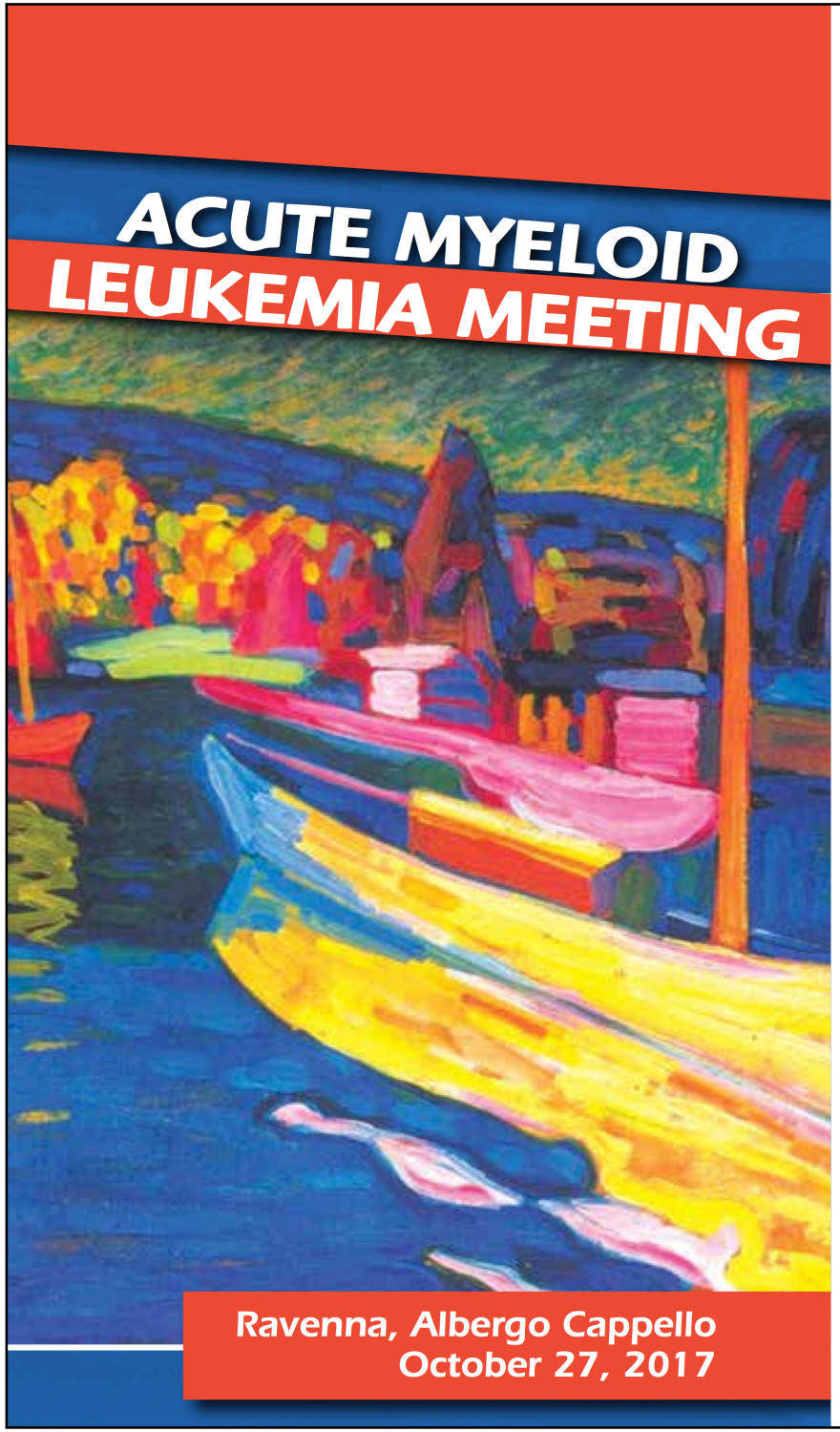

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Post remission therapy and "maintenance"?

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Institute of Hematology and Medical Oncology
"L. and A. Seràgnoli"

University of Bologna

Background

- After achievement of a first CR, **virtually all patients relapse** in the absence of further treatment

- The **aims** of a post-remission therapy are:

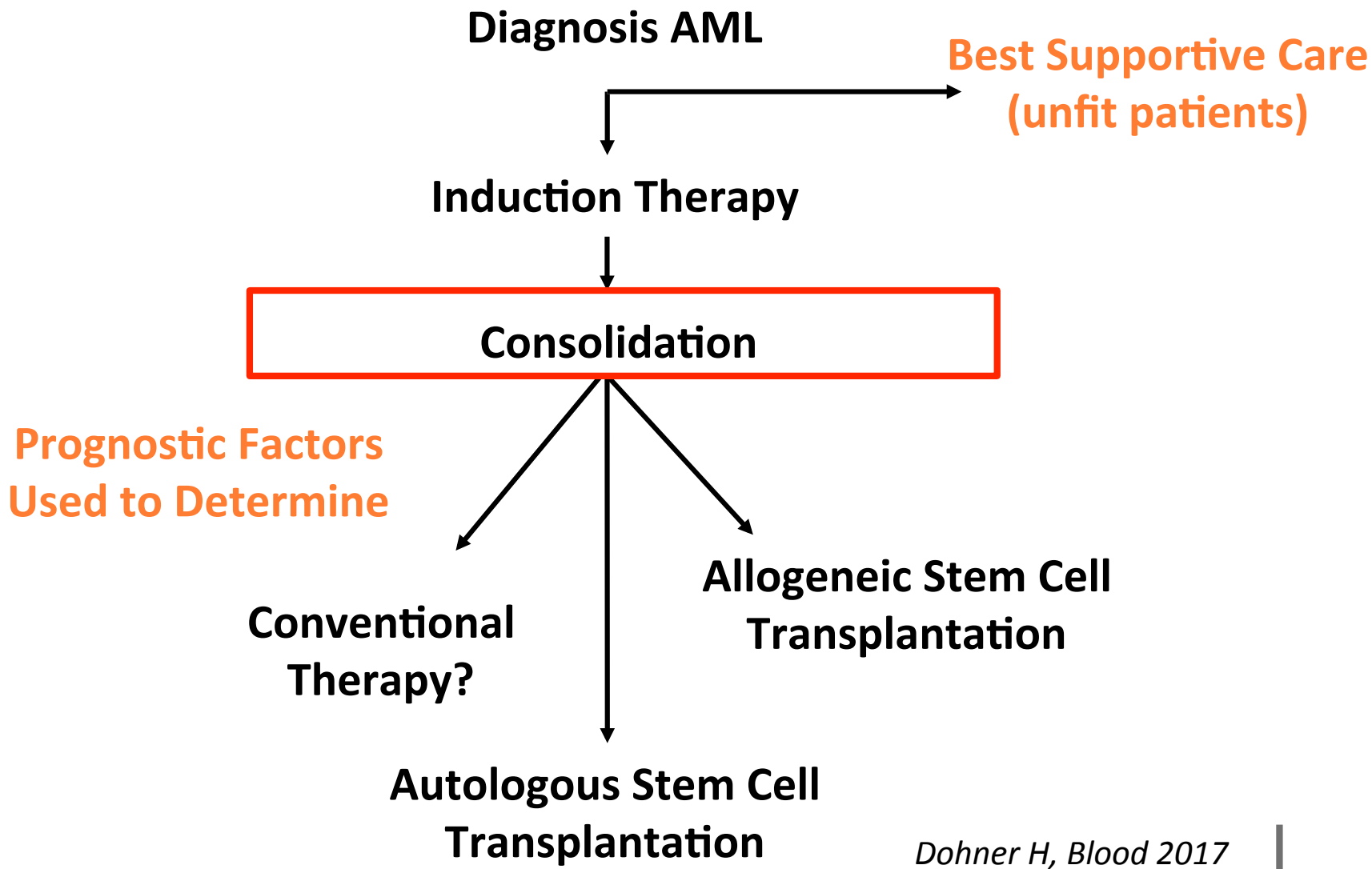
TO ERADICATE RESIDUAL LEUKEMIC CELLS

TO PREVENT RELAPSE

TO PROLONG SURVIVAL

Schlenk F.R., Haematologica 2014; Rashidi A, Blood 2016

Traditional Approach to AML Therapy



Dohner H, Blood 2017

Consolidation AML Therapy: 2017 ELN recommendations

Younger patients, eligible for intensive chemotherapy	
Favorable-risk genetics	✓ 2-4 cycles of IDAC (1000-1500 mg/sqm IV over 3h q12h, d 1-3; or 1000-1500 mg/sqm IV over 3 h d 1-5 or 6)
Intermediate-risk genetics	✓ Allogeneic HCT from matched-related or unrelated donor ✓ 2-4 cycles of IDAC (1000-1500 mg/sqm IV over 3h q12h, d 1-3; or 1000-1500 mg/sqm IV over 3 h d 1-5 or 6), or ✓ High-dose therapy and autologous HCT
Adverse-risk genetics	✓ Allogeneic HCT from matched-related or unrelated donor

