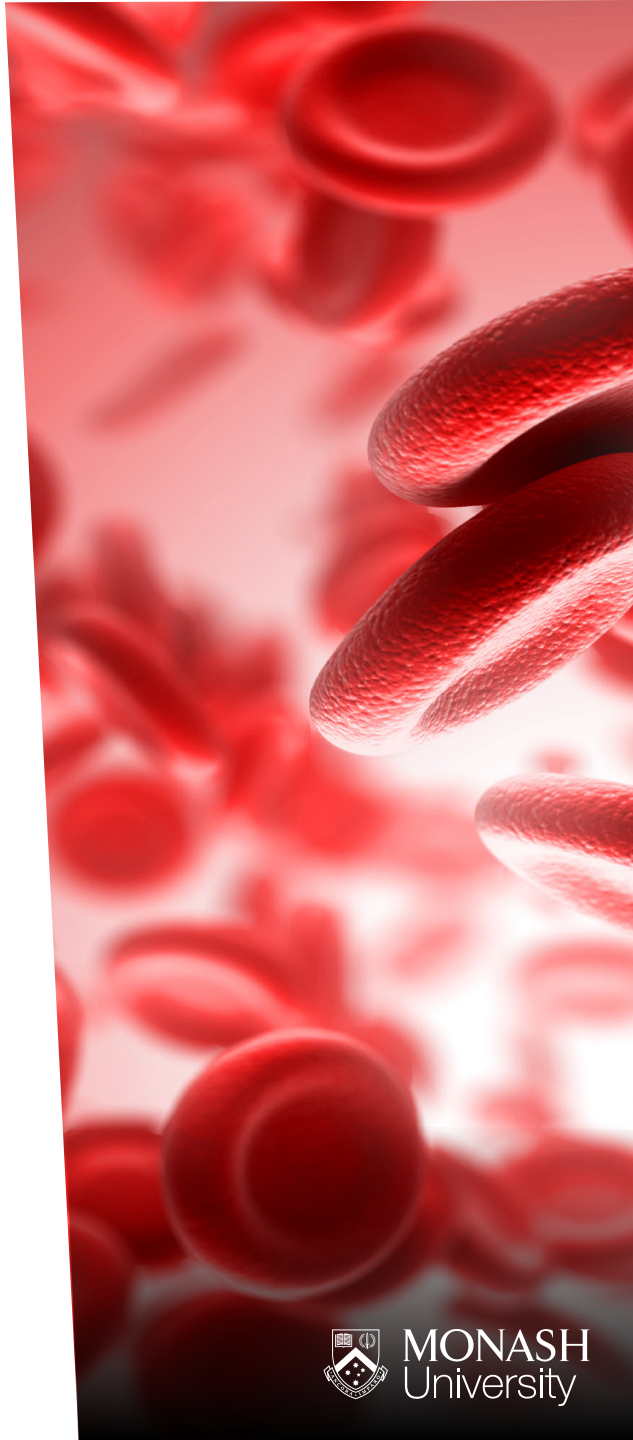
Management of AML in Elderly Patients

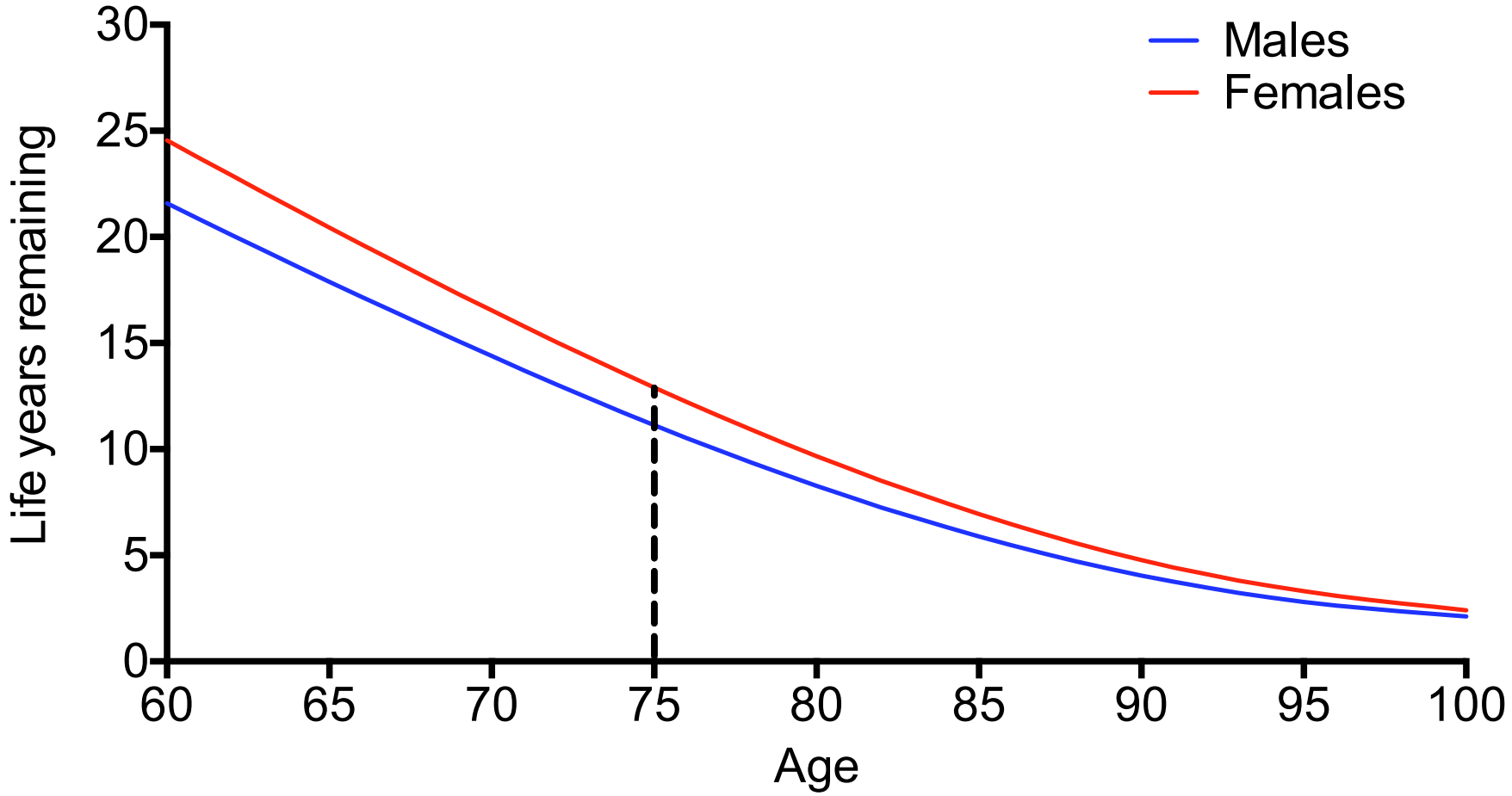
Andrew Wei

TheAlfred



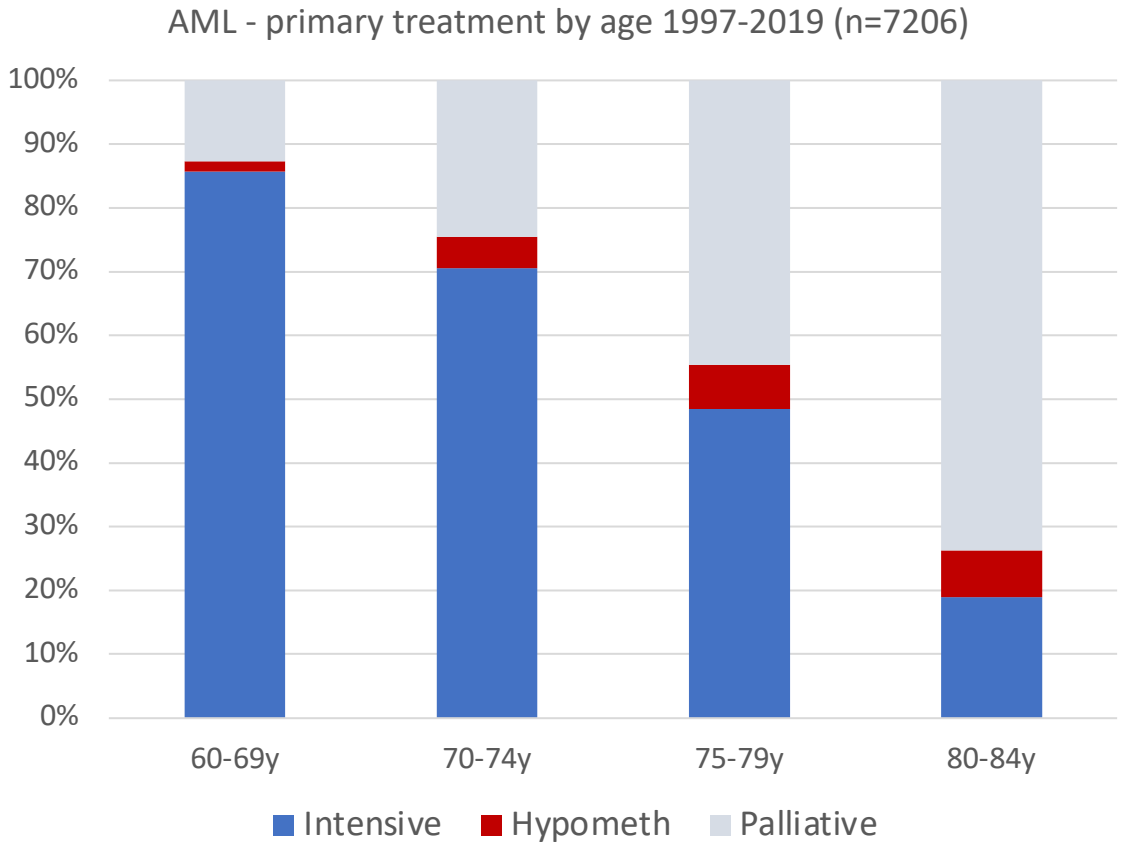
MONASH University

Life expectancy in older people



Courtesy of Andrew H Wei, MBBS, PhD

Intensive chemo outcomes in older AML



Intensive chemo	60-69	70-74	75-79	80-84
N	1349	746	542	175
ED	7.2%	9.7%	13.1%	16.6%
CR	63%	54%	49%	43%
2y OS	42%	28%	20%	

Personal communication Gunnar Juliusson on behalf of the Swedish Registry (1997-2019)

