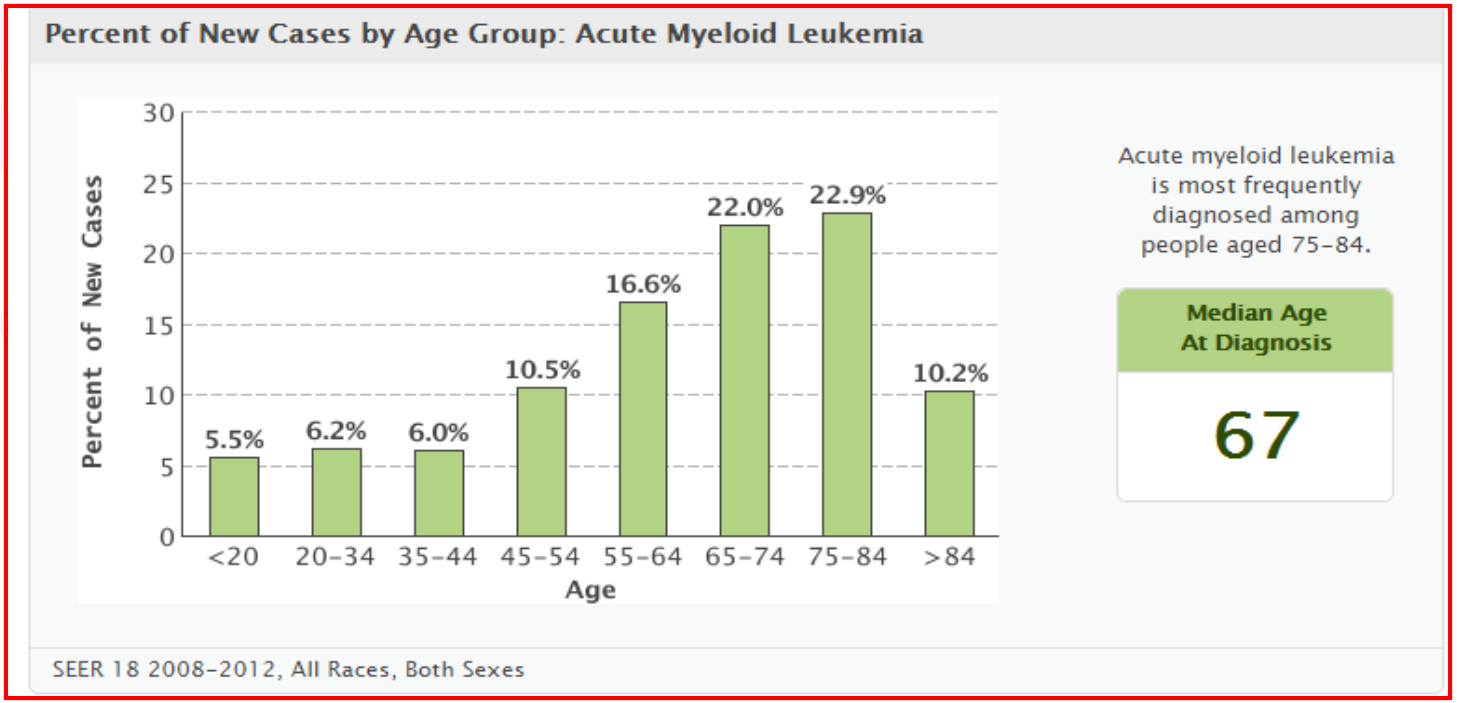
	Common Types of Cancer	Estimated New Cases 2015	Estimated Deaths 2015
1.	Breast Cancer (Female)	231,840	40,290
2.	Lung and Bronchus Cancer	221,200	158,040
3.	Prostate Cancer	220,800	27,540
4.	Colon and Rectum Cancer	132,700	49,700
5.	Bladder Cancer	74,000	16,000
6.	Melanoma of the Skin	73,870	9,940
7.	Non-Hodgkin Lymphoma	71,850	19,790
8.	Thyroid Cancer	62,450	1,950
9.	Kidney and Renal Pelvis Cancer	61,560	14,080
10.	Endometrial Cancer	54,870	10,170
	–	–	–
	Acute Myeloid Leukemia	**20,830**	**10,460**

Acute myeloid leukemia represents 1.3% of all new cancer cases in the U.S.



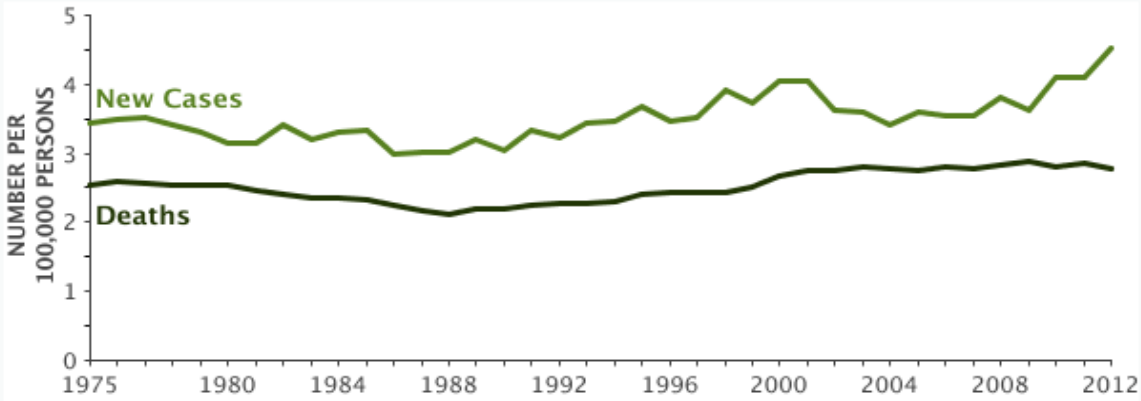
In 2015, it is estimated that there will be 20,830 new cases of acute myeloid leukemia and an estimated 10,460 people will die of this disease.

- AML, yaşlılıkta daha çok görülen bir hastalıktır



- Görülme sıklığı artmakla birlikte yaşam oranlarında da artma vardır

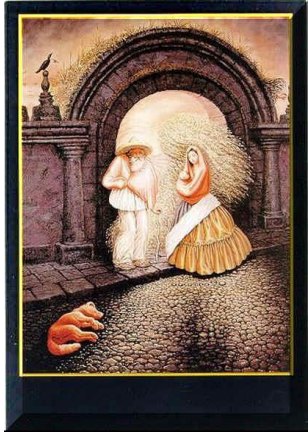
New Cases, Deaths and 5-Year Relative Survival View Data Table

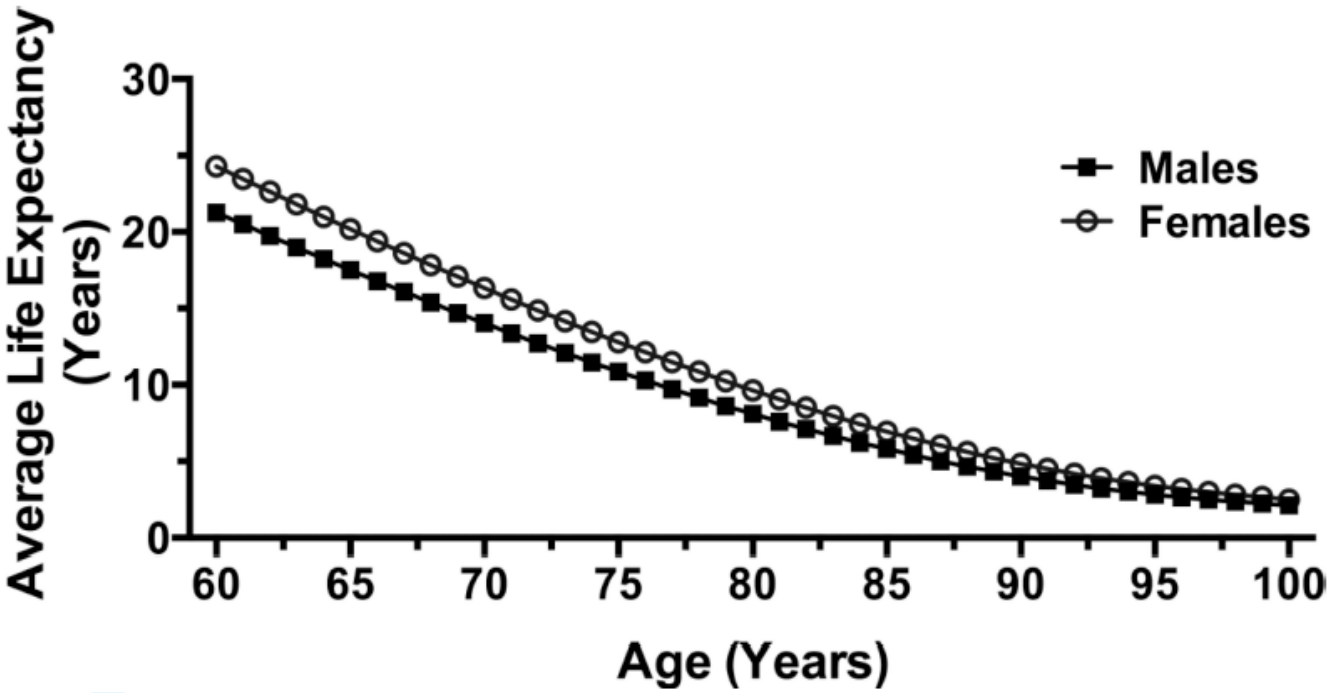


Year	1975	1980	1985	1990	1995	1999	2003	2007
5-Year Relative Survival	6.3%	6.8%	13.1%	11.4%	17.3%	18.3%	23.0%	23.9%

SEER 9 Incidence & U.S. Mortality 1975-2012, All Races, Both Sexes. Rates are Age-Adjusted.

Yaşlılıkta yaşam beklentisi (ABD)





RB Walter and E Estey, Leukemia 2015

YAŞLI AML

KİM YAŞLI???