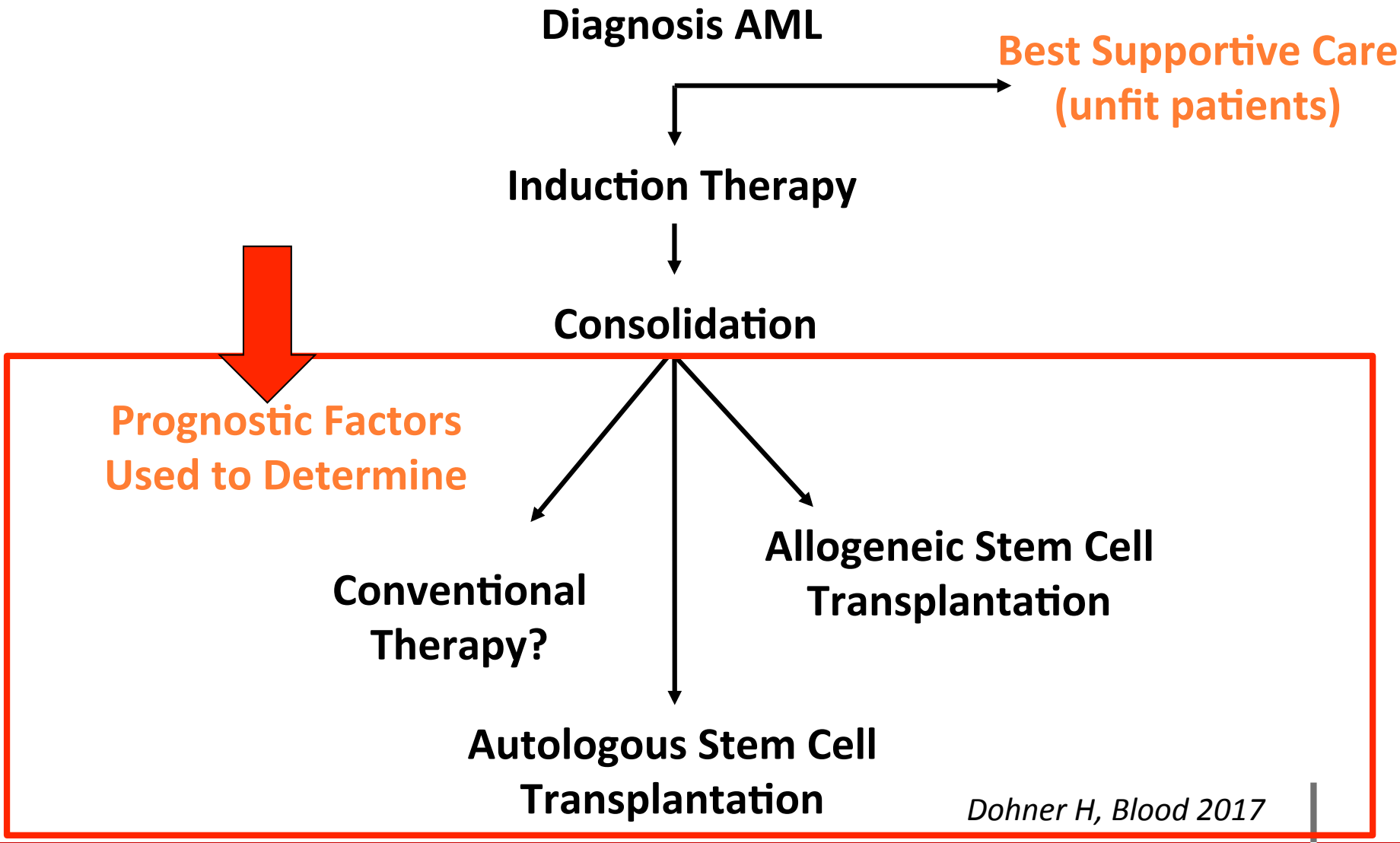
Dohner H, Blood 2017

Consolidation: where do we stand now?

- No convincing evidence that cytarabine regimens at 3000 mg/sqm are more effective than regimens at intermediate-dose levels at 1000 to 1500 mg/sqm, with or without the addition of an anthracycline
- How many cycles of consolidation therapy? Usually 2 to 4
- Intensified postremission chemotherapy in high-risk patients is without clear benefit (especially older patients)

Schaich M, J Clin Oncol 2011; Burnett AK, J Clin Oncol 2013; Miyawaki S, Blood 2011; Thomas X, Blood 2011; Lowemberg B, Blood 2013; Burnett AK, J Clin Oncol 2013; Itzykson R, Haematologica 2011

Traditional Approach to AML Therapy



Dohner H, Blood 2017

Prognostic Factors

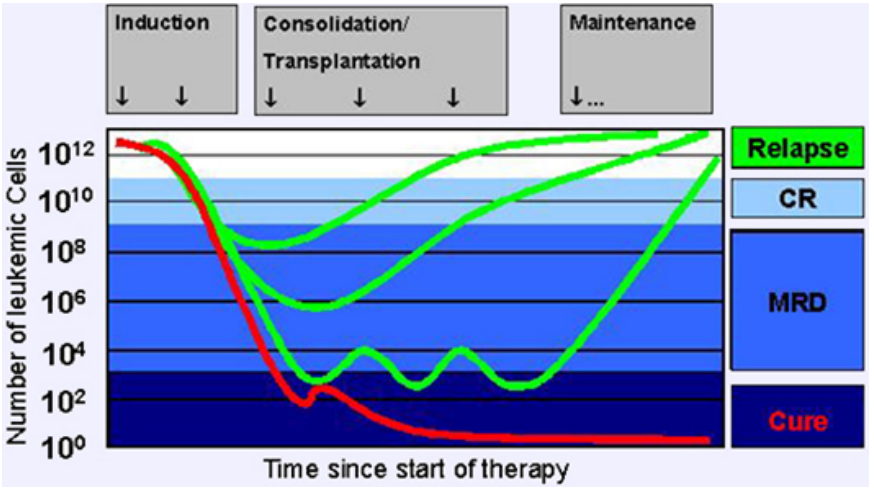
PRETREATMENT FACTORS

- Patient-related factors (age, PS, comorbidities)
- AML-related genetic factors

Risk Category[b]	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low(c)] Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD[high(c)] Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD[low(c)] (w/o adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*[d] Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,[e] monosomal karyotype[f] Wild type *NPM1* and *FLT3*-ITD[high(c)] Mutated *RUNX1*[g] Mutated *ASXL1*[g] Mutated *TP53*[h]

FACTORS AFTER DIAGNOSIS

- MRD monitoring



Dohner H, Blood 2017

After Consolidation: 2017 ELN recommendations

Younger patients, eligible for intensive chemotherapy	
Favorable-risk genetics	✓ 2-4 cycles of IDAC (1000-1500 mg/sqm IV over 3h q12h, d 1-3; or 1000-1500 mg/sqm IV over 3 h d 1-5 or 6)
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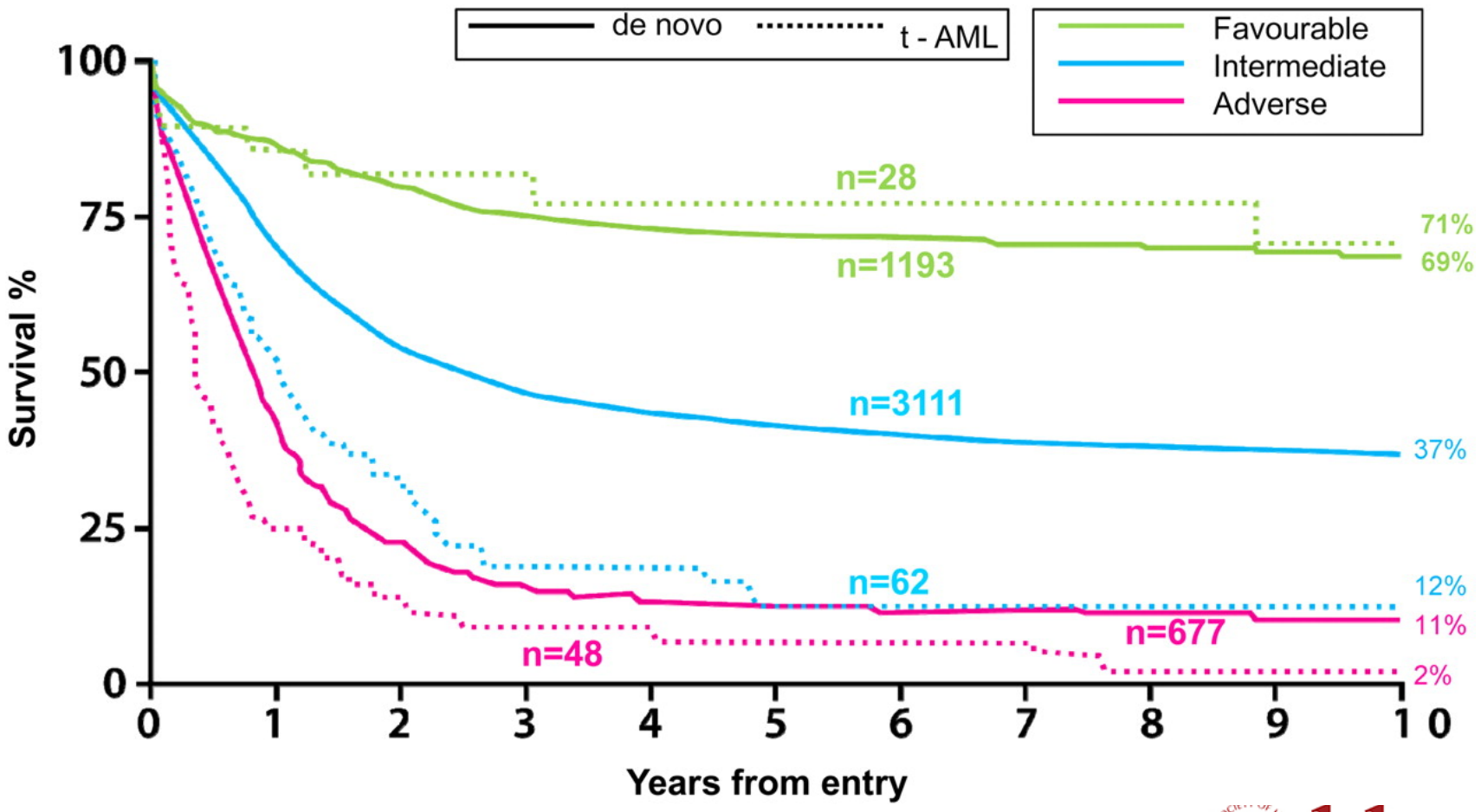
Adverse-risk genetics	✓ Allogeneic HCT from matched-related or unrelated donor

MRD

Dohner H, Blood 2017

AML outcome (<60 years)



Jacob M. Rowe, and Martin S. Tallman Blood 2010;116:3147-3156

How can we improve these results? Maintenance in AML?