Courtesy of Andrew H Wei, MBBS, PhD

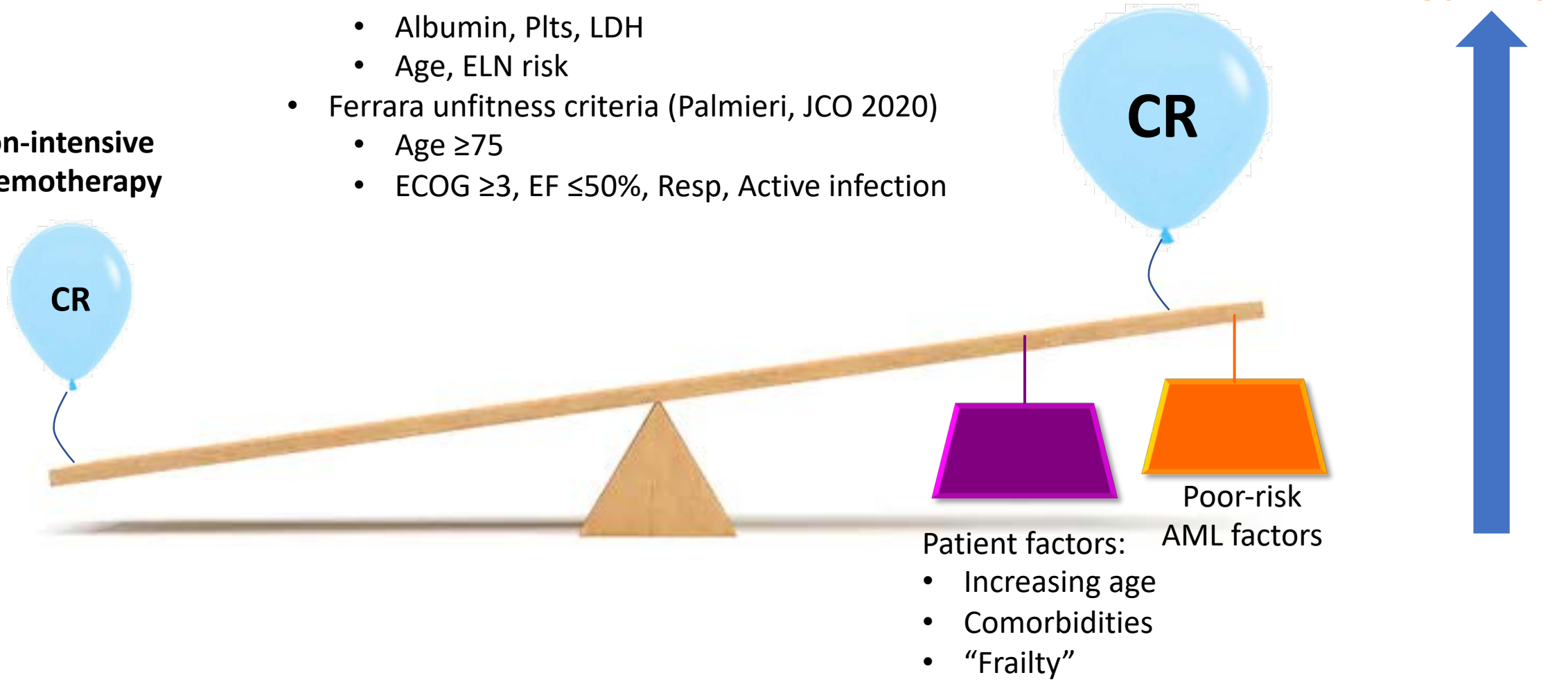
Assessing fitness for intensive chemotherapy

Prognostic tools

- AML composite score (Sorror, JAMA 2017)
  - HCT-CI
  - Albumin, Plts, LDH
  - Age, ELN risk
- Ferrara unfitness criteria (Palmieri, JCO 2020)
  - Age ≥75
  - ECOG ≥3, EF ≤50%, Resp, Active infection

Non-intensive chemotherapy

Intensive chemotherapy



Patient factors:

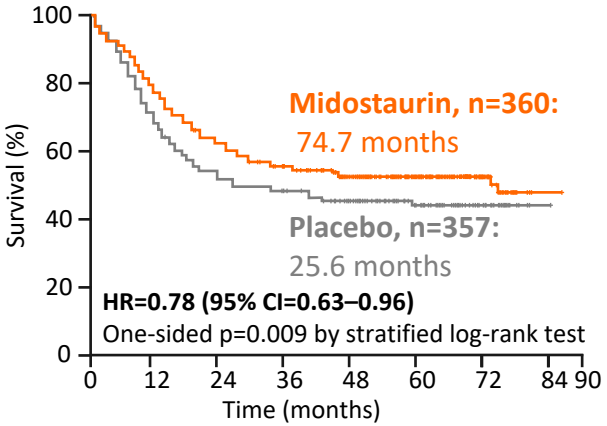
- Increasing age
- Comorbidities
- "Frailty"