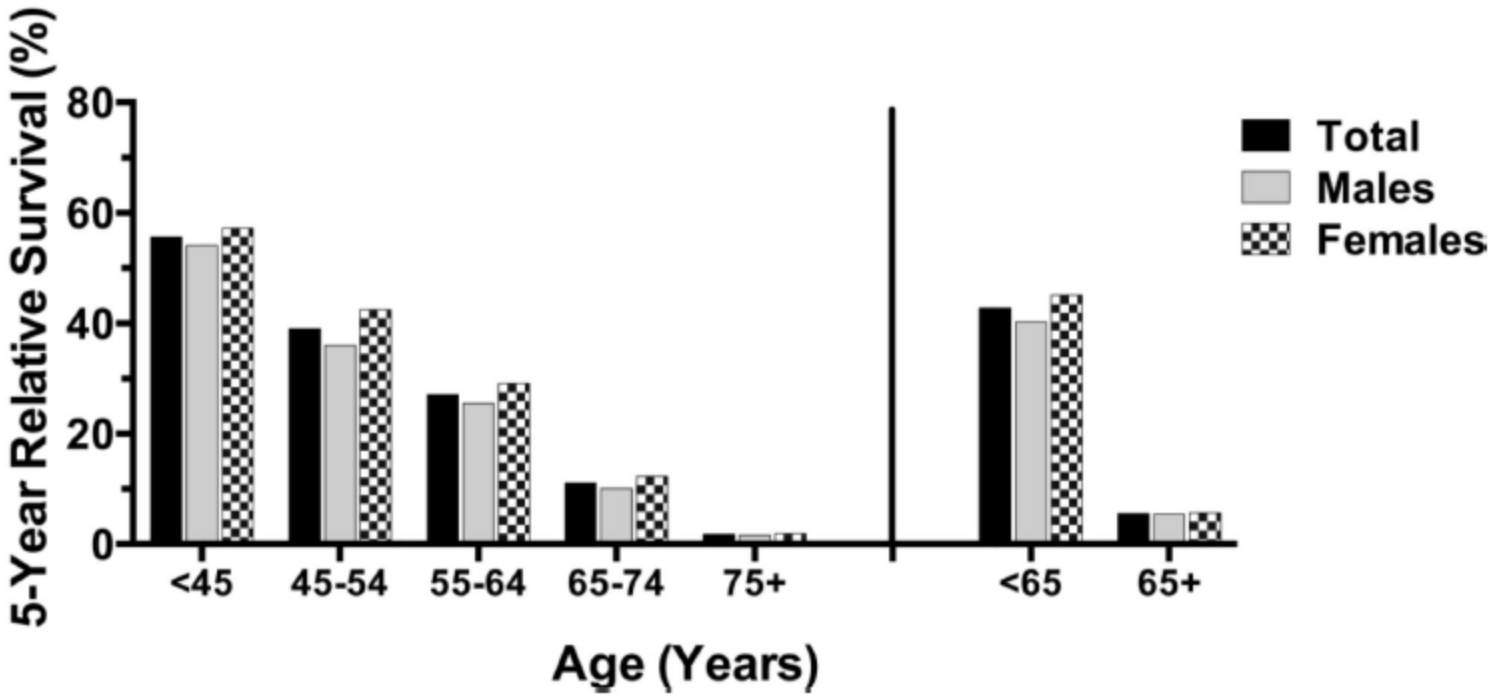
60 yaş altı

- Yeni tanı konan hastaların %75'inin remisyona girmesi beklenir
- %40-50 uzun süre yaşam

60 yaş üstü

- Hasta ve hastalık heterojen
- Erken ölüm riski yüksek
- Remisyon oranı düşük
- PFS ve OS düşük
- >65 y medyan yaşam 3.5 ay-5 yıl yaşam <%5

- **>65 y 5 yıllık yaşam %5 dolayındadır**



RB Walter and E Estey, Leukemia 2015

- SWOG, 968 hasta, ileri yaşta
  - iyi sitogenetik daha az
  - kötü PS
  - daha düşük lökosit sayısı
  - daha düşük Kİ blast %
  - İndüksiyon KT'ye daha düşük cevap (%33)
  - daha fazla erken ölüm
  - daha kısa OS (75 y üstü 3.5 ay)
  - kötü PS ile indüksiyon mortalitesi ilişkili

60 yaş üstü AML

Hastalık biyolojisinde farklılık var !

- Önceden bir hematolojik hastalık sık (MDS gibi)
- Sekonder AML (multilineage, ilaç direnci +)
- Kötü sitogenetik ↗, iyi sitogenetik ↙
  - çoğ. İntermediate risk grubu
  - monosomiler daha sık
  - kompleks karyotip
  - olumsuz non-kompleks karyotip
  - NK
- Prognostik moleküler belirteçler
  - FLT3-ITD
  - NPM1
  - CEBPA
  - MDR1

Risk group	MRC	US Intergroup
Good	M3, t(15;17), t(8;21), inv (16)	t(15;17), inv(16), t(8;21)
Standard/Intermediate	Not good or poor	+8, -Y, +6, del(12p), normal
Poor	-5/del(5q), del(7p), 3q-, complex	-5/del(5q), -7/del(7q), inv(3q), 11q, 20q, 21q, 17p, del(9q), t(6;9), t(9;22), complex

Slovak ML. Blood.2000

Sitogenetik analiz yaşlı AML'de tedavi seçiminde dikkate alınmalı mı?
(MRC AML 11, 14, German-Austrian Austrian AML)

Tedavi öncesi sitogenetik sonuçlar beklenmeli mi?

Hastaya ait olumsuz özellikler sık!

- Daha kötü fonksiyonel kapasite
- Komorbiditeler
- İlaçların farmakodinami ve farmakokinetiğinde yaşla değişiklikler→ geç ilaç klirensi → artmış toksisite → tedavi morbidite ve mortalitesi
- **PS ≥2 iken 30 günlük ölüm**

  56-65 y → %18-24

  75 y üstü → %50-82
- Bakım veren kişi eksikliği

Hastanın fonksiyonel kapasitesi ve prognostik durumu nasıl değerlendirilmeli?

- Tıbbi durumu
- Eşlik eden hastalıkları, organ yetmezliği
- Enfeksiyon
- Sitogenetik

- ECOG, Karnofsky PS
- Komorbidite indeksleri (Charlson CI, CCI)
- Geriatrik değerlendirme testleri (CGA)
- Hematopoietik cell tx komorbidite indeksi (HCTC-CI)
- German aml-score
- MDACC prognostik model
- Wheatley skor modeli (MRC AML14)

Table 1. Selected risk models predictive of outcome with intensive chemotherapy in elderly acute myeloid leukemia

	Risk factors	CR/ED rate (%)	Overall survival (%)
Malfuson *et al.* [7]	Poor cytogenetics		(At 1 year)
(ALFA-9803)	Age ≥75		Poor: 19
	PS ≥2		Others: 58
	WBC ≥50 × 10^9/l		
Wheatley *et al.* [8]	Cytogenetics		(At 1/3 years)
(MRC AML14)	Age		Good: 60/29
	WBC		Standard: 48/17
	PS		Poor: 30/9
	De novo versus sAML		
Kantarjian *et al.* [9]	Age ≥80	(By n. risk factors)	(At 3 years)
(MDACC)	Complex karyotype	0: 57/16	0: 22
	PS ≥2	1: 52/31	1: 7
	Creatinine >1.3 mg/dl	2: 29/55	2: 6
		≥3: 16/71	≥3: 0
Rollig *et al.* [10]	Cytogenetics		(At 3 years)
(SAL AML-96)	Age		Good: 39.5
	WBC >20 × 10^9/l		Intermediate/good: 30
	LDH >700 U/l		Intermediate/poor: 10.6
	CD34 >10%		Poor: 3.3
	NPM1 mutation		

CR, complete remission; ED, early death; LDH, lactate dehydrogenase; NPM1, nucleophosmin1; PS, performance status; sAML, secondary AML; WBC, white blood cell count.

Amadori et al, CurrOpinOncol 2014

Table 1. Hematopoietic cell transplantation co-morbidity index.

Item	Definition	HCTCI score
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmia	1
Cardiac other[a]	Myocardial infarction or coronary artery disease	1
	Heart valve disease, except mitral valve prolapse	3
Cerebrovascular	Transient ischemic attack, cerebrovascular accident	1
Diabetes	Requiring insulin or oral hypoglycemics	1
Peptic ulcer	Requiring treatment	2
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Moderate pulmonary[a]	Dyspnea on slight activity or DLCO and/or FEV_1 66-80%	2
Moderate/severe renal	Serum creatinine >176.8 mM/L, on dialysis, or prior renal transplantation	2
Mild hepatic[a]	Chronic hepatitis, bilirubin 1.0-1.5 ULN, AST/ALT 1.0-2.5 ULN	1
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1
Psychiatric disturbance	Depression or anxiety requiring psychiatric consultation or treatment	1
Obesity	Body mass index >35 kg/m^2	1
Infection	Requiring continuation of antimicrobial therapy after day 0	1
Prior solid tumor[b]	Treated at any past time point, excluding non-melanoma skin cancer	3

Adapted from Sorror et al.[8] [a]congestive heart failure, severe pulmonary, and moderate/severe liver disease are not mentioned, as never observed in the study population; [b]prior exposure to chemotherapeutic agents and/or radiotherapy was a non-eligibility criterion for the study population; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; CTD: connective tissue disease; DLCO: diffusion capacity of carbon monoxide; FEV1: forced expiratory volume in 1 second; ULN: upper limit of normal: AST: aspartase transferase; ALN: alanine transferase.

German AML score, aml-score.org

Body temperature (°C)	(≤38, >38)
Hemoglobin (g/dl)	(≤10.3, >10.3)
Platelets (K/µl)	(≤28, >28-≤53, >53-≤104, >104)
Fibrinogen (mg/dl)	(≤150, >150)
Age at diagnosis (years)	(60-64, >64-67, >67-72, >72)
Type of leukemia	(de novo, secondary)

The Cytogenetic and molecular risk is classified into the following groups:

Low:
Low cytogenetic risk OR low molecular risk (normal karyotype and mutated Nucleophosmin [NPM1] and no Flt3-ITD mutation).

Intermediate normal:
Normal karyotype, intermediate molecular risk (all other combinations of NPM1 / Flt3 mutational status OR unknown mutational status).

Intermediate, not normal:
Intermediate cytogenetic risk, abnormal karyotype.

High:
High cytogenetic risk.