Biology of AML: heterogeneous disease

Many molecular alterations

"THE alteration=THE therapy" is not applicable

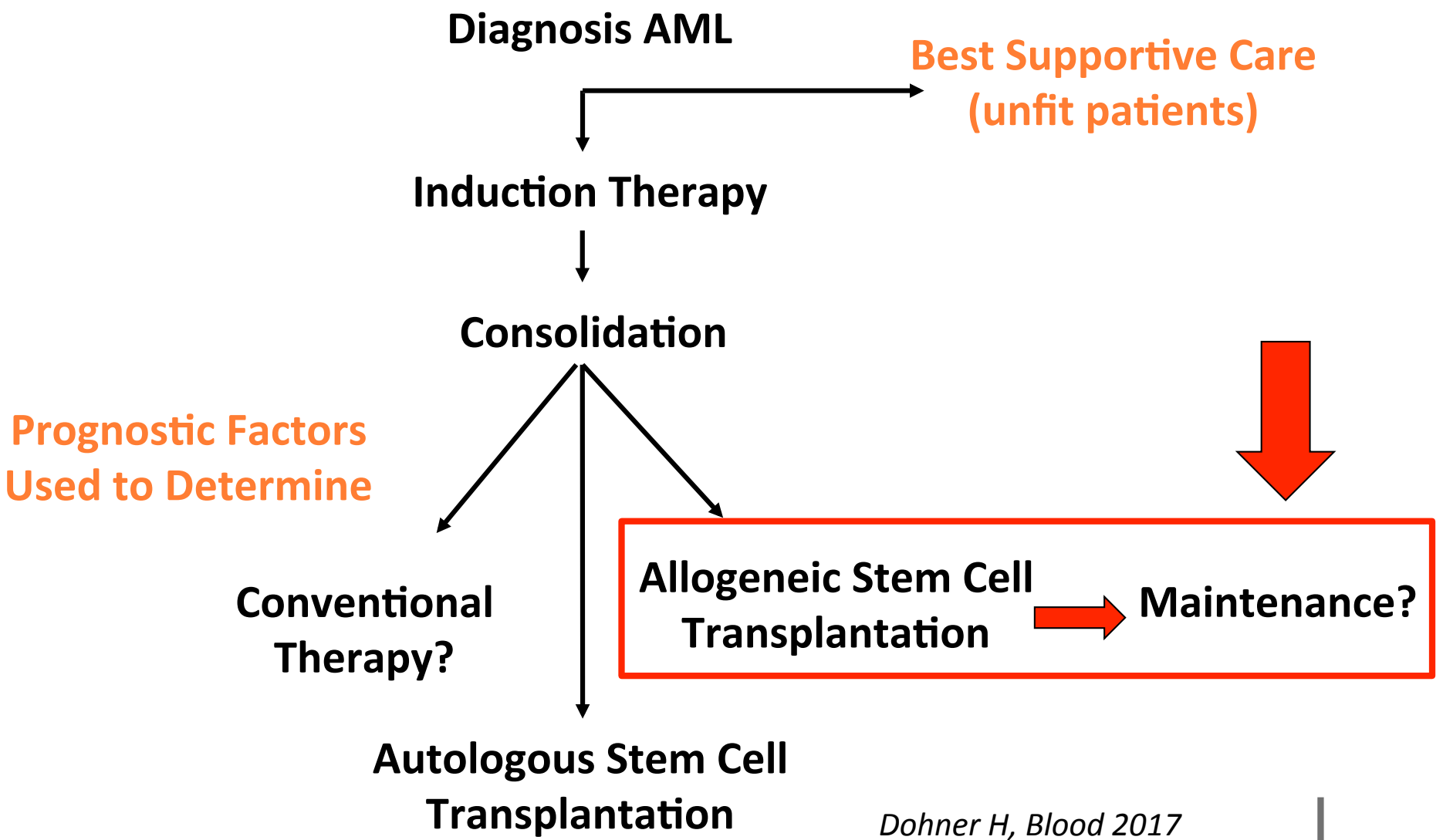
NGS technologies can deeply characterize every single AML

Some mutations are **druggable**

Toxicities seem to be **manageable**

Immunotherapy is emerging

1st setting for maintenance: after BMT



Dohner H, Blood 2017

Maintenance therapy after BMT

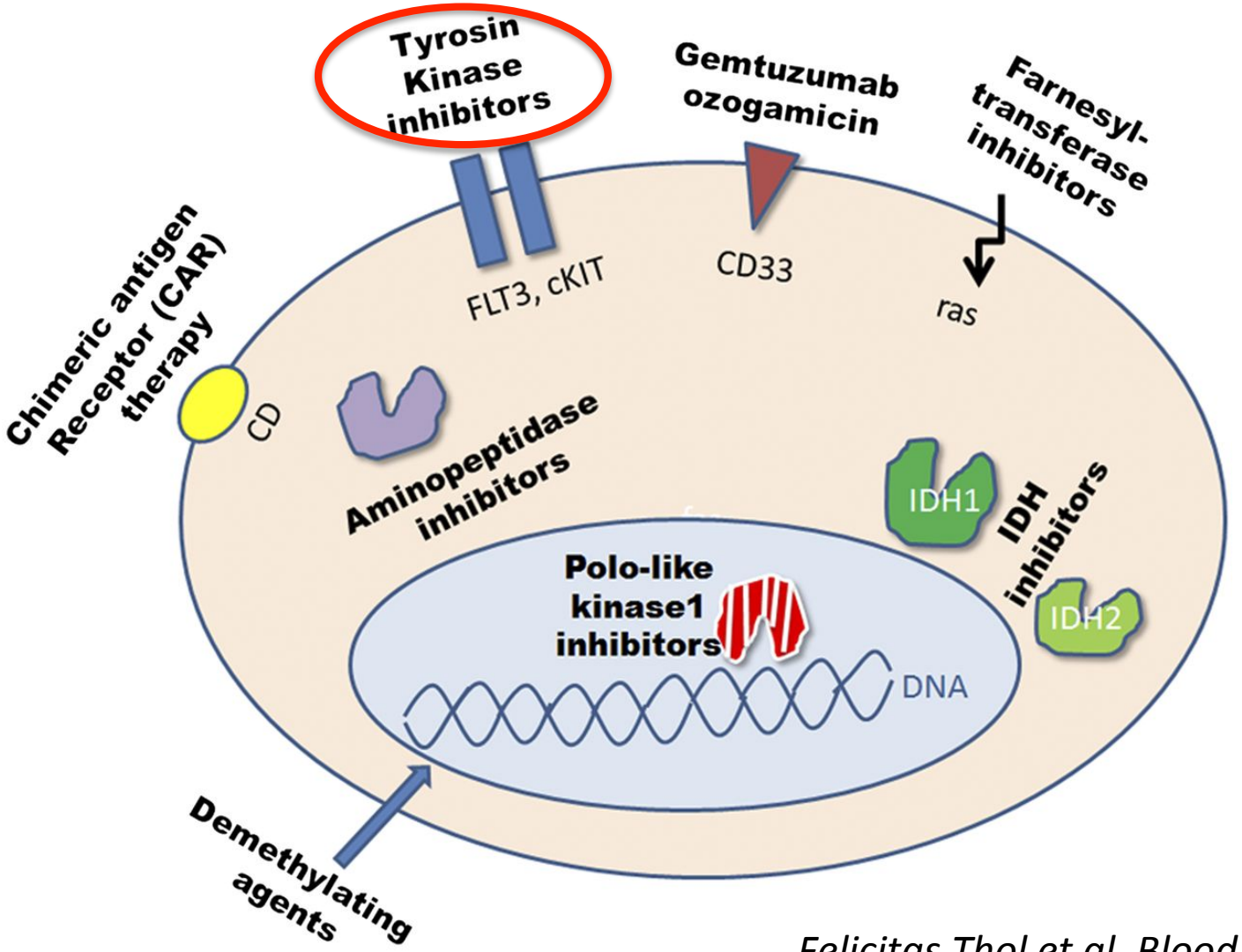
- Maintenance therapy can, at least theoretically, contribute to cure by **maintaining the disease burden in a minimal state until the immunological effect of graft-versus-leukemia becomes dominant**, potentially resulting in eradication of residual disease

- No maintenance Randomized Clinical Trials has yet been concluded in this setting

- Many early-phase studies have been performed to assess safety an feasibility of new drugs

Rashidi A, Blood 2016

Drugs in clinical development…after BMT?



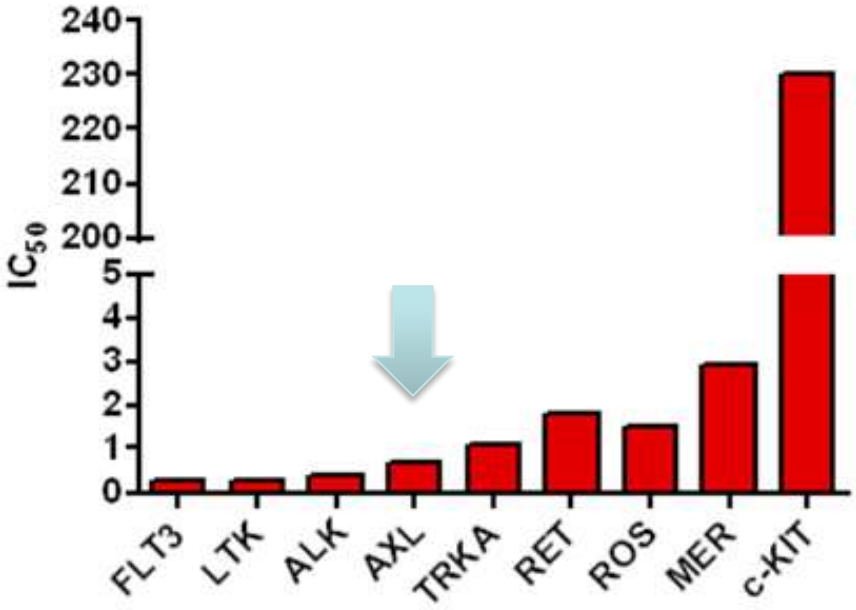
Felicitas Thol et al. Blood 2015

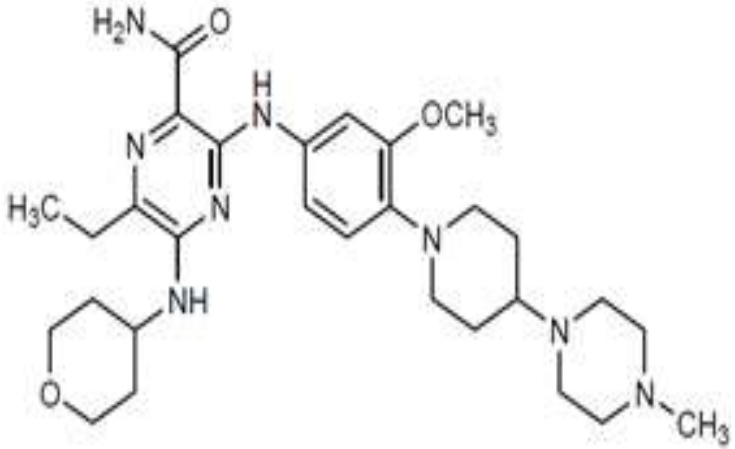
Ongoing Clinical Trials: FLT3 inhibitors as maintenance post BMT