Courtesy of Andrew H Wei, MBBS, PhD

Recent FDA-approved drugs for AML (Survival Outcomes)

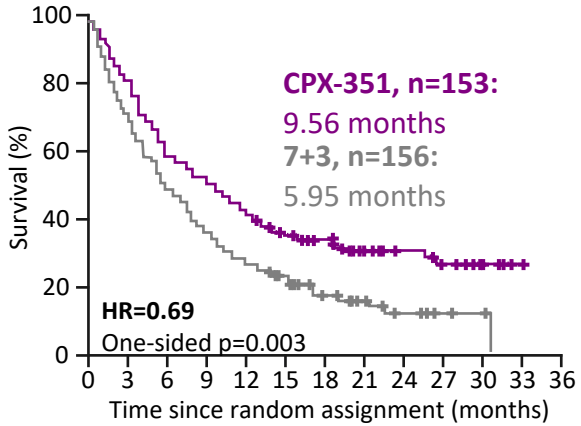
Phase III CALGB-10603 Trial

7+3 + midostaurin[1]



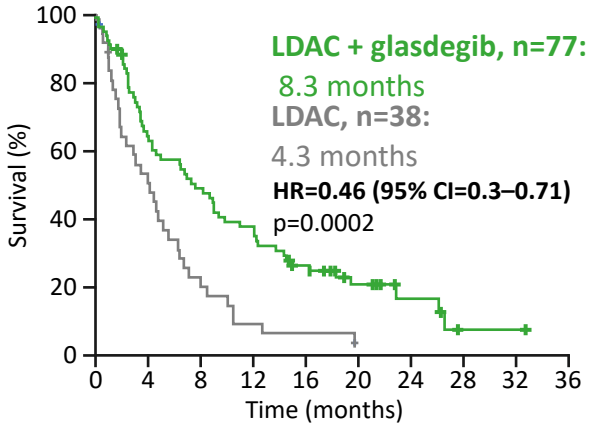
Phase III Study 301

CPX-351[2]



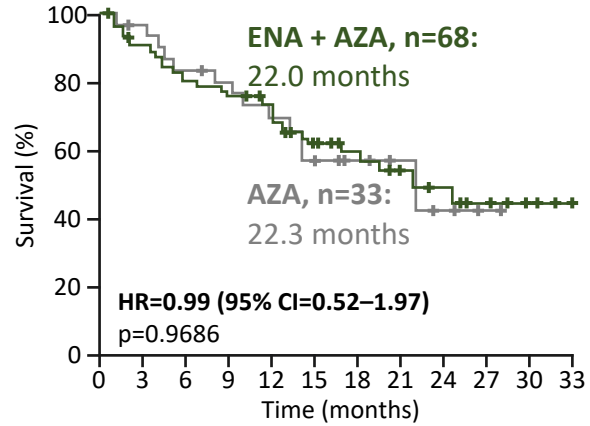
Phase II BRIGHT AML 1003 Trial

LDAC + glasdegib[3]



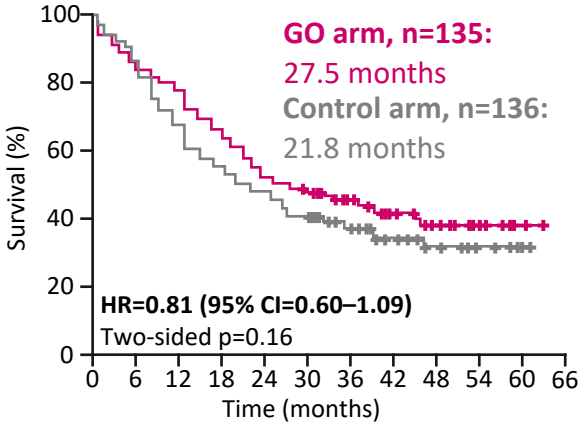
Phase I/II Trial

AZA + enasidenib[4]



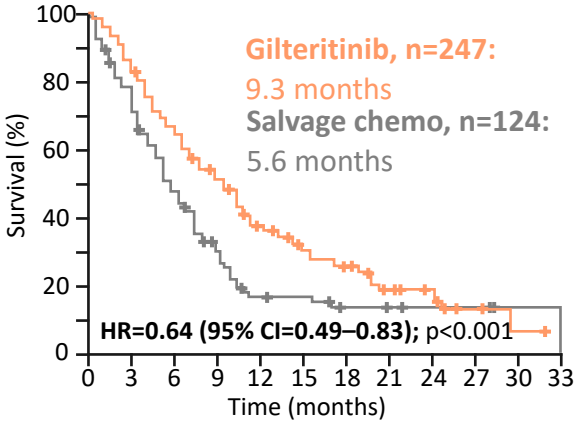
Phase III ALFA-0701 Trial

7+3 + GO[5]



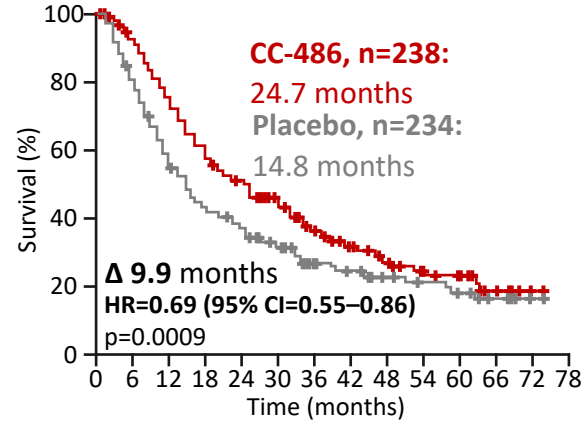
Phase III ADMIRAL Trial

Gilteritinib[6]



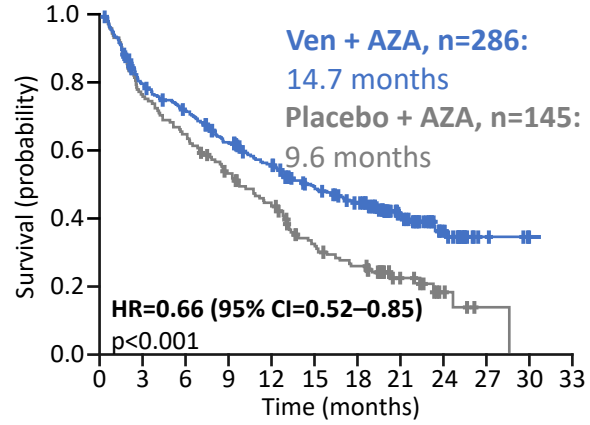
Phase III QUAZAR AML-001 Trial

CC-486[7]



Phase III VIALE-A Trial

AZA + venetoclax[8]



AZA, azacitidine; ENA, enasidenib; GO, gemtuzumab ozogamicin; LDAC, low-dose cytarabine; Ven, venetoclax.