Prognostic models for elderly patients with AML – MD Anderson model

Parameter	Hazard risk
Age ≥ 75	1.3
Performance status ≥ 2, ECOG	1.5
Complex karyotype	1.4
Treatment outside laminar airflow room	3.1
ADH duration ≥ 12 months	1.4
Creatinine > 1.3 mg/dl	1.4

Risk group	No. Adverse factors	8 weeks mortality %	CR %	Median OS (months)	1-year survival %
Low	0	10	59	16	58
Intermediate	1-2	19-36	57-40	9-4	35-22
High	≥ 3	65	19	1	8

Nazha A, Leuk Lymphoma 2014

Yaşlı AML'de Tedavi

- Geçmişte hastaların çoğuna tedavi verilmiyor (hasta ve hekim tercihi)
  - Menzin ve ark. 1991-1996 ≥65y yeni AML %30 KT (+)

  OS 2 ay, 2 yıllık yaşam %8 iken KT (+) → 8 ay

- Yeni verilere göre agresif KT ile uzun süreli remisyon, yaşamda uzama ve yaşam kalitesinde iyileşme mümkün- **KT, destek tedaviden üstün**

  (EORTC AML7, İsveç ALR, Japon)

	İntensive KT (DaunVCRARAC)	Palyatif (HU/ARA C)
CR	%58	%0
DFS	%17	%0
0S (2.5 y)	%13	%0
Hast.yatış	%55	%50

Lowenberg, JCO 1989

- Yoğun KT için uygun olmayanların dahi lösemi-spesifik tedaviden yarar görmesi mümkün

  MRC AML 14- Düşük doz cytarabine, HU+destek tedaviden üstün-iyi/orta sitogenetikli hastalar- CR %18 vs %1, OS %25 vs %6

Kime hangi tedaviyi vermeli???

- *Skorlama sistemleri yoğun KT'ye uygun-fit hastaları belirlemede önemli araç olabilir*

Tedavi Seçenekleri

- **İntensif-Standart kemoterapi** (→ Postremisyon/konsolidasyon/idame ?)
- **Orta/Düşük yoğunluklu tedavi** (ne kadar süre/idame ?)
- Klinik çalışmalar (yeni ajanlar, yeni+eski kombinasyon KT)
- Kök hücre nakli (azaltılmış yoğunluklu?)
- En iyi destek tedavi (BST-Transfüzyon, Antibiyotik, Hidroksiüre)

- Mevcut tedavilere cevap oranının düşük, ölüm oranının yüksek olması
- Çoğu hastanın yoğun tedavilere uygun olmayışı
- Hastalıkla ilgili moleküler bilgilerin artışı
- Monoklonal antikorların geliştirilmesi
- Başka amaçla kullanılan ilaçların etkinliklerinin anlaşılması/araştırılması

Farklı-yeni tedavi yaklaşımları…

- İntensif tedavi alanlarda yaşam daha uzun (İsveç) -Eski çalışmalarda aksi bulgular da var

- Tanıdan sonraki 1 ay içinde tedavi → erken ölüm oranı düşük (ABD)
  (<80 y ve komorbidite yoksa)

Nasıl Yorumlamalı?

- KT şemaları/bireysel doz ayarlamaları???
- Non-random tedaviler ??
- Yoğun KT alanlara daha yoğun antibiyotik ve transfüzyon desteği
- Destek bakımın özel-donanımlı merkezlerde yapılması sonuçları iyileştiriyor

- **Hematolojik yanıt (+) → Yaşam daha uzun**

  CR> CRp >Refrakter hastalık

- **Daha iyi destek tedavi** →Son 20 yılda, yoğun KT rejimleri değişmese de erken ölümler (TRM) azalmıştır

TRM	Direnç olas.	Önerilen tedavi
Düşük	Düşük	Standart yoğun
Düşük	Yüksek	İnvest. yoğun
Yüksek	Düşük	Azaltılmış yoğunluklu
Yüksek	Yüksek	İnvest. azaltılmış

Walter ve Estey, Leukemia, 2015

Decision making in elderly AML based on expected outcomes

Induction Mortality	CR Rate	3-year Survival	Conventional Chemotherapy
< 15%	> 40%	> 15%	YES
> 30%	< 20%	< 10%	NO*
15-30%	20-40%	> 10%	?**

* Clinical trials of novel, investigational agents recommended

** Clinical trials comparing standard regimens to new strategies recommended CR = complete remission

Nazha A, Leuk Lymphoma, 2014

- **Standart tedavi mi Araştırma Tedavisi mi?**

- Hasta ve hastalığa ilişkin faktörler?
- Sitogenetik ve moleküler profil ? → WBC düşük yaşlılarda 1-2 hf sonuç beklenebilir ?
- Etik sorunlar? → Sonu/cu belli olmayan bir tedavi kararı

PS<2
Komorbidite (-) → Standart İndüksiyon KT
3 gün Antrasiklin (Daunorubisin/İdarubisin)+7 gün Sitarabin)

- 60-65 y Standart 7+3 rejiminde **DAUNOMİSİN dozu**nun **90 mg/m2 →** Cevap ve yaşam oranında olumlu etkisi (Faz III-Lowenberg ve ark, 2009)
- Ancak bu tartışmalı !!!

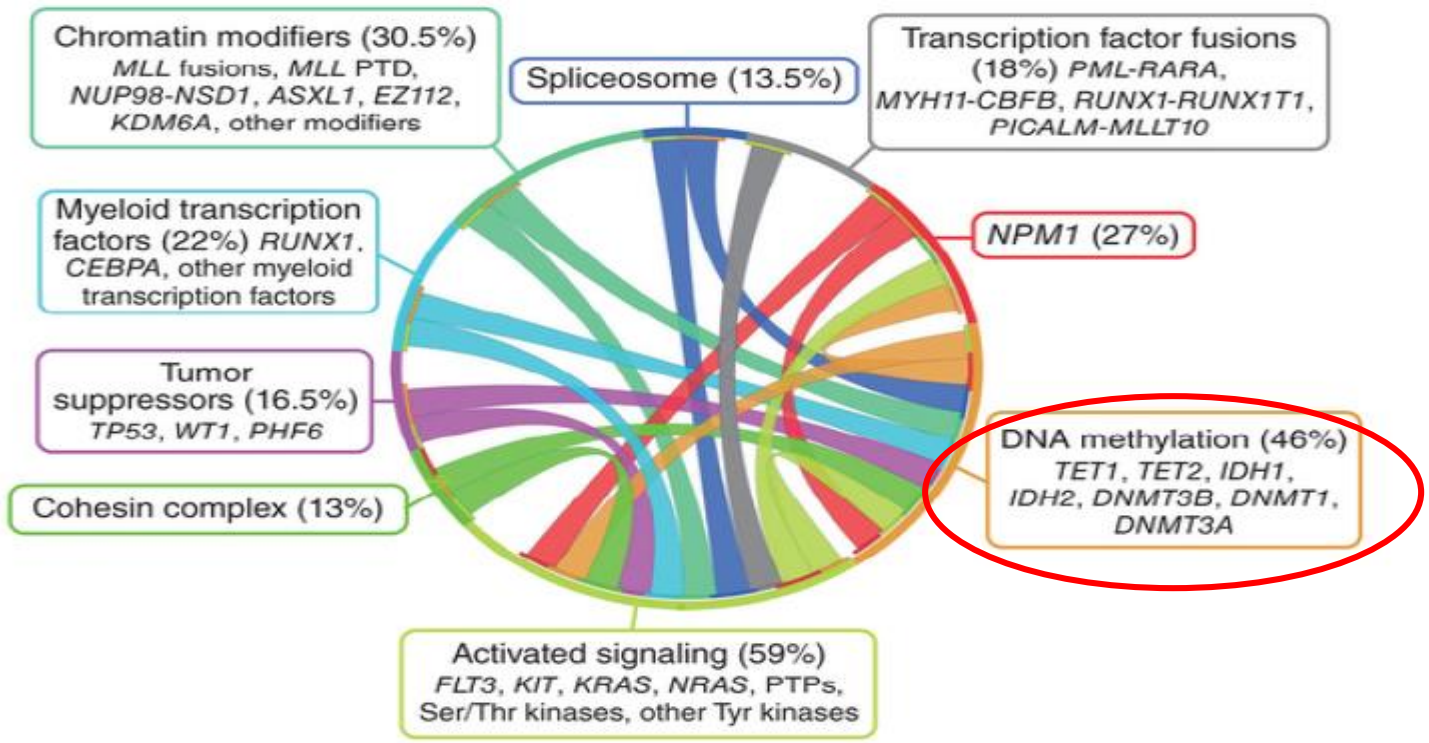
BLOOD, 18 JUNE 2015 • VOLUME 125, NUMBER 25

A randomized comparison of daunorubicin 90 mg/m^2 vs 60 mg/m^2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients

Alan K. Burnett,[1] Nigel H. Russell,[2] Robert K. Hills,[1] Jonathan Kell,[3] Jamie Cavenagh,[4] Lars Kjeldsen,[5] Mary-Frances McMullin,[6] Paul Cahalin,[7] Mike Dennis,[8] Lone Friis,[9] Ian F. Thomas,[1] Don Milligan,[10] and Richard E. Clark,[11] on behalf of the UK NCRI AML Study Group