	Phase	NCT	Locations
Crenolanib Maintenance Following Allo SCT in FLT3-positive AML patients	II	NCT02400255	USA
A Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allo SCT for Patients With FLT3 ITD AML	III	NCT02997202 	Australia, Denmark, Japan, Italy, Germany, Korea, Poland, Spain
Protocol in Acute Myeloid Leukemia With FLT3-ITD (Midostaurin)	II	NCT01477606	Austria, Germany

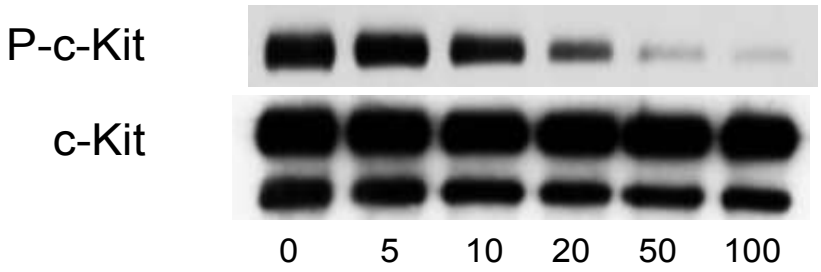
www.ClinicalTrials.gov

Gilteritinib (ASP2215)

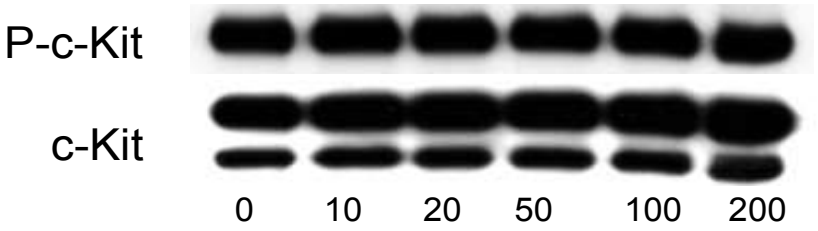




Quizartinib



Gilteritinib



Axl in AML

- *Axl* is a member of the Tyro3, Axl, Mer (TAM) receptor family and **mediates proliferation and survival of AML cells**
- *Axl* overexpression in AML confers **drug r**esistance and is associated with adverse prognosis
- AML cells **induce expression of the *Axl* ligand *Gas6 i*n bone marrow stroma cells,which amplifies their growth and therapy resistance**
- ***Axl* inhibition suppresses the FLT3 positive AML in vivo**
- *Axl* inhibition is also active in FLT3 negative (but *Axl* expressing) AML in vivo

Ben Batalla et al, Blood 2013; Park et al, Blood 2013

Phase I-II Trial

Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1–2 study

Alexander E Perl, Jessica K Altman*, Jorge Cortes, Catherine Smith, Mark Litzow, Maria R Baer, David Claxton, Harry P Erba, Stan Gill, Stuart Goldberg, Joseph G Jurcic, Richard A Larson, Chaofeng Liu, Ellen Ritchie, Gary Schiller, Alexander I Spira, Stephen A Strickland, Raoul Tibes, Celalettin Ustun, Eunice S Wang, Robert Stuart, Christoph Röllig, Andreas Neubauer, Giovanni Martinelli, Erkut Bahceci, Mark Levis*

Patients population: >=18 years, with AML refractory to induction therapy or relapsed after achieving remission with previous treatment.

Seven dose-escalation or dose-expansion cohorts assigned to receive once-daily doses of oral gilteritinib (20 mg, 40 mg, 80 mg, 120 mg, 200 mg, 300 mg, or 450 mg).

Primary endpoints: safety, tolerability, and PK of gilteritinib

Perl A.E. et al, Lancet Oncology 2017

Results: Safety (I)

- 252 adults enrolled (dose-escalation (n=23) or dose-expansion (n=229) cohorts)

- **MTD: 300 mg/day**
- **DLTs: grade 3 diarrhoea; grade 3 elevated aspartate aminotransferase**
- **Grade 3–4 adverse events** irrespective of relation to treatment:

-febrile neutropenia (97 [39%] of 252)

-anaemia (61 [24%])

-thrombocytopenia (33 [13%])

-sepsis (28 [11%])

-pneumonia (27 [11%])

Perl A.E. et al, Lancet Oncology 2017

Results: Safety (II)

- Commonly reported **treatment-related adverse events**:

-**diarrhoea** (92 [37%])

-anaemia (86 [34%])

-fatigue (83 [33%])

-elevated aspartate aminotransferase (65 [26%])

-increased alanine aminotransferase (47 [19%])

- **Serious adverse events** occurring in 5% or more of patients:

-**febrile neutropenia** (98 [39%] of 252; five related to treatment)

-progressive disease (43 [17%])

-sepsis (36 [14%]; two related to treatment)

-pneumonia (27 [11%])

Perl A.E. et al, Lancet Oncology 2017

Results: Efficacy

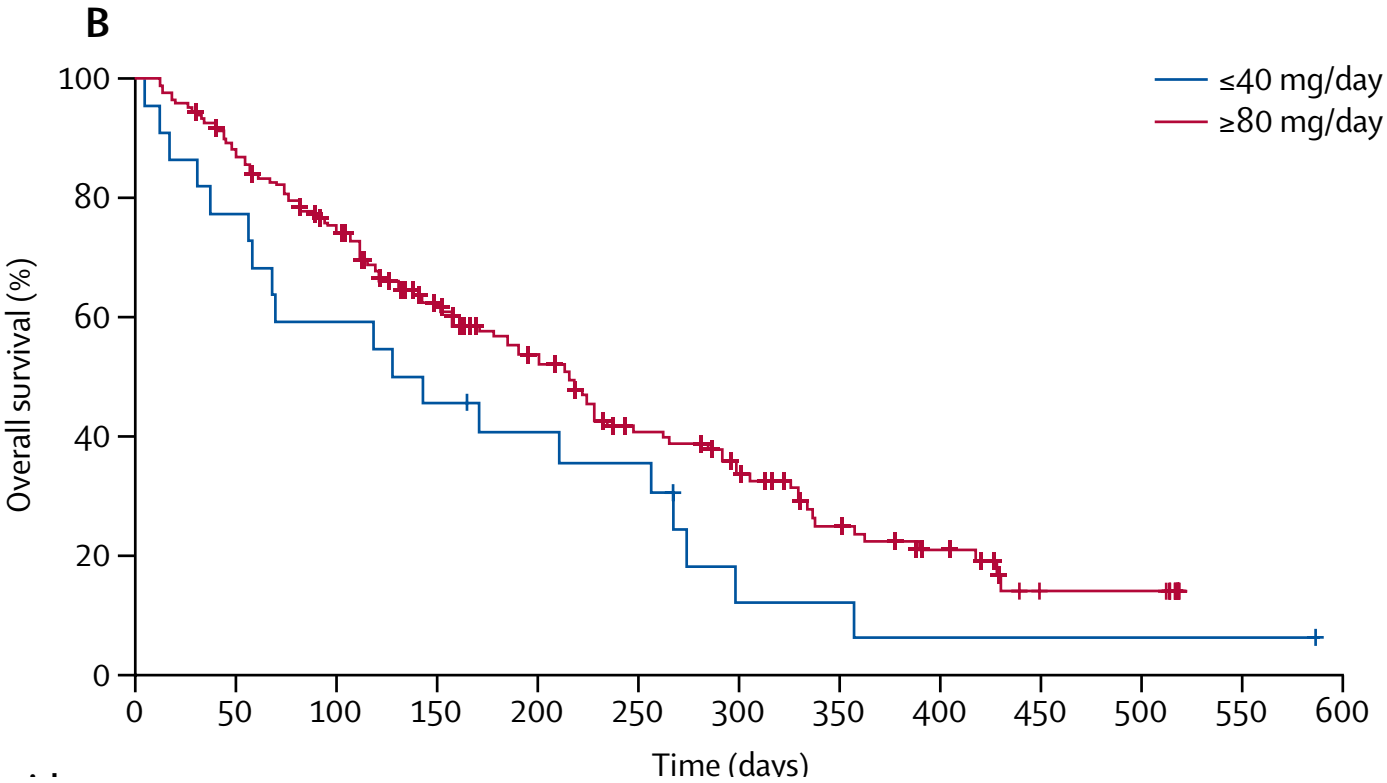
	Full analysis set (n=249)	*FLT3*^{WT} (n=58)	*FLT3*$^{mut+}$ (n=191)	
			All patients (n=191)	Patients receiving ≥80 mg/day (n=169)
Complete remission	19 (8% [5–12])	1 (2% [0–9])	18 (9% [6–15])	18 (11% [6–16])
Complete remission with incomplete platelet recovery	10 (4% [2–7])	0	10 (5% [3–9])	10 (6% [3–11])
Complete remission with incomplete haematological recovery	46 (18% [14–24])	4 (7% [2–17])	42 (22% [16–29])	41 (24% [18–31])
Partial remission	25 (10% [7–15])	2 (3% [0–12])	23 (12% [8–18])	19 (11% [7–17])
Composite complete remission	75 (30% [25–36])	5 (9% [3–19])	70 (37% [30–44])	69 (41% [33–49])
Overall response	100 (40% [34–47])	7 (12% [5–23])	93 (49% [41–56])	88 (52% [44–60])
Duration of response (weeks)	17 (14–29)	12 (3–17)	20 (14–33)	20 (14–33)
Overall survival (weeks)	25 (20–30)	17 (11–21)	30 (23–33)	31 (24–59)

Data are number of patients (% [95% CI]), or median (95% CI). The full analysis set included all patients who received at least one dose of study drug and who had at least one datapoint post-treatment. *FLT3*$^{mut+}$=*FLT3* mutation-positive. *FLT3*^{WT}=wild-type *FLT3*.