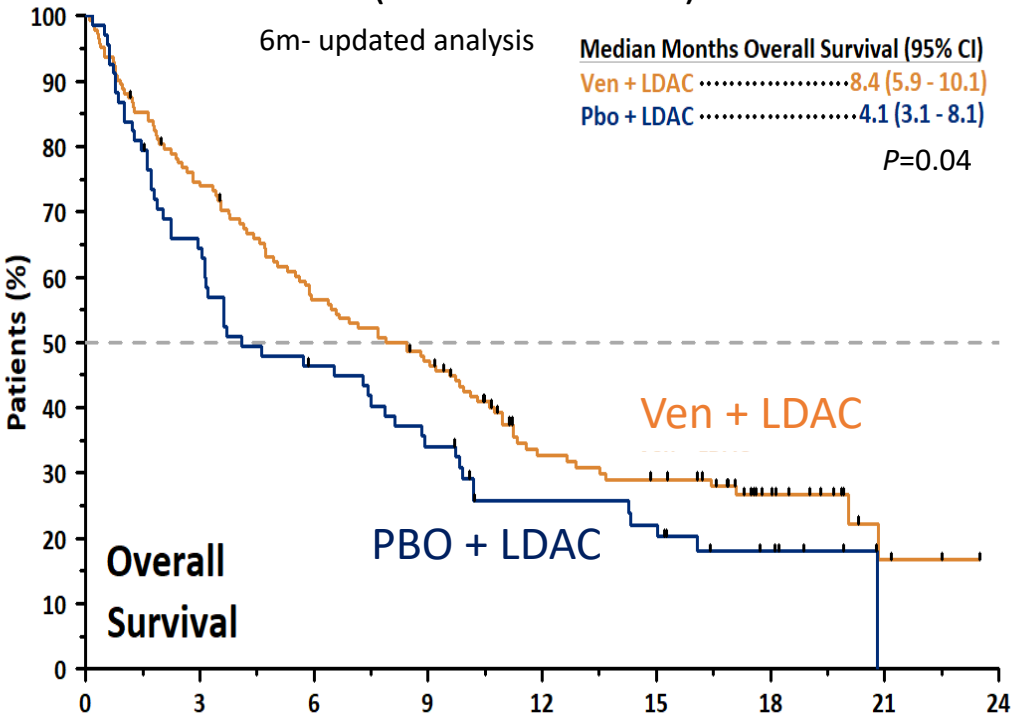
1. Stone M, *et al. N Engl J Med* 2017; **377:**454–464; 2. Lancet JE, *et al. J Clin Oncol* 2018; **36**:2684–2692; 3. Norsworthy KJ, *et al. Clin Cancer Res* 2019; **25:**6021–6025; 4. DiNardo CD, *et al. EHA* 2020; oral presentation S139 5. Lambert J, *et al. Haematologica* 2019; **104**:113–119; 6. Perl AE, *et al. N Engl J Med* 2019; **381:**1728–1740; 7. Wei AH, *et al.* ASH 2019; oral presentation LBA3; 8. DiNardo CD, *et al. N Engl J Med* 2020; **383**:617–629.

Courtesy of Andrew H Wei, MBBS, PhD

Ph3 studies of venetoclax + AZA or LDAC in unfit 1L AML

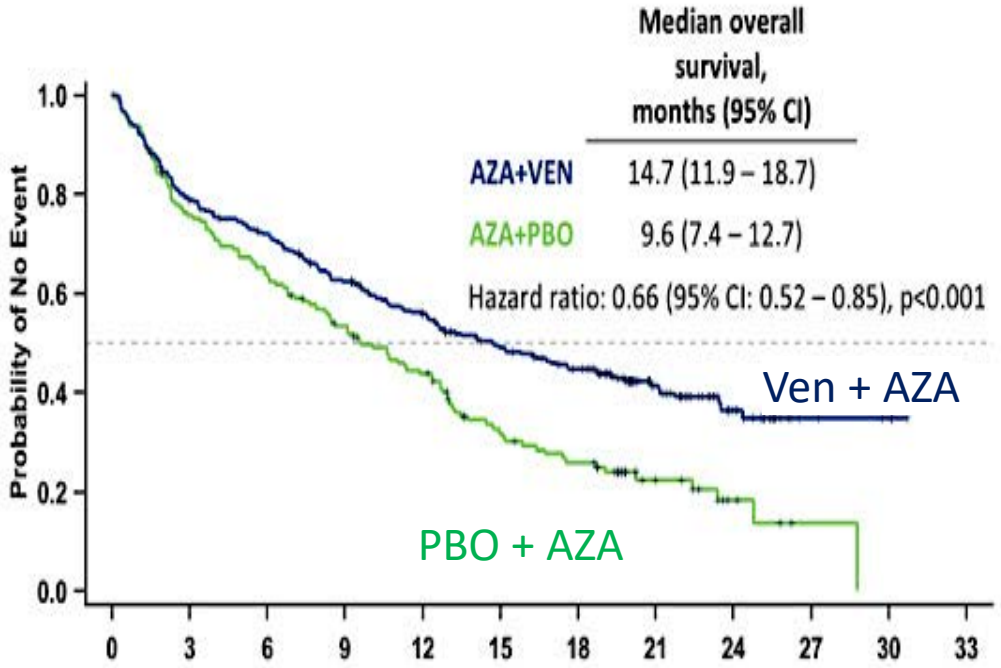
VIALE-C	VEN 600mg+ LDAC	PBO+LDAC
N	143	68
CR/CRi	**48%**	13%
OS	8.4m	4.1m
30d TRM	13%	16%

(Prior HMA 20%)