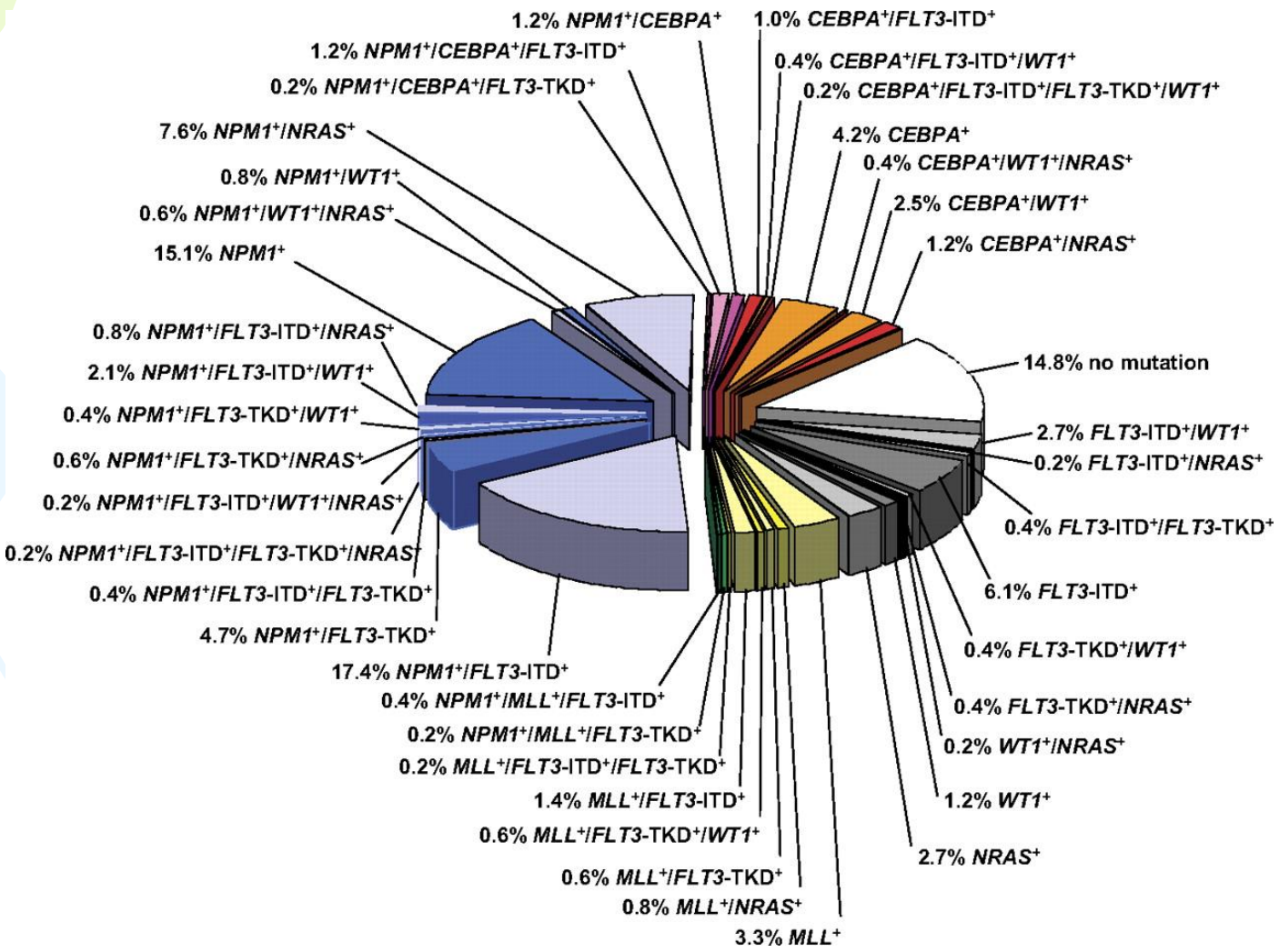
- In a first randomized comparison of daunorubicin dose in induction (90 mg/m^2 vs 60 mg/m^2) for AML, no evidence of overall benefit was seen with the 90 mg/m^2 dose.
- There was no disease subgroup in which benefit could be shown.

AML'de Moleküler Genetik



Hedefe yönelik tedavi???

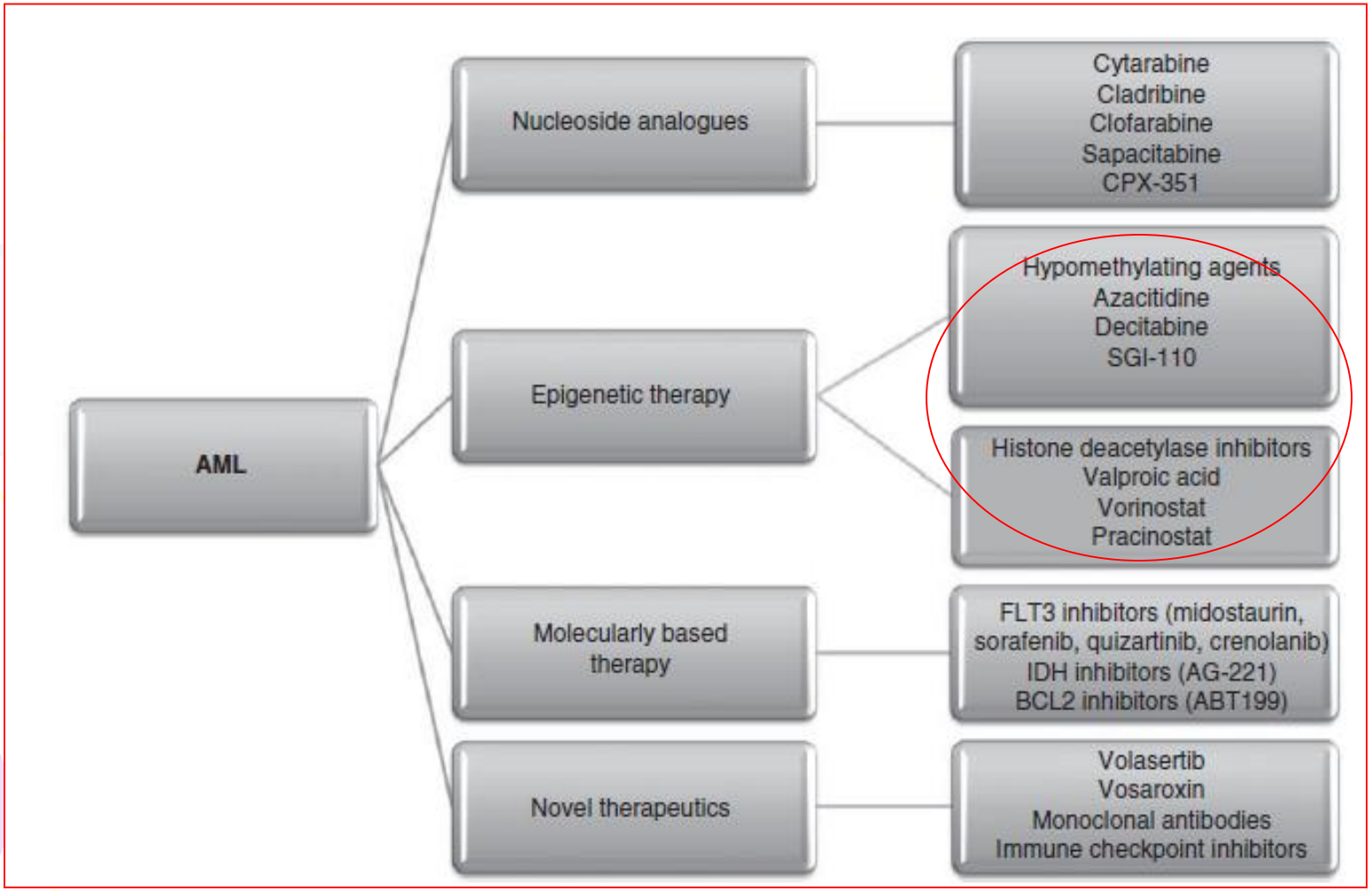
The molecular heterogeneity of cytogenetically normal AML based on mutations in the NPM1, CEBPA, MLL, FLT3 (ITD and TKD mutations at codons D835 and I836), NRAS, and WT1 genes.



Hartmut Döhner et al. Blood 2010;115:453-474

©2010 by American Society of Hematology

AML'de tedavi stratejileri



- **Alternatif indüksiyon rejimleri ??**

  - Çalışma protokolleri çok sayıda
  - Çalışmalara daha iyi hastalar alınır
  - OS, sonraki tedavilerden etkilenir

Standart tedaviye eklenen ajanların yararı?

- 60 y üstü İndüksiyon KT + **ATRA** eklenmesinin CR, EFS, OS'a olumlu etkisi (Schlenk ve ark, 2004)

- 50-70y Standart tedavi + **Gemtuzumab Ozogamicin** (GO-antiCD33 Ab konjugat immünotoksin) → CR aynı, 2 yıl EFS ve OS artışı (ALFA 071, UK AML16)

  - Toksisite nedeniyle üretici tarafından GO çekilmiştir

- **Clofarabine (2. jen. Nukleozid analogu)** monoterapi veya kombinasyon- OS'a yansımayan artmış CR

  kötü risk karyotipli yaşlı hastalarda olumlu sonuçlar (+) (ECOG-Faz III)

- **CR, her zaman OS'ın artması anlamına gelir mi?**

  Hayır

- **Remisyonlar uzun süreli mi?**

  Çoğu 6-12 aydan uzun değil

- **Refrakter demek için kaç kür vermeli?**

  7+3 için 2 kür, diğerleri?

- **Yaşam kalitesi**

  AML için standart değerlendirme yok

Epigenetik Tedavi

Epigenetik değişiklik→ DNA dizisi değişmeksizin gen ekspresyonunun etkilenmesi

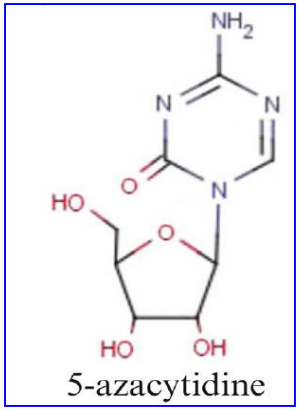
1- DNA metilasyonu

2- Histon ucunda değişiklikler (öz. asetilasyon ve metilasyon)

- N fizyolojik gelişimin bir parçasıdır
- Disregülasyonu AML ve başka kanserlerin patogenezinde önemli rol oynar
- Aberran DNA metilasyonu ve histon metilasyon/ deasetilasyonu AML gelişiminde önemli (>%70)
- Epigenetik regülasyonda önemli genlerde mutasyonlar gösterilmekte (DNMT3A, IDH1/2, TET2)
- **Henüz AML için uygun epigenetik tedavi yok**

- **Hipometilleyiciler (HMA)**
  - Azasitidin
  - Desitabine
  - SGI-110 (2. jenerasyon, dinükleotid-decitabin ve deoksiguanozin)
- **Histon deasetilaz inhibitörleri (HDACi)**
  - Pracinostat (SB939), oral
  - Panabinostat (LBH589)
  - Vorinostat, oral
  - Valproik asit (antiepileptik)
- Histon metilasyon inhibitörleri
- Histon demetilaz inhibitörleri
- Bromodomain içeren epigenetik "reader" BET proteinler
- Mutant izositrat dehidrogenaz inhibitörleri