Table 4: **Responses to gilteritinib, overall and by *FLT3* mutation status (full analysis set)**

Perl A.E. et al, Lancet Oncology 2017

Results: Overall Survival

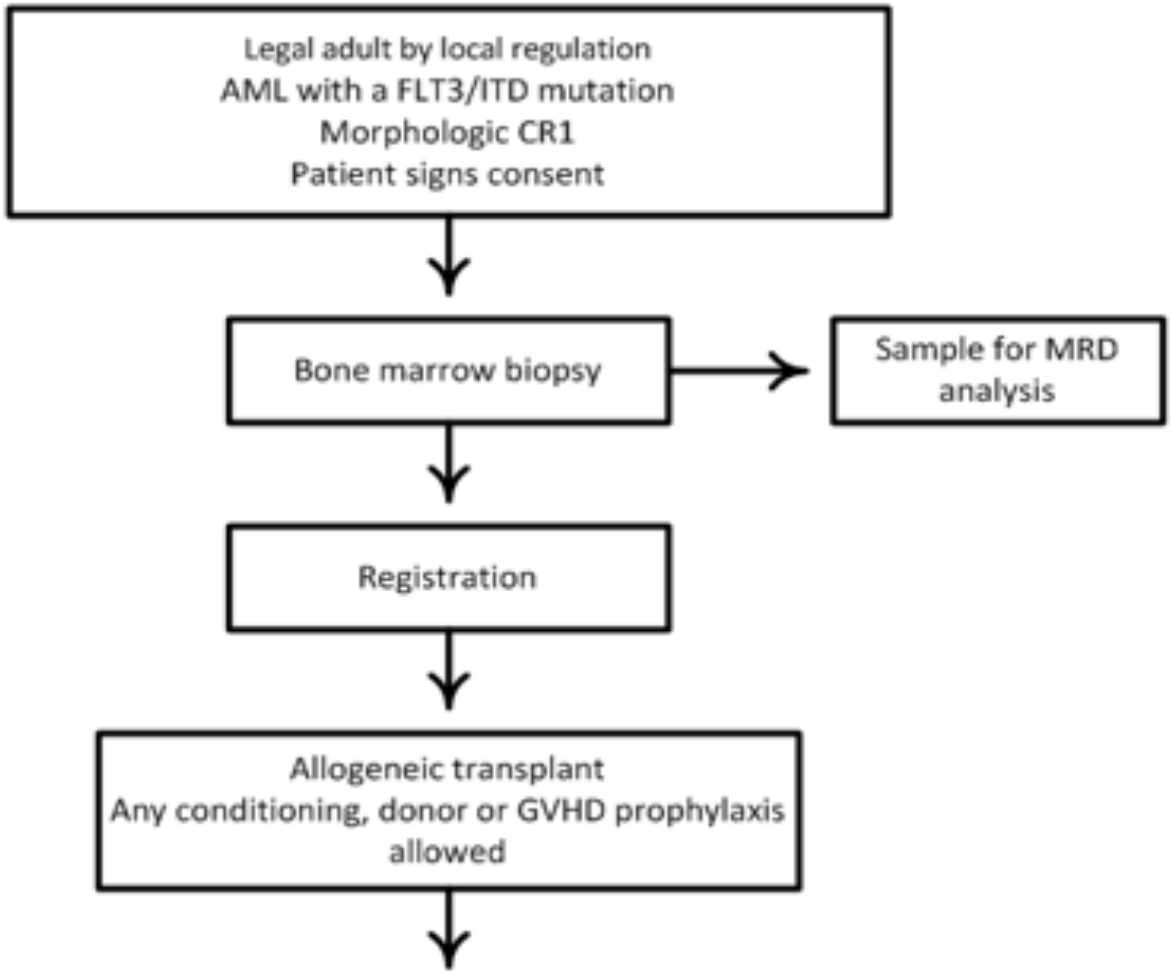


Perl A.E. et al, Lancet Oncology 2017

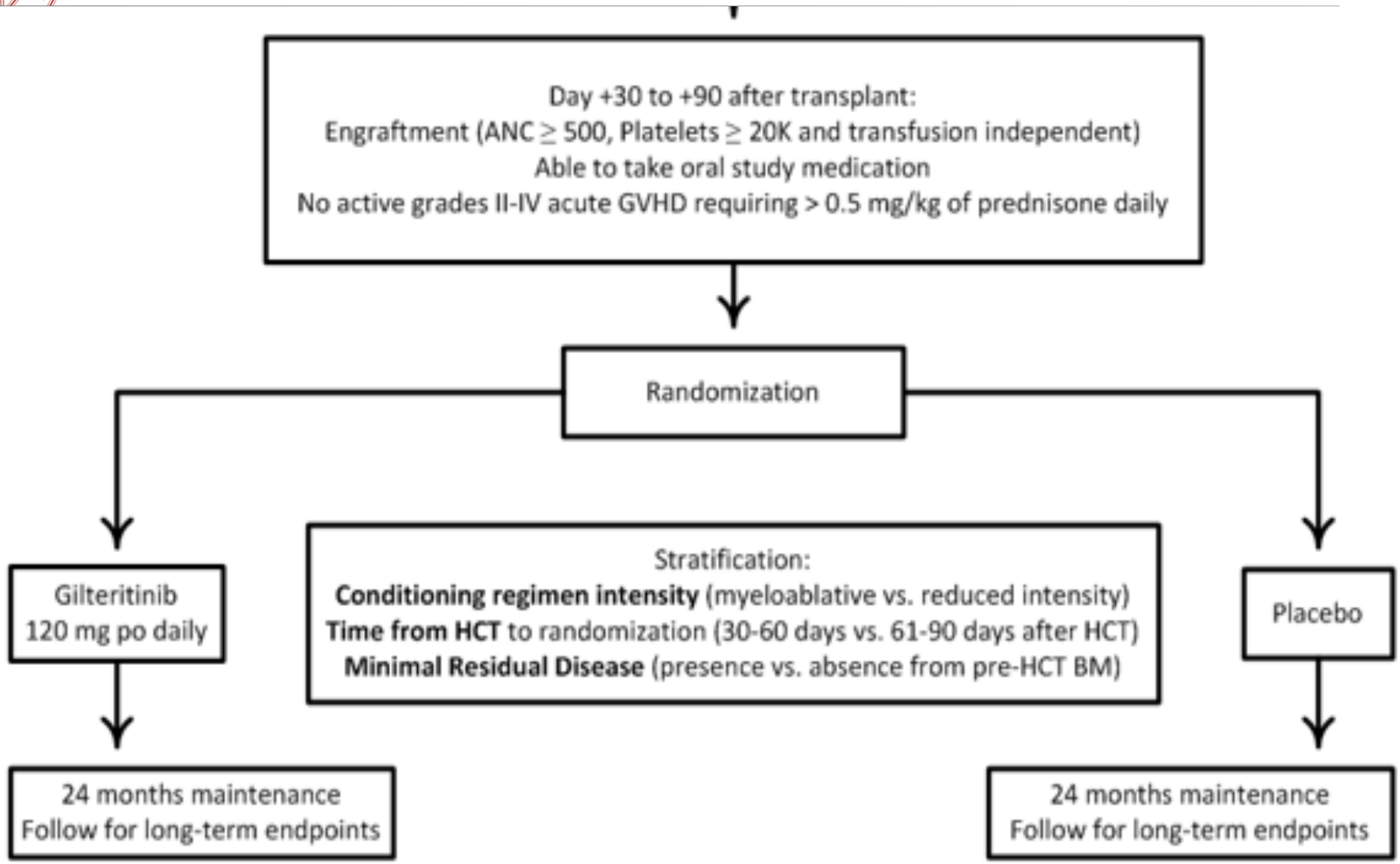
Gilteritinib as Maintenance after BMT

Study Information	Details
Study Number	**ASTELLAS PROTOCOL 2215-CL-0304** **BMT CTN PROTOCOL 1506**
Full Title	**A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3/ITD AML**
Treatment	Gilteritinib vs. Placebo as 2 yr. maintenance after HSCT
Participants	FLT3/ITD + AML in Complete Response 1 (CR1) • ~ 1000 Screened • 532 Registered • 346 Randomized
Sites	145 sites in NA, EU, APAC

Flow-chart (Part 1)



Flow-chart (Part 2)



2215-CL-0304 Objectives

- **Primary**
  - To **compare relapse-free survival (RFS)** between participants with FLT3/ITD AML in CR1 who undergo HCT and are randomized to receive gilteritinib or placebo beginning after the time of engraftment for a two year period
- **Secondary**
  - To determine the **safety and tolerability** of gilteritinib after HCT.
  - To **compare overall survival (OS), non-relapse mortality (NRM) and event-free survival (EFS)** in participants treated with gilteritinib as maintenance therapy after HCT compared to those treated with placebo.
  - To compare **6-month cumulative incidence of grades II-IV and III-IV acute GVHD** and **12-month and 24-month cumulative incidence of mild, moderate, and severe GVHD** in participants treated with gilteritinib as maintenance therapy after HCT compared to those treated with placebo.
  - To examine the **effect of pre- and post-transplant MRD on RFS and OS**

The questions we hope to answer:

346 post-transplant FLT3/ITD AML patients

173 patients
Placebo

173 patients
Gilteritinib

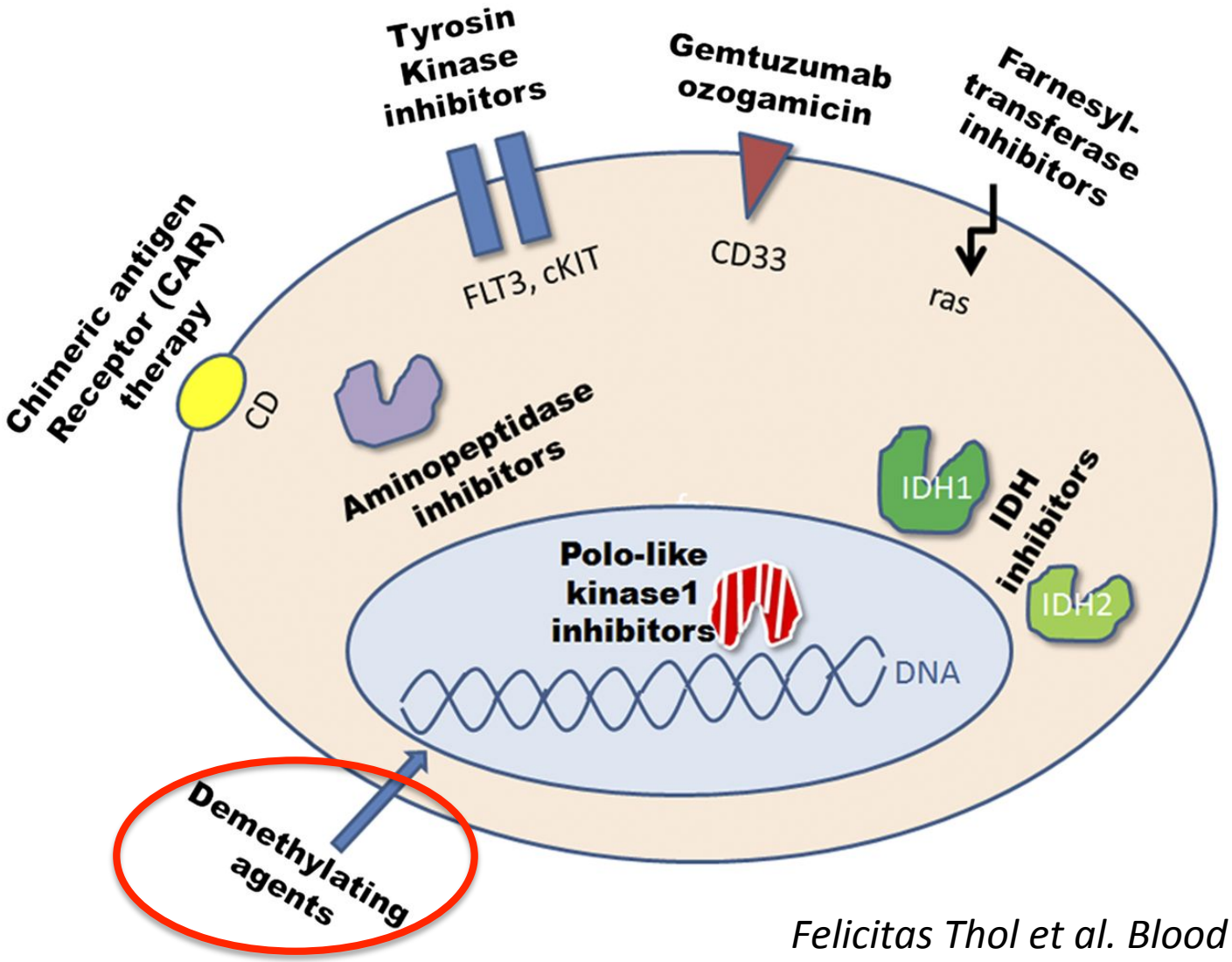
?

Is there a benefit to FLT3 inhibition post-transplant?

Does the detection of a FLT3/ITD mutation by a validated, sensitive MRD assay predict relapse?

Does a potent FLT3 inhibitor prevent relapse when the MRD assay detects a FLT3/ITD mutation?

Drugs in clinical development…after BMT?



Felicitas Thol et al. Blood 2015

Ongoing Clinical Trials: HMA as maintenance after BMT

Rationale for 5Azacitidine after BMT:

-up-regulates putative tumor antigens, inducing a CD8+ T cell response that could increase a graft vs leukemia effect (Craddock, 2015)

-reduces risk of relapse and GVHD post-allograft (Platzbecker, 2012; de Lima, 2010)

	Phase	NCT	Locations
Maintenance Low Dose **5'-Azacitidine** Post T Cell Depleted AlloBMT for Patients With MDS and AML With High Risk for Post-Transplant Relapse	II	NCT01995578	USA
Haplo-SCT vs ASCT With or Without **Decitabine** in AML CR1	III	NCT02059720	China
Vidaza and Valproic Acid Post Allogeneic Transplant for High Risk AML and MDS	II	NCT02124174	USA

www.ClinicalTrials.gov

CC-486-AML-002: Phase I/II Trial of CC-486 in Post-Transplant MDS/AML

Study Design

QUAZAR® Post-Transplant

Study start: 7/2013 → **COMPLETED**

N = 31 planned

Post-alloSCT MDS or AML

Within 42-84 days following alloSCT

→

3 + 3 Design (28-day cycles)

Cohort	CC-486 Maintenance
1 (n = 3)	200 mg QD days 1-7
2 (n = 3)	300 mg QD days 1-7
3a (n = 3)	150 mg QD days 1-4
3 (n = 3)	200 mg QD days 1-14
Expansion cohort (n = 11)	

→

Continue treatment until PD, intolerable AEs, or maximum duration of therapy[a]

- Key endpoints
  - Primary: MTD
  - Secondary: incidence of acute/chronic GVHD, disease recurrence/ relapse rate, safety, PK, preliminary efficacy

[a] 12 months; however, patients not meeting discontinuation criteria may elect to continue treatment.

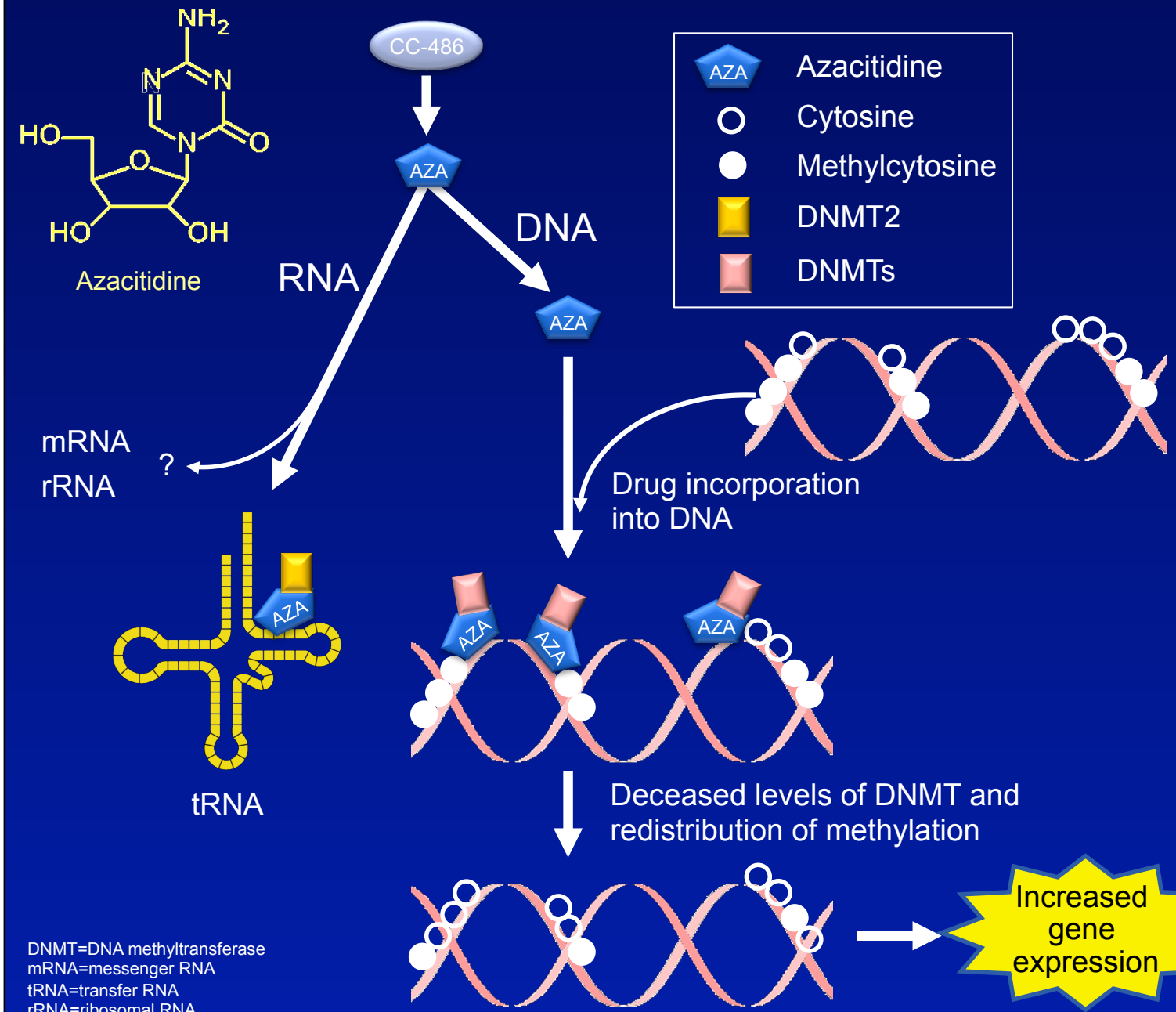
ClinicalTrials.gov. http://clinicaltrials.gov/show/NCT01835587. Accessed September 30, 2016.

CC-486 (oral azacitidine) vs Vidaza®: key differences

	CC-486	Vidaza®
Brand name	TBD	Vidaza®
Formulation	Tablet	Lyophilized powder in 100-mg, single-use vials[1]
Route of administration	Oral	Injection (subcutaneous or intravenous)[1,2]
Dosing	Planned: 300 mg QD x14 days/28-day cycles for AML maintenance[3]	Approved: 75 mg/m^2/day on days 1-7 of 28-day cycles[1]
Phase in development	Phase 3[3,4]	Marketed
Approvals	Not currently approved for any indication	Approved in the US for the treatment of all FAB subtypes of MDS[1] Approved in the EU for CMML, higher-risk MDS, and AML, in patients not eligible for SCT

1. Vidaza® (azacitidine for injection) package insert. Summit, NJ: Celgene Corporation; 2015
2. Vidaza® Summary of Product Characteristics. Uxbridge, UK: Celgene Europe Limited; 2015
3. http://www.clinicaltrials.gov/ct2/show/NCT01757535

CC-486 mechanism of action



Azacitidine undergoes phosphorylation and is incorporated into RNA (~80%) and DNA (~20%)