Wei et al, Blood 2020

VIALE-A	VEN 400 mg +AZA	PBO+AZA
N	286	145
CR/CRi	**66%**	28%
OS	14.7m	9.6m
30d TRM	7%	6%

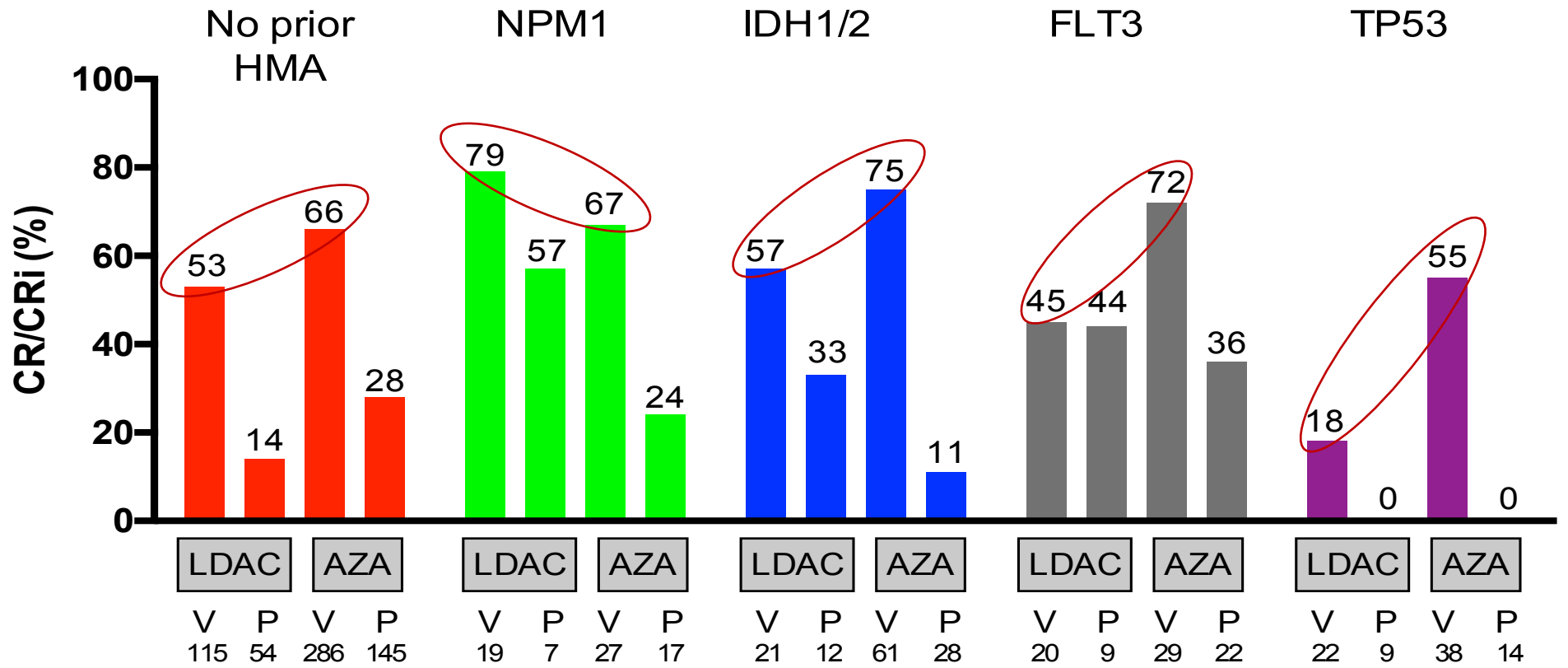


Di Nardo et al, NEJM 2020

Courtesy of Andrew H Wei, MBBS, PhD

Comparison of HMA or LDAC + venetoclax responses

		VIALE-C		VIALE-A	
		VEN (n=143)	**PBO (n=68)**	**VEN (n=286)**	**PBO (n=145)**
Response	CR/CRi	48%	13%	66%	28%
	CR	28%	7%	37%	18%
	Duration of CR	**17 mo**	8 mo	**17.5 mo**	13.5 mo

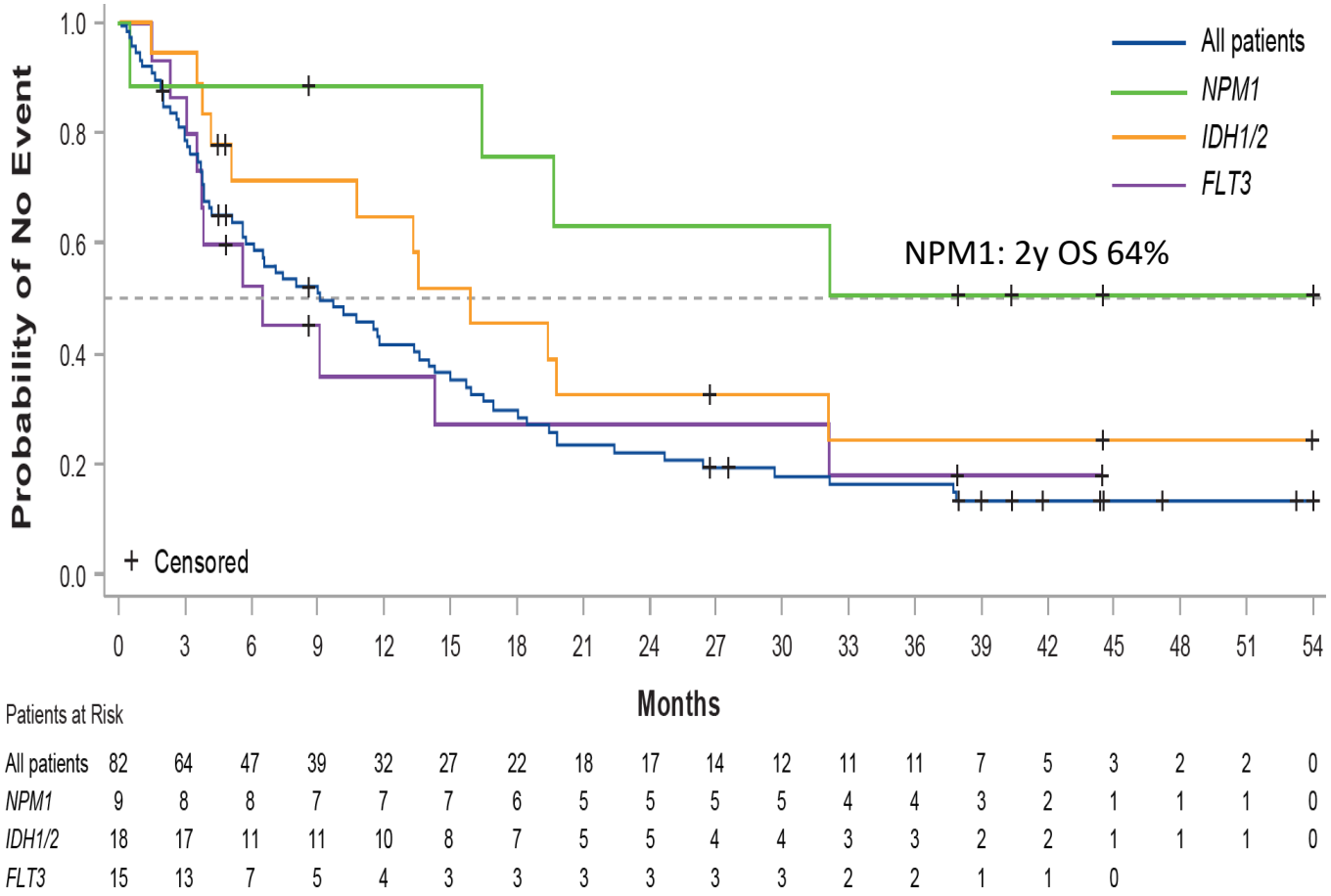


Wei et al, Blood 2020; EHA 2020, Di Nardo et al, EHA 2020

Courtesy of Andrew H Wei, MBBS, PhD

Phase I/II Study: Venetoclax has robust activity in *NPM1* mutant AML

3.5y F/U after VEN + LDAC (Ph1b/2)