Azanükleotidler



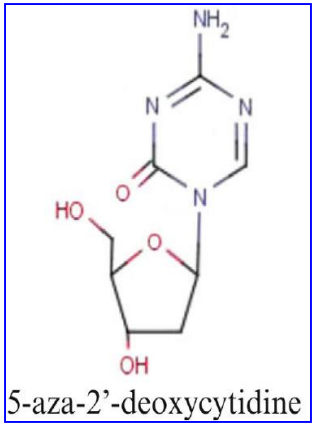
5-azacytidine

- **Azasitidin**, *Cytidine* nükleozid analogu

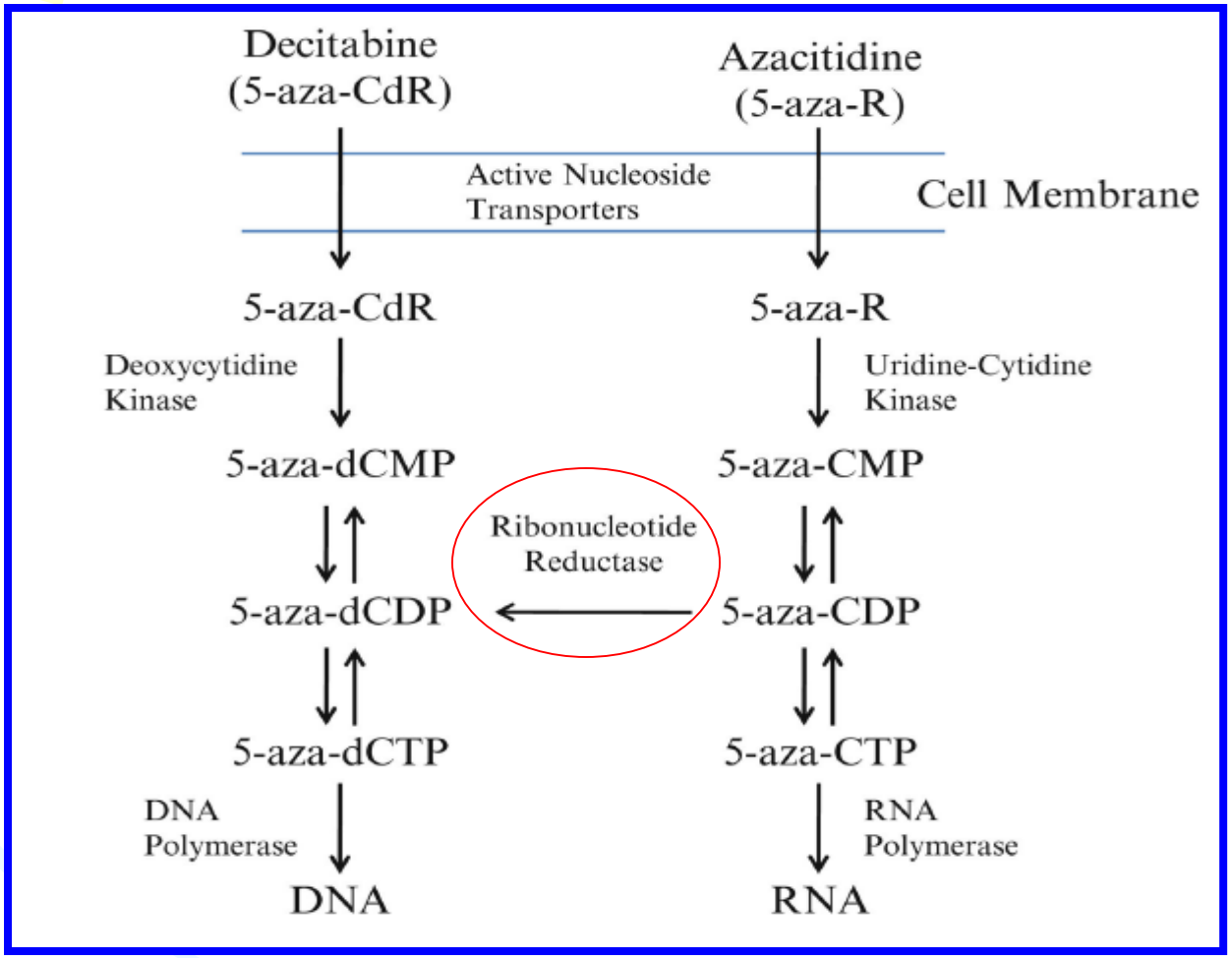
- %60-80'i RNA'yapısına girer→Protein sentezi ve RNA metab. etkilenir

- *%20-40'ı deoksiribonükleotid-Dac'e dönüşür*→ DNA'ya katılır→ Hücre replikasyonu sırasında hipometilasyon ve DNA hasarı

- 1960-1970'lerde sentezlenmiş→ toksisite !!!
- 1978, P. Jones → Aza ve deoksi analogu Dac'ın diferansiyasyon, metilasyon ve MDS etkileri
- **1990'lar MDS'de Faz I-II çalışmalar**
- **2004 MDS'de FDA onayı**



5-aza-2'-deoxycytidine



Griffiths EA, Gore SD, Adv Exp Med Biol, 2013

MDS RAEB-t → AML (WHO-2008)

- **CALGB →** AZA iv/sc 75 mg/m2/g 7 gün (28 günde bir)

  %36 cevap, cevap süresi 7.3 ay

- **AZA-MDS-001** → Doz aynı, Düşük blastlı (%20-30) alt grup

  medyan yaşam 24.5 ay vs Kontrol 16 ay

- Yaşlı, Blast %20-30, AML-**AZA vs Konvansiyonel Tedavi** (standart KT/LDAC/BSC)

  OS 24.5 vs 16 ay

  2 yıl yaşam kötü sitogenetikli olgularda %38 vs %0

  (Fenaux ve ark, 2010)

- **%30 Blastlı AML (off-label)**

Avusturya Azacitidine Registry (2014)- 302 hasta

AZA-AML-001 (2010-2014)- İlk prospektif randomize çalışma, 488 hasta

Ann Hematol (2014) 93:1825–1838
DOI 10.1007/s00277-014-2126-9

ORIGINAL ARTICLE

Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: results from the Austrian Azacitidine Registry of the AGMT-Study Group

Lisa Pleyer · Sonja Burgstaller · Michael Girschikofsky · Werner Linkesch · Reinhard Stauder · Michael Pfeilstocker · Martin Schreder · Christoph Tinchon · Thamer Sliwa · Alois Lang · Wolfgang R. Sperr · Peter Krippl · Dietmar Geissler · Daniela Voskova · Konstantin Schlick · Josef Thaler · Sigrid Machherndl-Spandl · Georg Theiler · Otto Eckmüllner · Richard Greil

- OS üzerine etkili ve güvenli bulunmuş,
-Yaş, BK, blast sayısı OS'ı etkilemiyor
- LDH, PS 2 ve üstü, komorbidite, monosomi bağımsız etkili

AZA-AML- 001

Blood. 2015 Jul 16; 126(3): 291–299.

International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts

Dombret H ve ark.

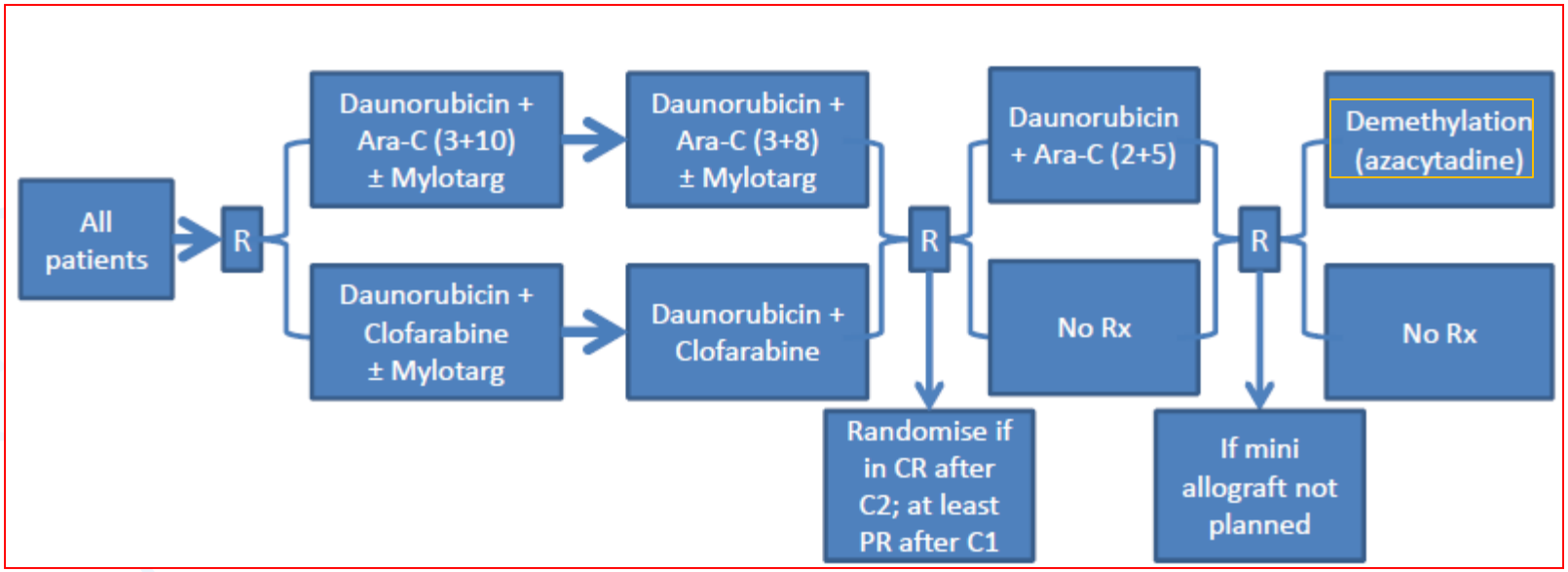
- 488 hasta, ilk kez prospektif randomize güvenlik, etkinlik çalışması
- **LDAC** (2x20 mg 10 g) vs **Standart IC** (7+3) vs **Destek tedavi** (dr seçimi) vs **AZA** (75 mg/m2, 7 g)
- Medyan OS'ı 3.8 ay arttırıyor, Öz. Kötü risk sitogenetik ve MDS benzeri değ. olanlarda anlamlı etki !
- 65 yaş üstü >%30 blastlı hastalarda güvenli