In tRNA, azacitidine traps DNMT2

Azacitidine activity with mRNA and rRNA is less clear

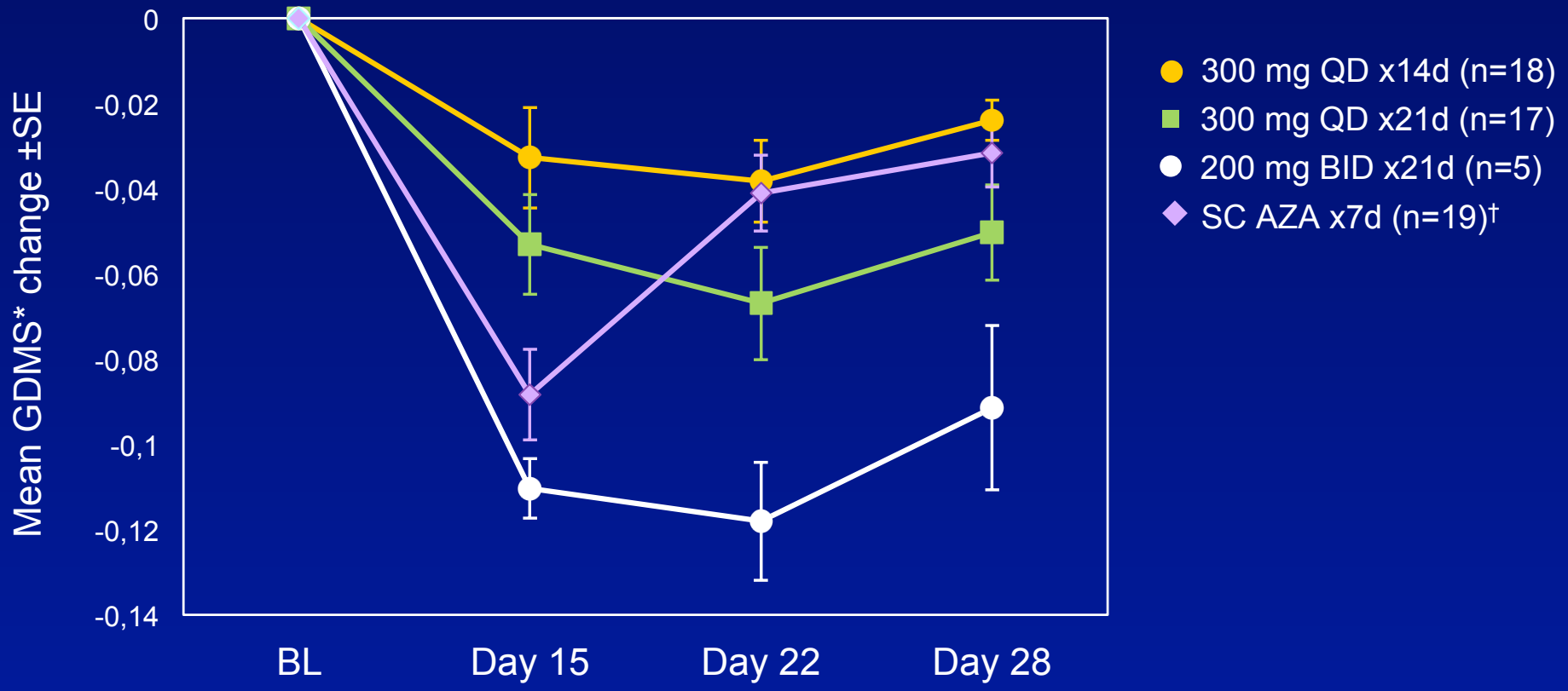
In DNA, azacitidine binds and traps DNMTs, leading to increased gene expression:

- DNA repair genes
- Tumor suppressors
- Signal transduction
- Angiogenesis inhibitors
- Tumor suppressor microRNA

DNMT=DNA methyltransferase
mRNA=messenger RNA
tRNA=transfer RNA
rRNA=ribosomal RNA

Jasielec et al. *Leukemia* 2014;28:1765–73

Methylation changes with CC-486 extended dosing regimens and SC azacitidine



Extended CC-486 dosing resulted in sustained methylation reductions over the entire treatment cycle[1,2]

*Global DNA Methylation Score : a single methylation score for each sample, based on the percentage of highly methylated loci
†75 mg/m^2/day
BL, baseline

1. Laille et al. *Plos One* 2015;10(8):e0135520
2. Savona et al. *Blood* 2015 126:452. Abstract 452

33

QUAZAR Trial Post-Transplant
CC-486-AML-002 Key Inclusion Criteria[1,2]

QUAZAR® Post-Transplant

- Age ≥ 18 years
- Diagnosis of MDS or AML[a] and undergoing alloSCT
- Post-alloSCT bone marrow blasts ≤ 5% within 21 days prior to starting therapy
- ECOG PS 0-2
- No treatment with any of the following therapies after alloSCT:
  - Chemotherapies or investigational agents
  - Hypomethylating agents
  - Lenalidomide, thalidomide, or pomalidomide

[a] According to WHO criteria.
alloSCT, allogeneic stem cell transplant; AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; MDS, myelodysplastic syndromes; WHO, World Health Organization.

1. http://www.clinicaltrials.gov/ct2/show/NCT01835587.
2. Celgene data on file.

CC-486-AML-002: Phase I/II Trial of CC-486 in Post-Transplant MDS/AML
Preliminary Results

- Data available for 21 patients (2 patients with IPSS Int-2 MDS and 19 patients with AML) across the 4 cohorts as of January 14, 2016

- 4 patients completed all 12 CC-486 cycles
  - 13 discontinued and 4 remain on study
- MTD was not reached

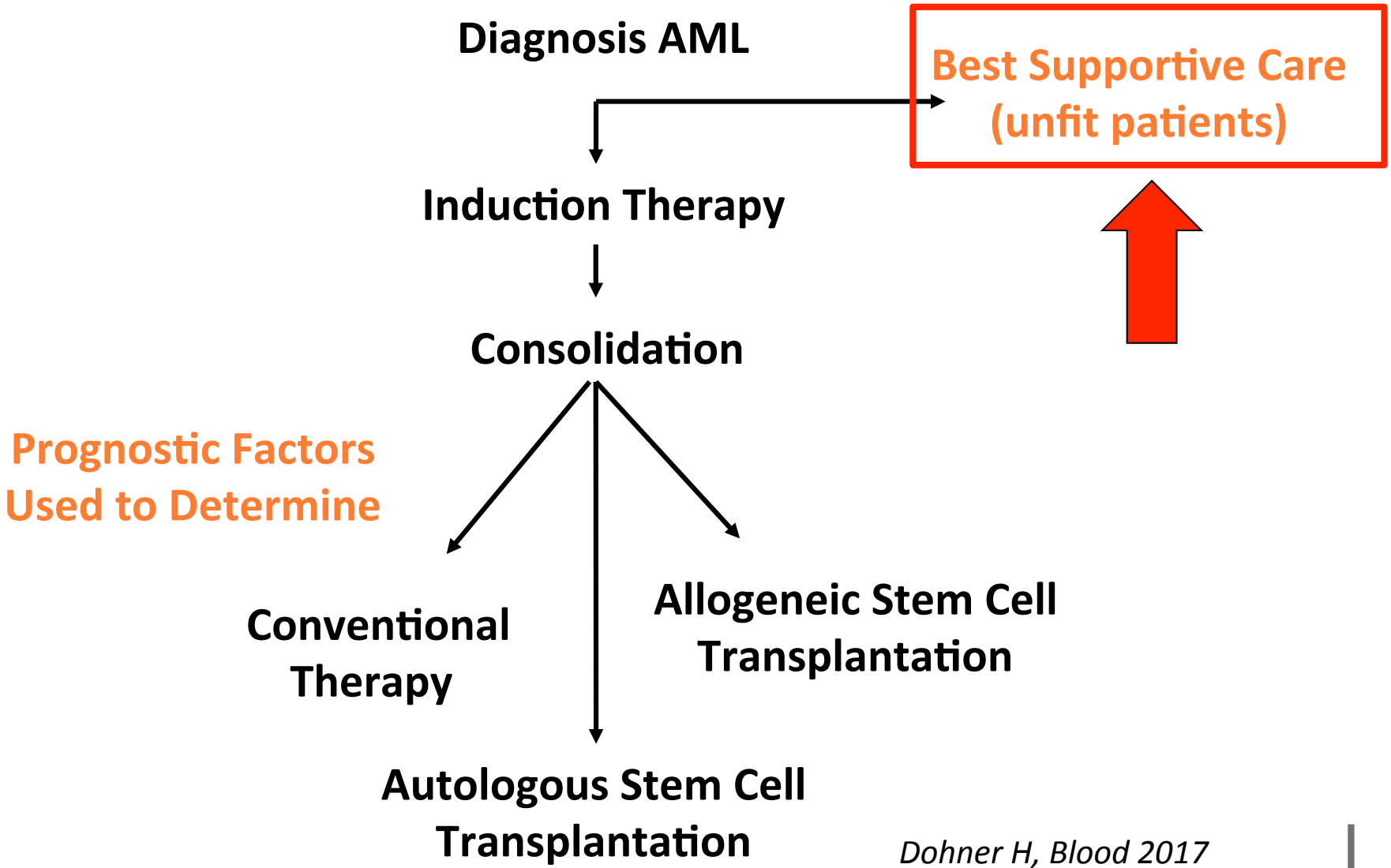
- 1 patient in Cohort 3 (200 mg × 14 days) had a DLT (grade 4 neutropenia, grade 3 pneumonia) and later died from thrombotic microangiopathy

- Most frequent grade 3/4 AEs were neutropenia, thrombocytopenia, and diarrhea (n = 4 each)
- 5 patients had GVHD at study entry
  - 2 cases worsened on treatment and 1 during follow-up
- 3 cases of gastrointestinal GVHD occurred on study

- Relapse was higher with 7-day (4/7, 57%) vs 14-day (3/14, 21%) dosing

De Lima M, et al. *Biol Blood Marrow Transplant.* 2016;22(3):S312-S313.