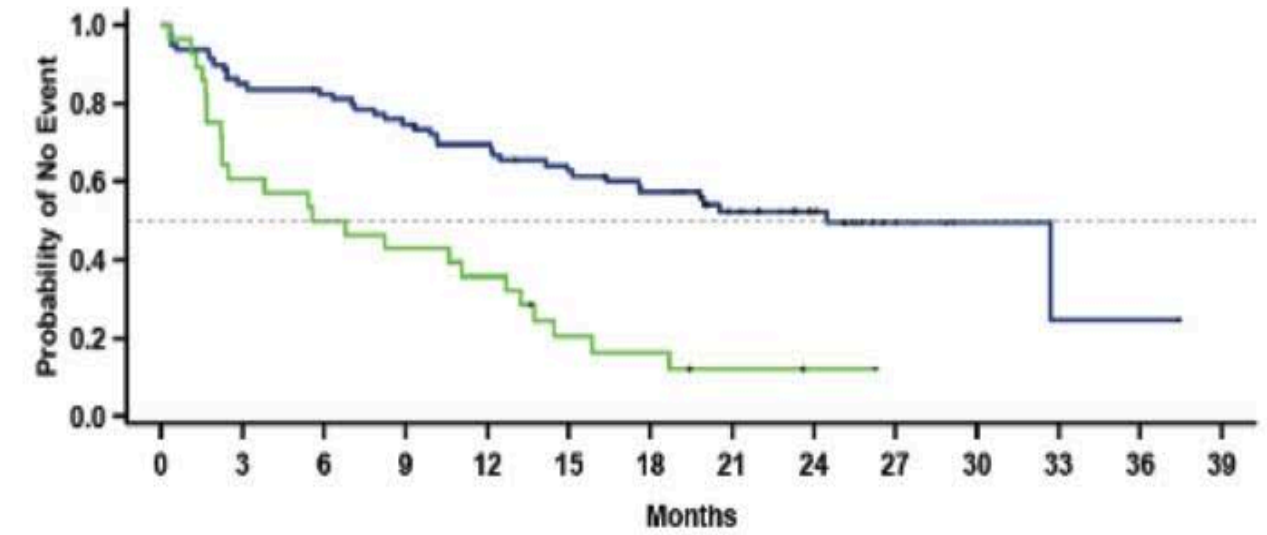


Courtesy of Andrew H Wei, MBBS, PhD

Wei *et al*, EHA 2020

VEN-AZA enhances OS in IDH mut AML in VIALE-A

IDH1/2 mut	VEN 400mg+ AZA	PBO+ AZA
N	79	28
CR/CRi	79%	11%
OS at 2 yrs	52%	12%



Patients at Risk

Ven+Aza	79	67	64	58	53	47	42	29	19	7	2	1	1	0
Pbo+Aza	28	17	14	12	10	5	4	2	1	0				

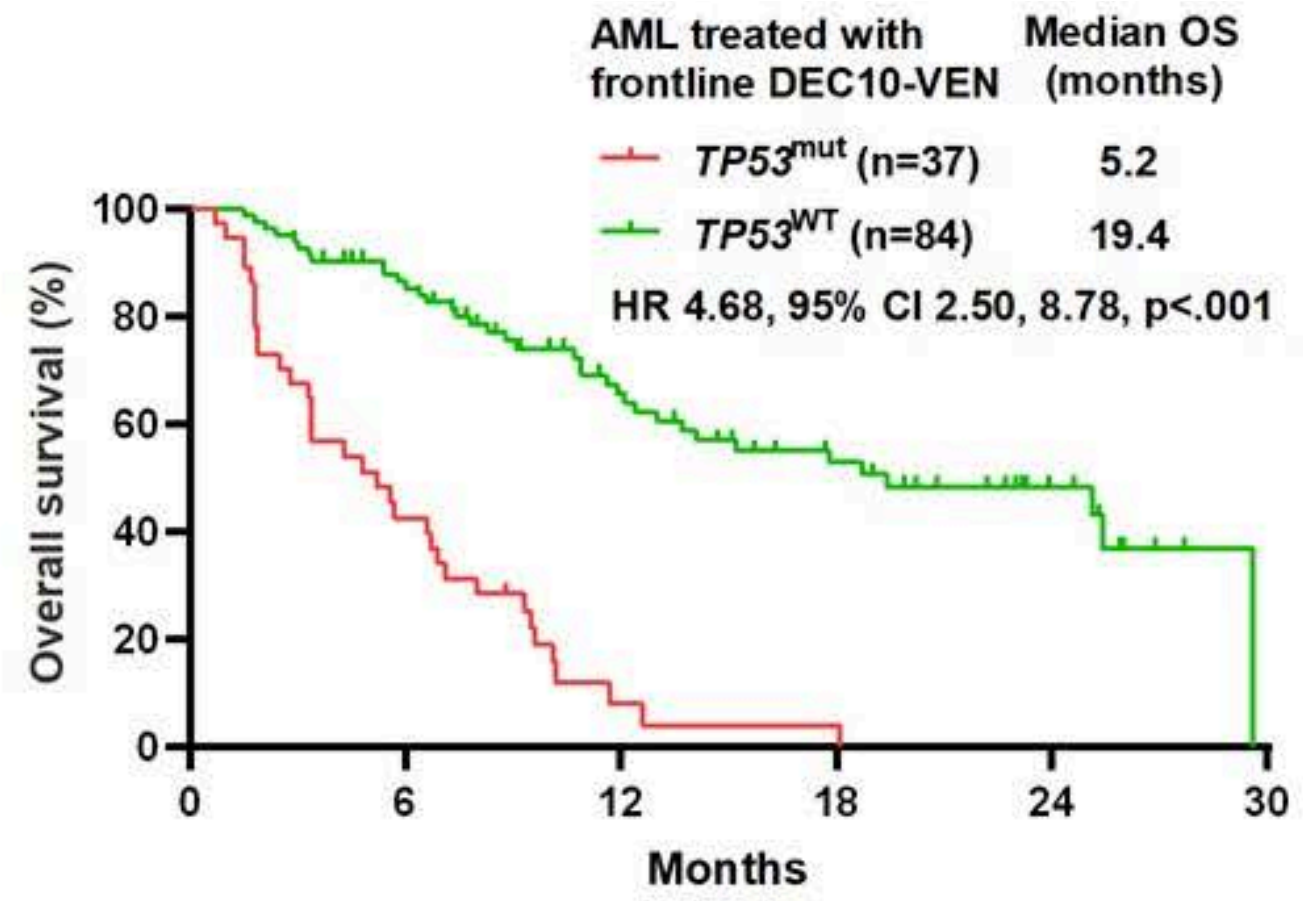
		Survival Estimate (%) (95% CI)			Median (Months)
	Events	Month 6	Month 12	Month 24	(95% CI)
Ven+Aza (N=79)	38	82.3 (71.9, 89.1)	69.3 (57.8, 78.3)	52.4 (40.4, 63.1)	24.5 (15.2, -)
Pbo+Aza (N=28)	24	50.0 (30.6, 66.6)	35.7 (18.9, 53.0)	12.2 (3.2, 27.8)	6.2 (2.3, 12.7)