Decitabine

- **Faz III DACO-16**

  Decitabine 20 mg/m2/g 5 gün→ %18 CR/CRp
  8 ay OS
  Low-AraC 20 mg/m2/sc 10 gün/ Destek → %8 ve 5 ay

  - Takipte OS artışı görülmesi ile **yoğun tedaviye uygun olmayan-unfit AML** hastaları için ***Avrupa'da onay aldı, ABD'de alamadı!*** (Kantarjian, 2012)



AML16 çalışması, yoğun tedavi şeması

Standart Antrasiklin ve ara-C dışındaki indüksiyon rejimleri

Author[ref.]	Phase, drug	Patient no.	Median age (range)	CR rates (%)	Comments
Burnett[31]	II, Clofarabine	106	71 (60–84)	48% CRp + CR and 32% CR	Day 30 mortality 18% Patients achieving a CR had better OS
Kantarjian[32]	II, Clofarabine	112	71 (60–88)	46% CRp + CR and 38% CR	Day 30 mortality 9.8% Clofarabine is as effective in poor prognostic cytogenetic groups as in other groups
Kantarjian[26]	III, Decitabine	485	73 (64–91)	CR + CRp + CRi 27.7% with Decitabine vs 10.7% with supportive care or low dose Ara-C	An *ad hoc* analysis showed Decitabine cohort had better OS
Cashen[29]	II, Decitabine	55	74 (61–87)	21% for intermediate risk 24% for poor risk	CR occurred at a median of 4.5 cycles (~4 months) Decitabine is as effective in poor prognostic cytogenetic groups as in other groups
Blum[28]	II, Decitabine	53	74	47% CR	Decitabine was given 10 consecutive day cycles Median cycle to reach CR was 3 Some patients received ATRA with Decitabine Decitabine is as effective in poor prognostic cytogenetic groups as in other groups Patients with age ⩾75 compared to age 75 had similar CR rates but shorter OS
Lübbert[27]	II, Decitabine	227	72 (56–86)	13% CR + 13% PR	
Pollyea[33]	II, Sequential therapy of Azacitidine followed by Lenalidomide	42	74 (62–86)	CR 19% + CRi 9% + PR 12%	Median time to reach CR/CRi was 12 weeks Median duration of CR/CRi was 28 weeks Early mortality rate was 17% OS was better in patients achieving a CR
Fehniger[34]	II, Lenalidomide	33	71 (62–86)	CR + CRi 30%	Median time to reach CR/CRi was 30 days Median OS was 4 months and 16 months in all patients and responders, respectively

Ustun C et al, BMT 2013

RESEARCH ARTICLE

AJH

Comparison of epigenetic versus standard induction chemotherapy for newly diagnosed acute myeloid leukemia patients ≥60 years old

Neha Gupta,[1] Austin Miller,[2] Shipra Gandhi,[1] Laurie A. Ford,[3] Carlos E. Vigil,[3] Elizabeth A. Griffiths,[3]
James E. Thompson,[3] Meir Wetzler,[3] and Eunice S. Wang[3]*

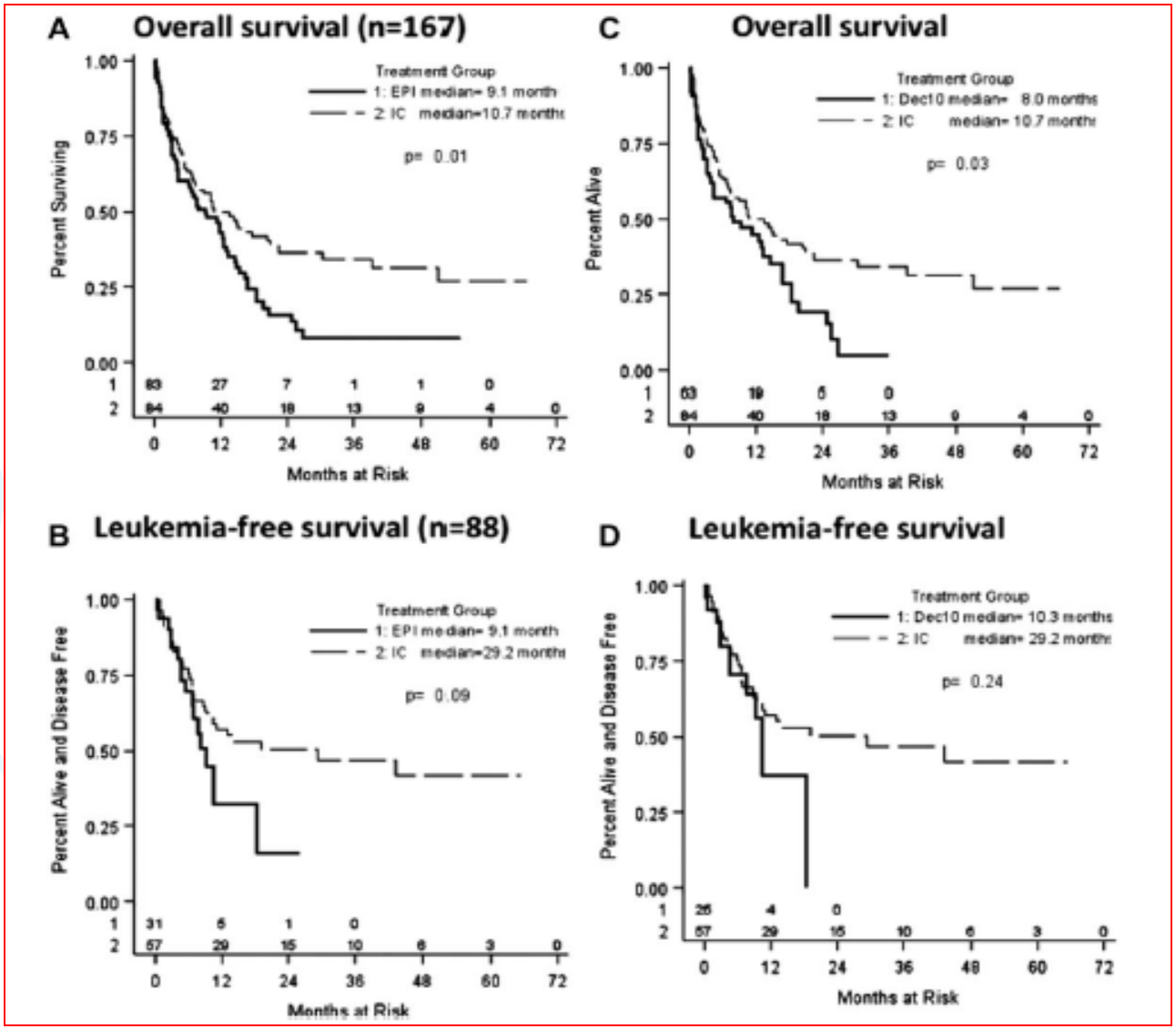
TABLE I. Baseline Characteristics of Older AML Patients by Induction Treatment Group

Characteristic	Overall	IC	Epi	*P*
Patients, *n* (%)	167 (100)	84 (50)	83 (50)	–
Male, *n* (%)	117 (70)	54 (64)	63 (76)	0.128
Age, years (range)	70 (60–92)	67.5 (60–87)	75.5 (60–92)	<0.001
ECOG PS 0–1, *n* (%)	139 (83)	71 (85)	68 (82)	0.68
Initial WBC count × 10^9/L, median (range)	5.5 (0.3–238)	12 (0–238)	5 (0–121)	0.03
Hemoglobin, g/dL, median (range)	9.3 (4.7–13)	9 (6–13)	9 (5–13)	0.87
Platelet count × 10^9/L, median (range)	61 (3–622)	69 (3–622)	54 (10–501)	0.94
BM blasts (%), median (range)	52 (4.2–96)	53 (4–96)	45 (10–96)	0.18
PB blasts (%), median (range)	16 (0–96)	21 (0–95)	9 (0–96)	0.06
Secondary AML, *n* (%)	82 (49)	36 (43)	46 (55)	0.12
Poor-risk cytogenetics, *n* (%)	77 (47)	23 (29)	31 (40)	0.2
FLT-3 mutation, *n* (%)	18 (11)	12 (15)	6 (7)	0.21
NPM-1 mutation, *n* (%)	23 (15)	15 (19)	8 (10)	0.17
Subsequent HSCT, *n* (%)	33 (20)	26 (31)	7 (8)	<0.001

Tek merkez, 2008-2013, 167 hasta, çoğ. yüksek riskli
Epigenetik (Desitabin 10 gün) vs 7+3

	IC	**EPI**
ORR	%50	%28
CRR	%43	%20
OS	10.7 ay	9.1 ay (univariate)
		Farksız (multivariate)

- **TRM Farksız**
- Kötü moleküler risk gruplarında prognoz farksız
- **NPM-1 mutantlarda IC ile cevap daha yüksek** (%80 vs %20)
- Toksisite farksız
- IC vs **10 gün Decitabine** prognozu farksız