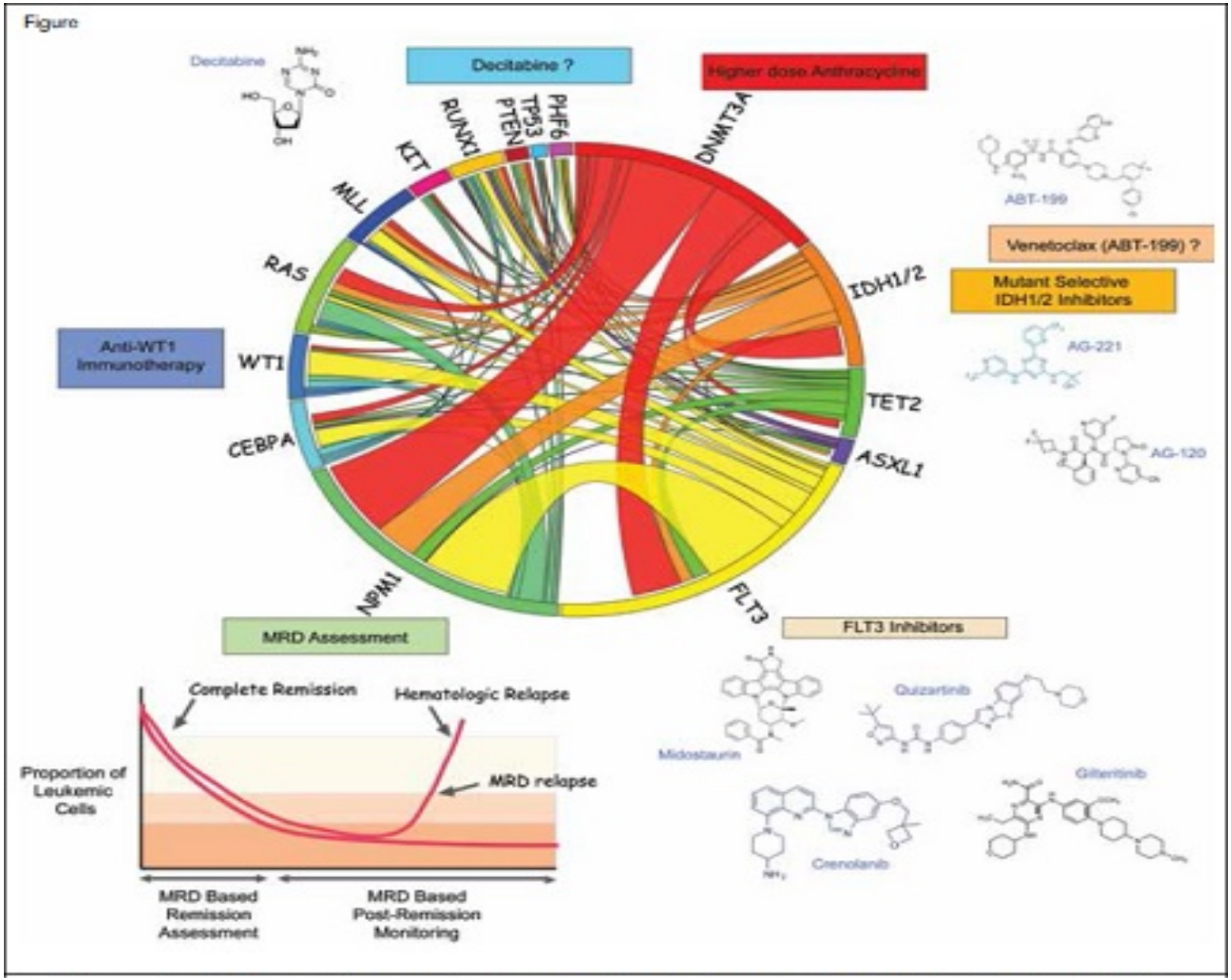
2nd setting: how to prolong response without SCT



Dohner H, Blood 2017

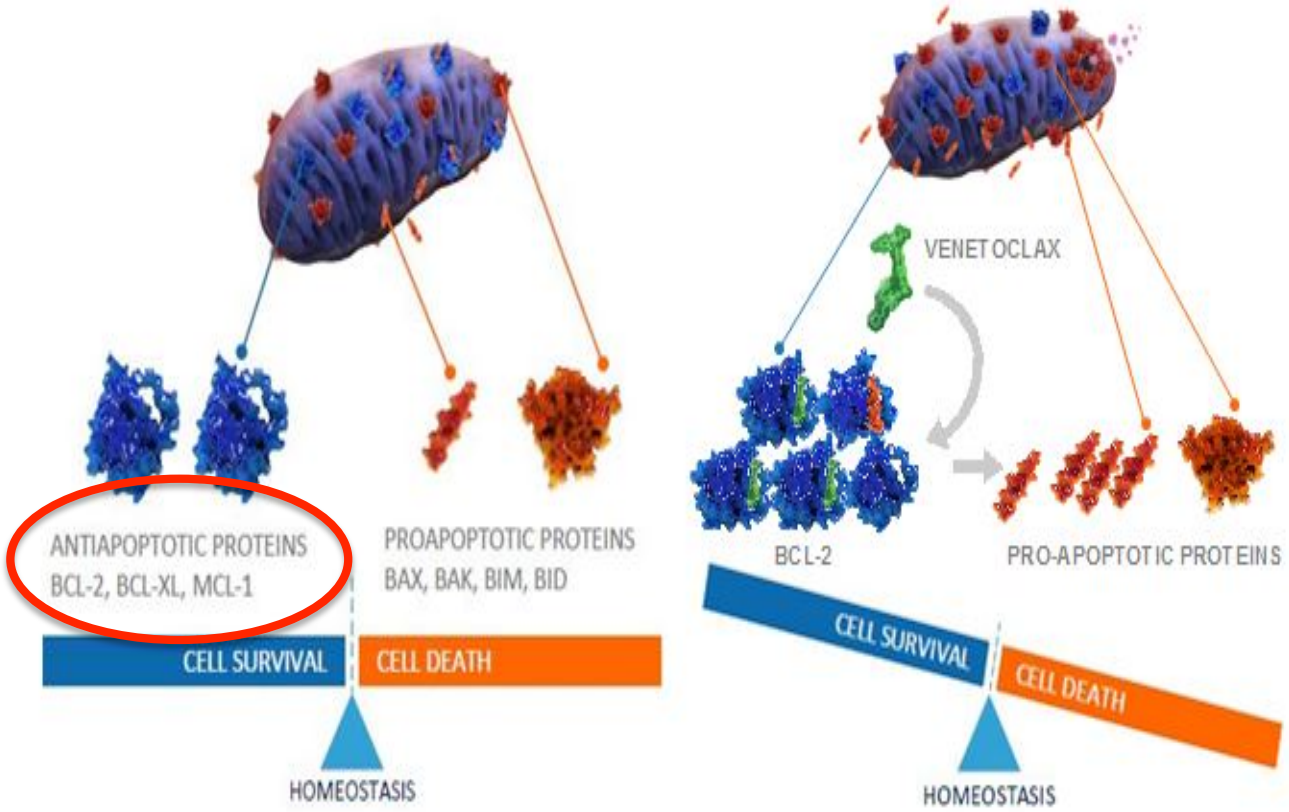
Progress and Promise: Precision Medicine for Patients With Acute Myeloid Leukemia

Taylor J, The Hematologist 2017



Promising targets: Bcl2 inhibition

- VEN is an oral (PO), potent, and selective BCL-2 inhibitor that demonstrated single-agent activity in heavily pretreated patients with relapsed/refractory AML[1]
- Binding of VEN to BCL-2 displaces a reserve of sequestered proapoptotic proteins in cancer cells, resulting in rapid cell death and antitumoral activity[2-5]



1. Konopleva M, et al. *Cancer Discov.* 2016;6:1-12.
2. Venetoclax full prescribing information. 2016.
3. Deng J, et al. *Cancer Cell*. 2007;12:171-85..
4. Cory S, et al. *Oncogene.* 2003;22:8590-607.
5. Hanahan D, Weinberg RA. *Cell*. 2011;144:646-74.

Venetoclax in combination with LDAC

Bcl2 inhibitor

A Phase 1/2 Study of ABT-199 in Combination with Low-Dose Cytarabine in Treatment-Naïve Subjects with Acute Myelogenous Leukemia Who Are ≥ 65 Years of Age and Who Are Not Eligible for Standard Anthracycline-Based Induction Therapy

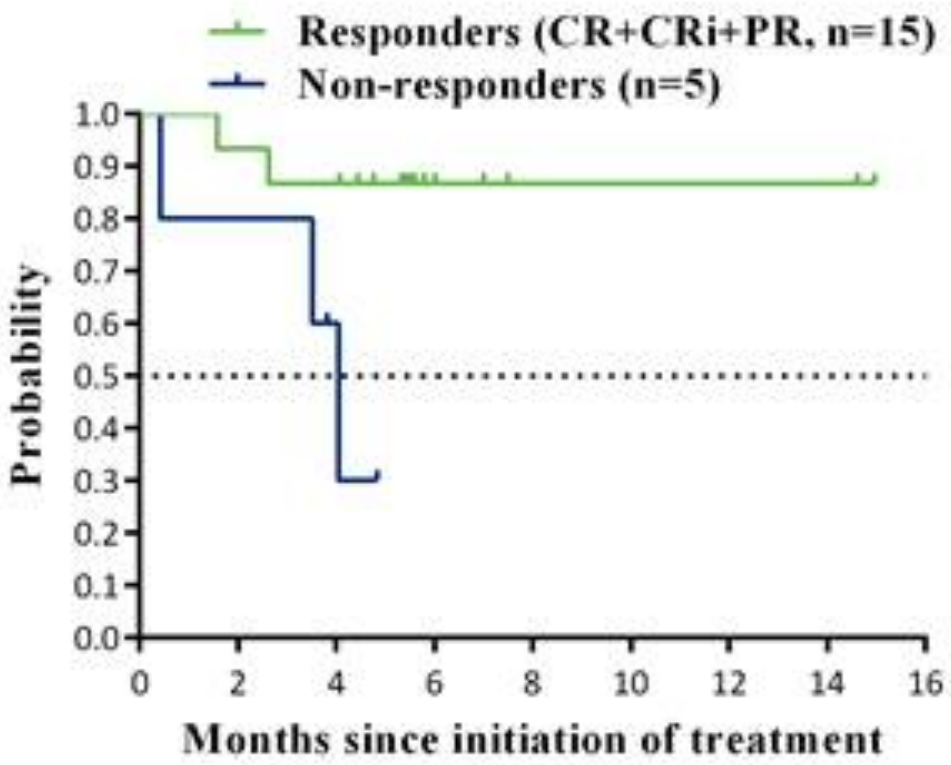
MCL1 inhibitor

8 Sites: USA (5)
Australia (1)
Italy (1)
Germany (1)

Lin TL, et al. ASCO 2016. Abstract 7007.

Efficacy

Figure 1. Overall survival in responders vs. non-responders



Median time to best response: 30 days (range 23-169)

Wei A et al, ASH 2016

Conclusions and open questions

- Consolidation and post remission treatment are defined according to genetics risk stratification, patients-related factors and MRD monitoring
- Grey zone: intermediate risk AML
- Maintenance setting: after alloBMT
- In the elderly setting: New compounds in clinical development; immunotherapy

-A lot to learn about biology of AML (driver mutations vs passenger mutations; mechanisms of resistance)
-New drugs: definition of their role
-Treat patients within clinical trials

Thank you!

Prof Giovanni Martinelli

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