Courtesy of Andrew H Wei, MBBS, PhD

Dan Pollyea, et al, Abstract 461

VEN + Decitabine (DEC) 10 does not improve outcomes in $TP53^{MUT}$ AML

	TP53 MUT	TP 53 WT
N	37	84
CR/CRi	54%	76%
OS (median)	5.2m	19.4m



Courtesy of Andrew H Wei, MBBS, PhD

Kunhwa Kim, et al, Abstract 693

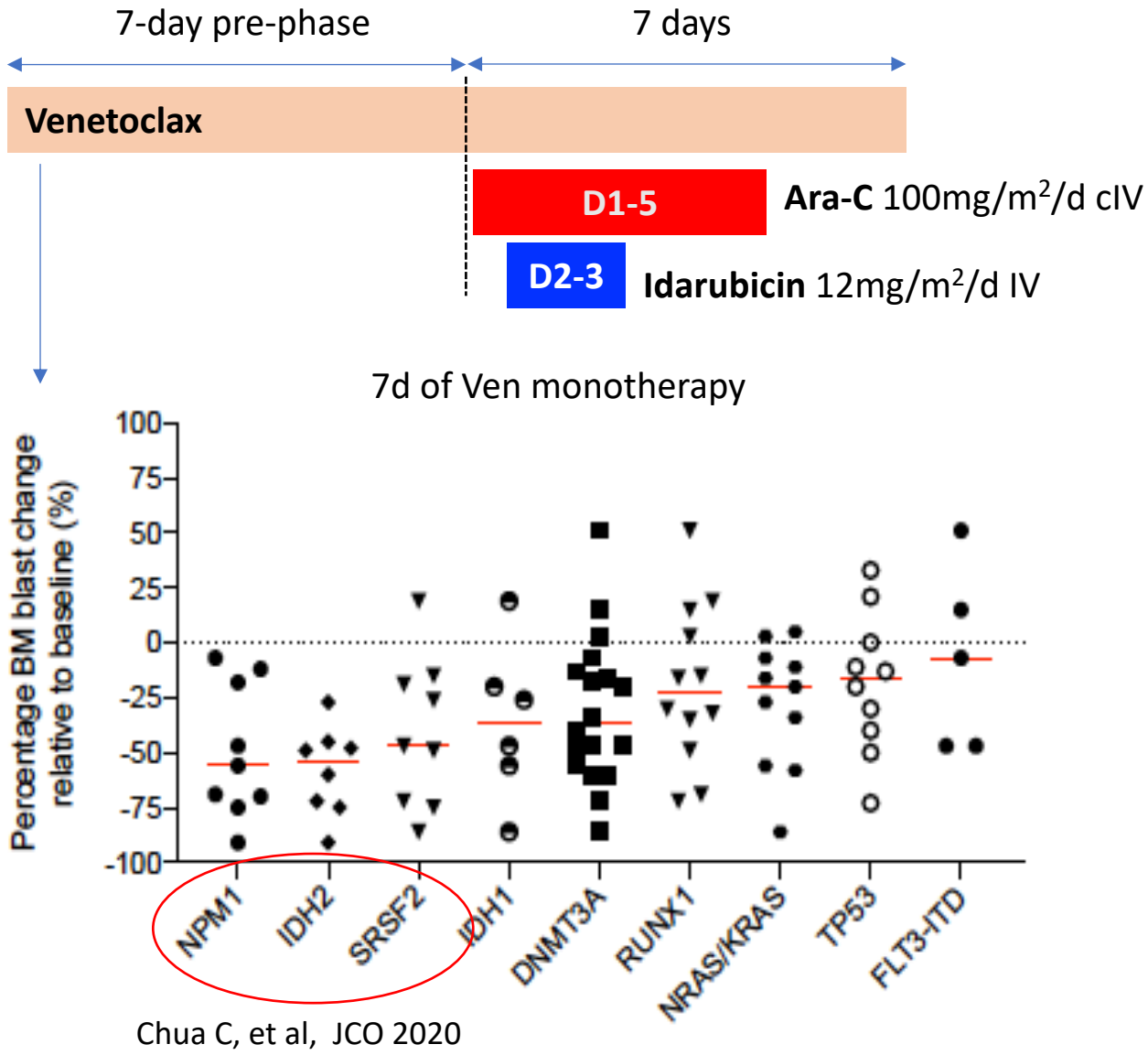
VEN-AZA dosing recommendations

- VEN D1-21 in cycle 1
- Bone marrow D21-28: if BM blasts <5% and <CRh → hold VEN and AZA until ANC ≥500/µL (for up to 14 days)
- Use G-CSF if no spontaneous recovery after 14 days of VEN interruption
- If ≥CRh: start next cycle with VEN D1-21 → hold VEN and AZA until ANC ≥500/µL (for up to 14 days). Intermittent G-CSF may be used.
- Further reductions to VEN D1-14, D1-10 or D1-7 if cumulative myelosuppression
- Cycles every 4-6 weeks based on count recovery; hold therapy if ANC <0.5, Plts <25
- Fungal prophylaxis if ANC <0.5
  - If using posaconazole, only commence after dose ramp-up and adjust VEN dose to 50 mg. If using isavuconazole, adjust VEN dose to 200 mg

Courtesy of Andrew H Wei, MBBS, PhD

Uncertainties with targeting BCL2 in AML

- Role of monotherapy
- Safety in MF-associated AML
- Optimal dose in combination with anti-fungal agents
- Role of VEN in prior HMA failure
- Management of VEN-AZA treatment failure



Chua C, et al, JCO 2020

Courtesy of Andrew H Wei, MBBS, PhD

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Antifungal	Package Insert Recommendation (ven mg/D)	Recommended Dose Adjustment (ven mg/D)
Posaconazole	70	50-100
Voriconazole	100	100
Isavuconazole	200	200
Caspofungin, echinocandins	400	400

Table courtesy of Naval Daver MDACC

Courtesy of Andrew H Wei, MBBS, PhD

Uncertainties with targeting BCL2 in AML

- Role of monotherapy
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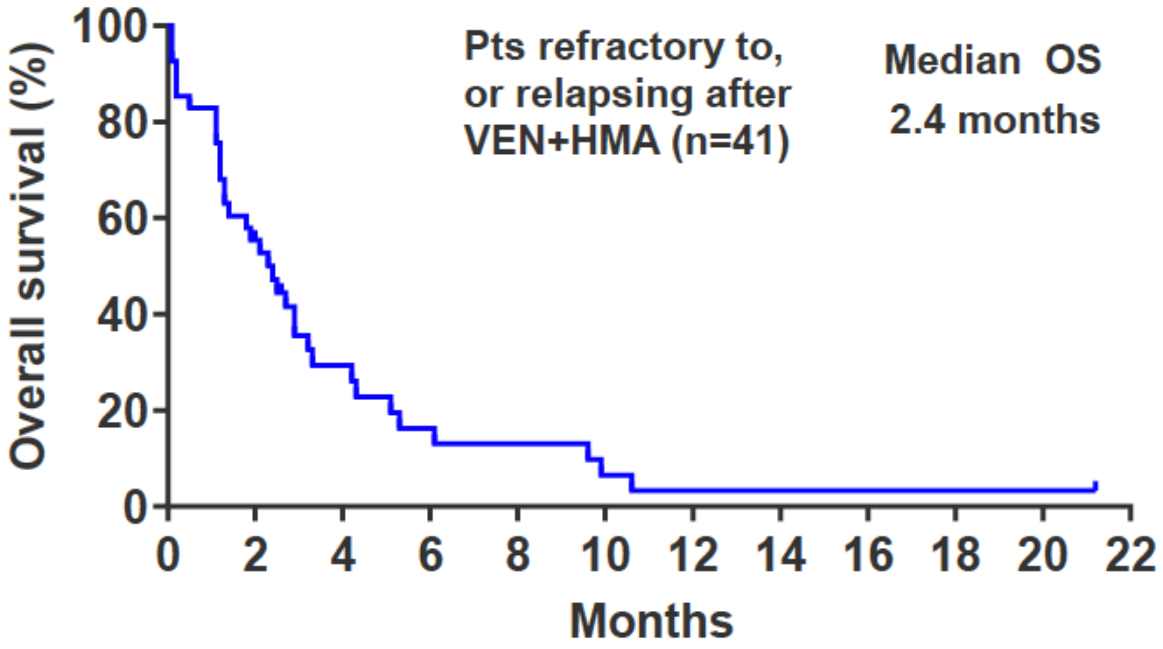