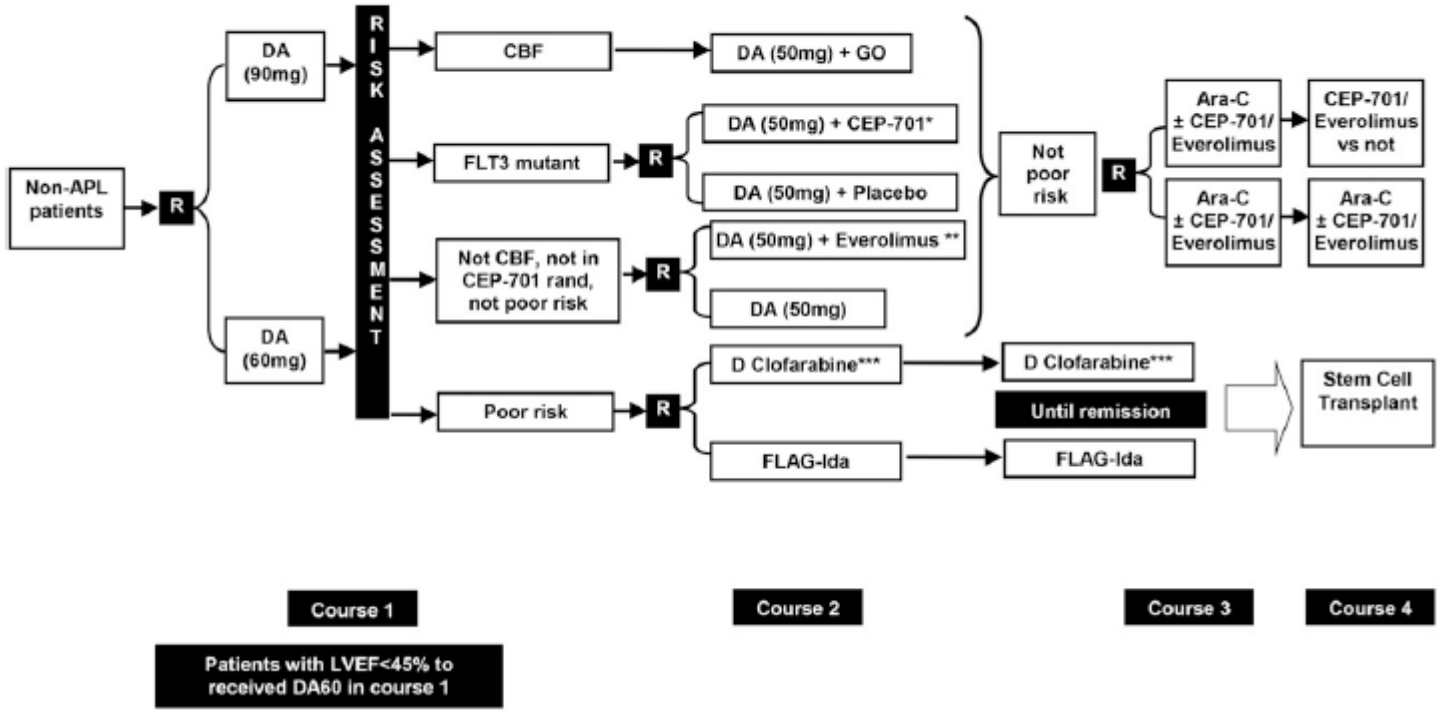

A
Overall survival (n=167)
Percent Surviving
1.00
0.75
0.50
0.25
0.00
Treatment Group
1: EPI median= 9.1 month
2: IC median=10.7 month
p= 0.01
1 83 27 7 1 1 0
2 84 40 18 13 9 4 0
0 12 24 36 48 60 72
Months at Risk
C
Overall survival
Percent Alive
Treatment Group
1: Dec10 median= 8.0 months
2: IC median= 10.7 month
p= 0.03
1 83 19 5 0
2 84 40 18 13 0 4 0
0 12 24 36 48 60 72
Months at Risk
B
Leukemia-free survival (n=88)
Percent Alive and Disease Free
Treatment Group
1: EPI median= 9.1 month
2: IC median=29.2 months
p= 0.09
1 31 5 1 0
2 57 29 15 10 6 3 0
0 12 24 36 48 60 72
Months at Risk
D
Leukemia-free survival
Percent Alive and Disease Free
Treatment Group
1: Dec10 median= 10.3 months
2: IC median= 29.2 months
p= 0.24
1 26 4 0
2 57 29 15 10 6 3 0
0 12 24 36 48 60 72
Months at Risk

Devam eden çalışmalar

- Hipometilleyicil-Histon deasetilaz inh. kombinasyonları (Faz I-II)
- Azanükleotidlerin diğer ilaçlarla kombinasyonları (Faz II-III)
- SGI-110
- Pracinostat
- Vorinostat
- Valproik asit

Table 3
Summary of novel agents in phase 2 or phase 3 development in combination with currently recommended low-intensity treatments for older or unfit patients with newly diagnosed AML.

Novel agent	Details of highest phase clinical trial to date[a]				Status
	Phase (trial identifier)	Trial design			
		Comparator (s)	Estimated enrolment	Patient age	
Azacitidine combined with:					
Gentuzumab ozogamicin	2 (NCT00658814)	N/A	*N* = 139	≥60 years	Ongoing, but not recruiting
Lenalidomide	2 (NCT01358734)	Single-agent lenalidomide Single-agent azacitidine	*N* = 120	≥65 years	Recruiting (no published data available)
Vorinostat	2 (NCT00948064)	Single-agent azacitidine	*N* = 80 (including patients with MDS)	≥18 years	Recruiting (no published data available)
Decitabine combined with:					
Bortezomib	2 (NCT01420926 [CALGB 11002])	Single-agent decitabine	*N* = 172	≥60 years	Ongoing, but not recruiting (no published data available)
Sapacitabine	3 (NCT01303796 [SEAMLESS])	Single-agent decitabine	*N* = 485	≥70 years	Recruiting (no published data available)
Tosedostat	2 (NCT01567059)	Tosedostat + cytarabine	*N* = 60 (including patients with MDS)	≥18 years	Recruitment is currently suspended due to a partial clinical hold being placed on tosedostat by the FDA in June 2013 [58]
LDAC combined with:					
Barasertib[b]	2/3 (NCT00952588 [SPARK-AML1])	Single-agent barasertib Single-agent LDAC	*N* = 417	≥60 years	Ongoing, but not recruiting
Clofarabine	2 (NCT00088218)	Single-agent clofarabine	*N* = 95 (included patients with MDS)	≥60 years	Completed
Gemtuzumab ozogamicin	3 (NCT00005823 [LRF AML 14]) 2/3 (NCT00454480 [NCRI AML 16])	Single-agent LDAC Single-agent LDAC	*N* = 2000 *N* = 2000 (both trials included patients with MDS; 'pick-a-winner' trial design)	≥60 years (or <60 years and unfit for intensive therapy)	Unknown/completed
Tipifarnib	2/3 (NCT00454480 [NCRI AML 16])	Single-agent LDAC	*N* = 2000 (included patients with MDS; 'pick-a-winner trial' design)	≥60 years (or <60 years and unfit for intensive therapy)	Completed
Volasertib	3 (NCT01721876 [POLO-AML-2])	Placebo + LDAC	*N* = 660	≥65 years	Recruiting (no published data available)



Schedule	Any limitations	Details
DA 90 mg		Daunorubicin 90 mg/m² d 1,3,5; ara-C 100mg/m² every 12 hours d 1-10
DA 60mg		Daunorubicin 60 mg/m² d 1,3,5; ara-C 100mg/m² every 12 hours d 1-10
DA 50mg		Daunorubicin 50 mg/m² d 1,3,5; ara-C 100mg/m² every 12 hours d 1-8
GO		Gemtuzumab Ozogamicin 3mg/m² given on day 1 of course 2 of chemotherapy
CEP-701*	Until 22 Oct 2012	Lestaurtinib (CEP-701) 40-80mg bd (depending on azole antifungals) from 2 days post chemo to 2 days pre subsequent course, up to a maximum of 28 days
Everolimus**	Until 12 Oct 2012	Everolimus 5-10 mg/day, from 2 days post chemo to 2 days pre subsequent course, up to a maximum of 28 days
D Clofarabine ***	Until 3 Dec 2012	Daunorubicin 50 mg/m² d 1,3,5; Clofarabine 20mg/m² d 1-5
FLAG-Ida		Fludarabine 30 mg/m² (d 2-6); ara-C 2g/m² (4h post fludarabine), d 2-6; G-CSF 263μg s.c. d 1-7; Idarubicin 8 mg/m² d 4-6
Ara-C		Ara-C 3 g/m² 12-hourly, d1, 3, 5.

Figure 1. Trial design of AML17. Patients allocated either CEP-701 or everolimus post–course 1 carried this molecule forward into subsequent courses. *After closure of the CEP-701 randomization, patients were guided by risk score to either poor risk or not poor risk options. **After closure of the everolimus randomization, patients in this group received daunorubicin (DA) 50 mg alone. ***After closure of the D clofarabine arm, patients were recommended to receive FLAG-Ida (which was also the case if renal criteria were not met).

- Yaşam % artışı 65-74 yaşları arasındadır

b. Five-year relative survival estimates in female patients (65 + yrs) with AML from 1977 to 2006

	12 months	24 months	36 months	48 months	60 months
Cohort I	16.3	9.6	5.5	3.8	3
Cohort II	26.1	14.4	9.4	7.5	6.1
Cohort III	30.7	18.4	13.7	11.2	9.3

	12 months	24 months	36 months	48 months	60 months
Cohort I	14.9	7.8	5	4.1	2.6
Cohort II	11.6	6.2	3.9	3.3	2.7
Cohort III	14.9	6.4	3.3	1.6	1.1

	12 months	24 months	36 months	48 months	60 months
Cohort I	9.3	5.3	3.4	3	1.9
Cohort II	4.8	1.9	1.1	1.1	1.1
Cohort III	7.3	1	0.6	0	0

a. Five-year relative survival estimates in male patients (65 + yrs) with AML from 1977 to 2006

	12 month	24 month	36 month	48 month	60 month
Cohort I	20.1	10.1	5.5	3.5	2.8
Cohort II	25.1	12.3	7.5	4.9	3.9
Cohort III	30.3	15.8	9.8	7.0	6.8

	12 month	24 month	36 month	48 month	60 month
Cohort I	10.8	3.3	2.3	2.1	1.6
Cohort II	11	4.1	2.7	1.7	1.3
Cohort III	14.8	5	3.5	2.6	1.5

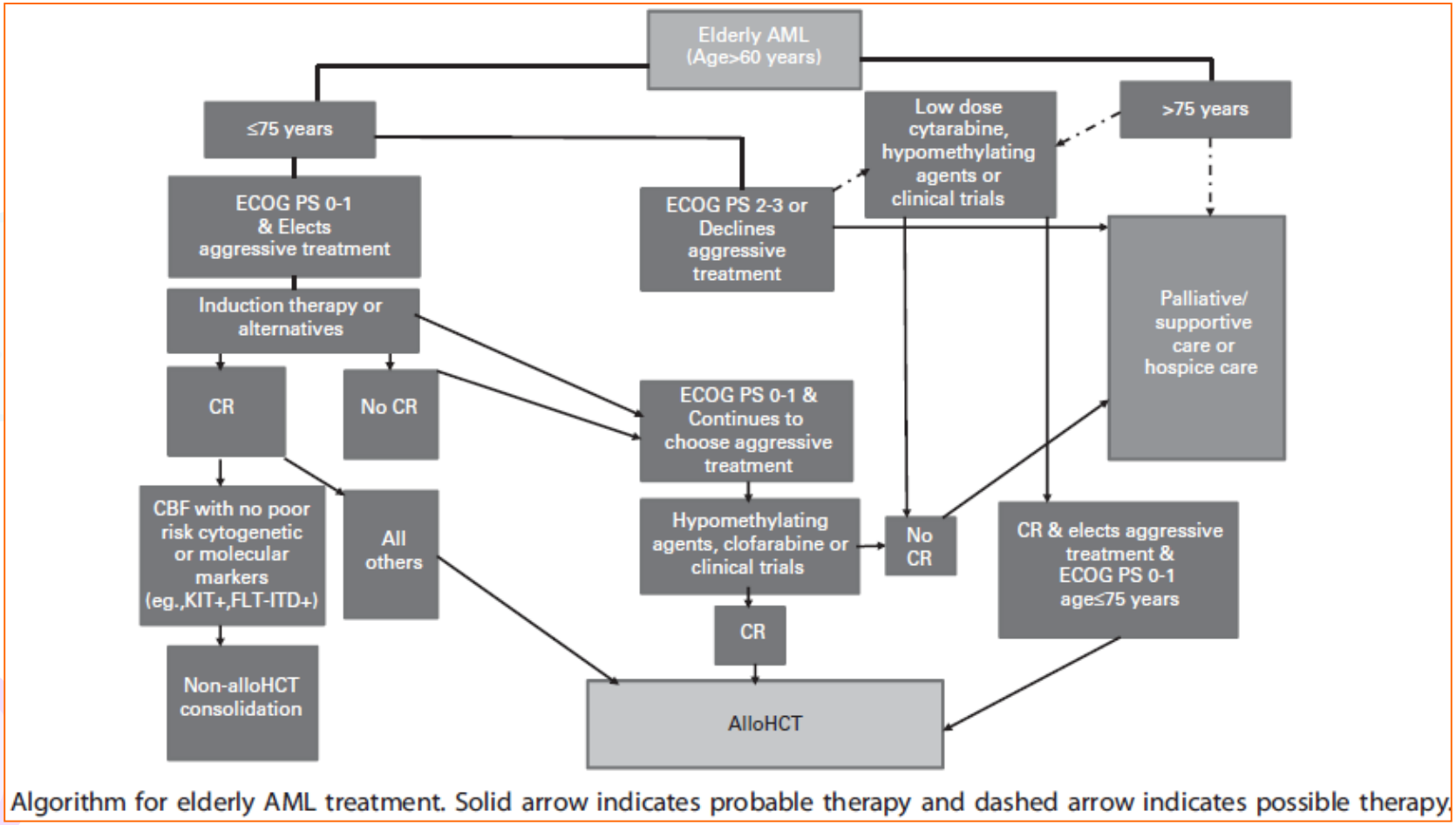
	12 month	24 month	36 month	48 month	60 month
Cohort I	10.6	7	4.4	1.3	1.3
Cohort II	6.8	1.7	0	0	0
Cohort III	7.8	1.7	1.2	1.2	1.2

Cancer. 2013 August 1; 119(15): . doi:10.1002/cncr.28129.

"Outcome of Older Patients with Acute Myeloid Leukemia: An analysis of SEER Data over Three Decades"

Mya S. Thein, MD[1,2], William B. Ershler, MD[3], Ahmedin Jemal, DVM, Ph.D[4], Jerome W. Yates, MD[3,5], and Maria R. Baer, MD[1]

Yaşlı AML tedavisi



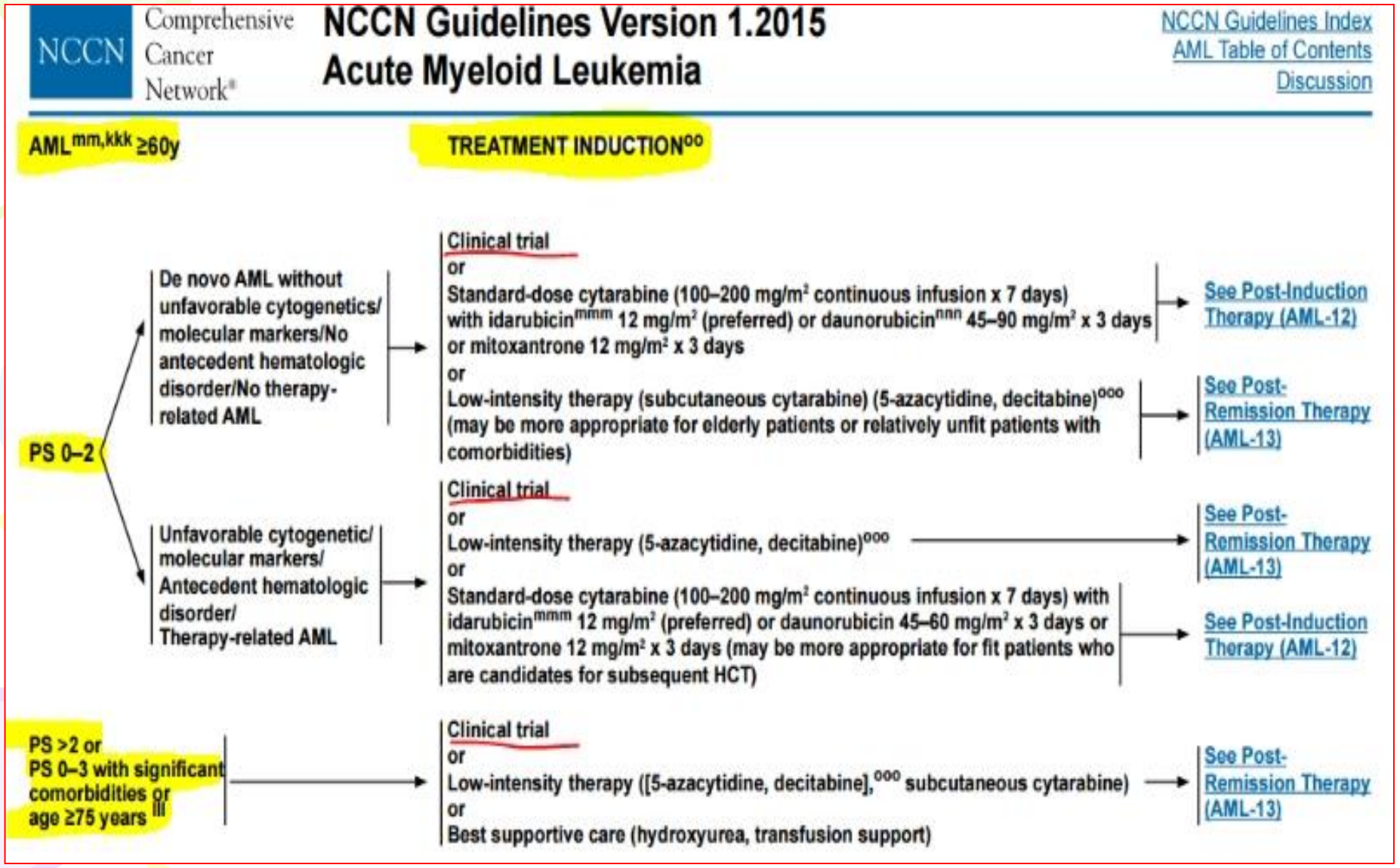
Algorithm for elderly AML treatment. Solid arrow indicates probable therapy and dashed arrow indicates possible therapy.

Ustun at al. BMT 2013

>65 y AML'de tedavi stratejisi

	BSC	LDAC	GO	Yoğun KT	HMA
CR %	0	15-20	15-20	50-55	15-20
Med OS	2	4	4-5	10	7-10
5y OS	0	0	?	10	Küratif değil Allo-HCT hariç
Kötü karyotip etkisi		Yok	Yok	Sınırlı	Orta

GO: gemtuzumab ozogamisin
Huls G, Bloodjournal.org, 2015


NCCN Comprehensive Cancer Network®
NCCN Guidelines Version 1.2015
Acute Myeloid Leukemia
NCCN Guidelines Index
AML Table of Contents
Discussion
AML[mm,kkk] ≥60y
TREATMENT INDUCTION[oo]
PS 0–2
De novo AML without unfavorable cytogenetics/ molecular markers/No antecedent hematologic disorder/No therapy-related AML
Clinical trial
or
Standard-dose cytarabine (100–200 mg/m² continuous infusion x 7 days) with idarubicin[mmm] 12 mg/m² (preferred) or daunorubicin[nnn] 45–90 mg/m² x 3 days or mitoxantrone 12 mg/m² x 3 days
See Post-Induction Therapy (AML-12)
or
Low-intensity therapy (subcutaneous cytarabine) (5-azacytidine, decitabine)[ooo] (may be more appropriate for elderly patients or relatively unfit patients with comorbidities)
See Post-Remission Therapy (AML-13)
Unfavorable cytogenetic/ molecular markers/ Antecedent hematologic disorder/ Therapy-related AML
Clinical trial
or
Low-intensity therapy (5-azacytidine, decitabine)[ooo]
See Post-Remission Therapy (AML-13)
or
Standard-dose cytarabine (100–200 mg/m² continuous infusion x 7 days) with idarubicin[mmm] 12 mg/m² (preferred) or daunorubicin 45–60 mg/m² x 3 days or mitoxantrone 12 mg/m² x 3 days (may be more appropriate for fit patients who are candidates for subsequent HCT)
See Post-Induction Therapy (AML-12)
PS >2 or PS 0–3 with significant comorbidities or age ≥75 years[lll]
Clinical trial
or
Low-intensity therapy ([5-azacytidine, decitabine],[ooo] subcutaneous cytarabine)
See Post-Remission Therapy (AML-13)
or
Best supportive care (hydroxyurea, transfusion support)

Sonuç

- Hastalığa ve yaş grubuna özgü nedenlerden, yaşlı AML tedavisi hala sorunlu-**küratif tedavi yok**
- Bugün için tedavilerin amacı, remisyon, yaşamı uzatma ve yaşam kalitesini arttırma
- **Prognostik risk grupları** tedavi kararında önemli
- İyileşme olasılığını arttırırken tedaviye bağlı kayıpların azaldığı yöntemlere ihtiyaç var
- Hedefe yönelik ve kişiselleştirilmiş tedaviler umut verici olabilir
- **Tüm yaşlı hastalar**

klinik çalışmalara alınmalı !

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