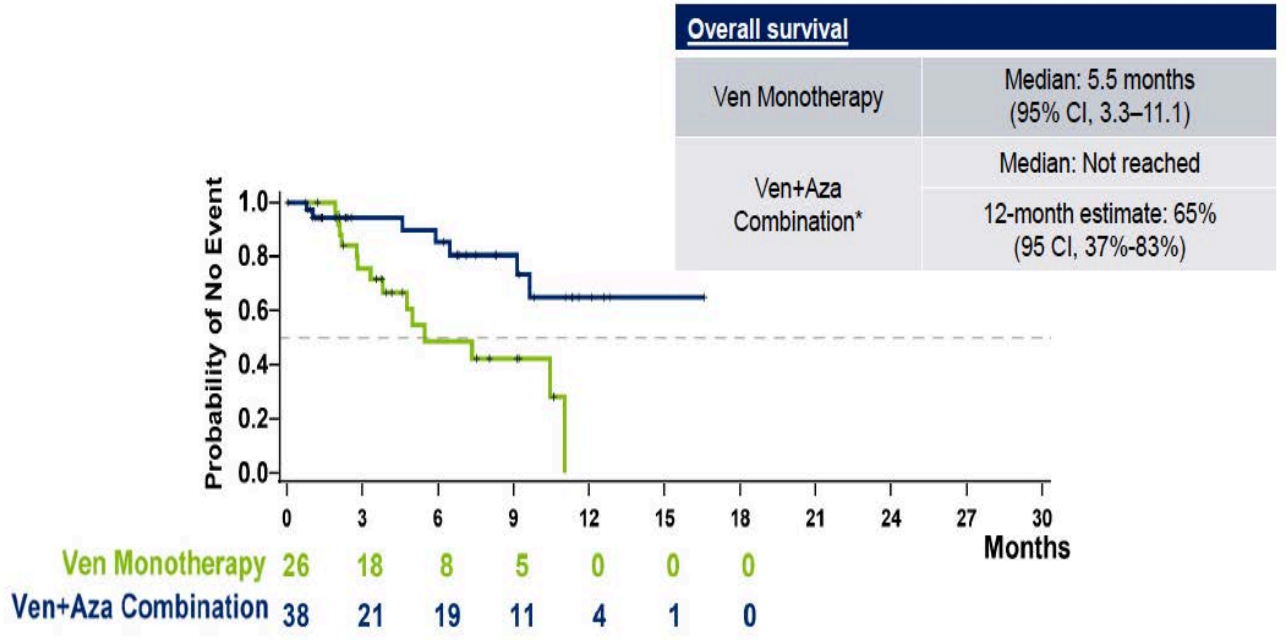
Maiti et al, Hematologica 2020

Courtesy of Andrew H Wei, MBBS, PhD

Uncertainties with targeting BCL2 in AML

- Role of monotherapy
- Safety in MF-associated AML
- Optimal dose in combination with anti-fungal agents
- Role of VEN in prior HMA failure
- Management of VEN-AZA treatment failure

Response	VEN (n=26)	VEN-AZA (n=38)
CR/CRi	8%	40%
CR	0%	8%
mCR	**8%**	32%



Courtesy of Andrew H Wei, MBBS, PhD

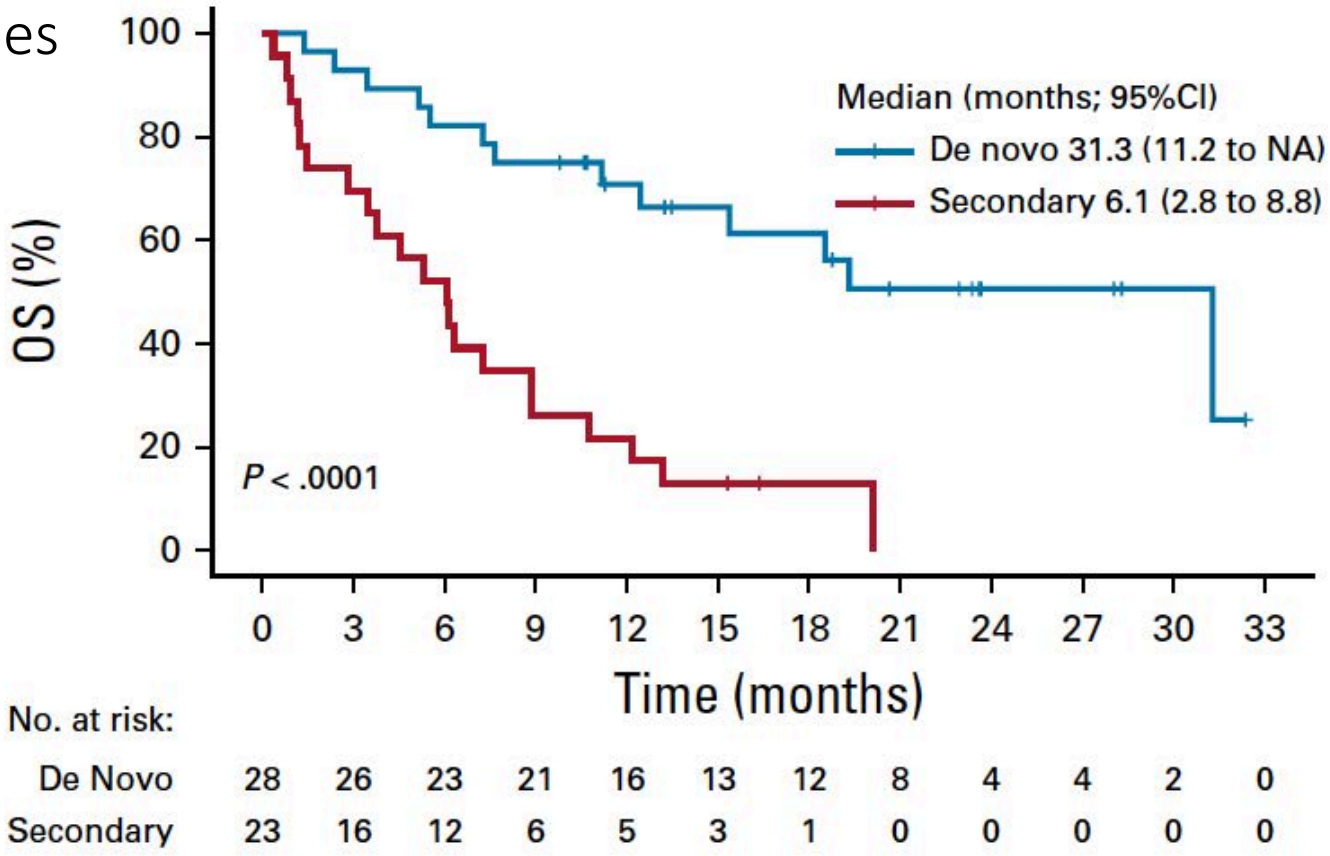
Zeidan et al, ASH 2019

Future directions

- More intensive combinations
- Combinations with targeted therapies
  - Targeted drugs
  - Immunotherapy
- Maintenance therapy
- More convenient regimens

Chemotherapy and venetoclax in elderly AML trial (CAVEAT)

N=51, median age 72 (63-80)
Median follow up: 23 months
Ven D1-14, 5+2 (from day 8)
***De novo* AML (CR/CRi 97%)**
sAML (CR/CRi 44%)



Chua et al, JCO 2020

Courtesy of Andrew H Wei, MBBS, PhD

Future directions

- More intensive combinations
- Combinations with targeted therapies
  - Targeted drugs
  - Immunotherapy
- Maintenance therapy
- More convenient regimens

ASH 2020;Abstract 332 Lachowiez et al
- Venetoclax + FLAG-IDA
- Newly Dx (n=24) ORR 84%
- Salvage (n=23) ORR 66%

ASH 2020;Abstract 1038 Stone et al
- Venetoclax + 7+3
- 2/6 DLTs in older patients
- Restricted to 18-60yo
- MTD Ven 400mg

Courtesy of Andrew H Wei, MBBS, PhD

Future directions

- More intensive combinations
- Combinations with targeted therapies
  - Targeted drugs- inhibitors of FLT3, IDH
  - Immunotherapy
- Maintenance therapy
- More convenient regimens

ASH 2020;Abstract 333 Daver et al

- Gilteritinib + venetoclax
- N=37
- MLFS 54%, CR/CRi 16.2%, CRp 13.5%

ASH 2020;Abstract 2809 Zeidan et al

- Ven-AZA vs Ven-AZA- Pembro
- MRD neg after 6 cycles

Courtesy of Andrew H Wei, MBBS, PhD

Future directions

- More intensive combinations
- Combinations with targeted therapies
  - Targeted drugs
  - Immunotherapy
- Maintenance therapy- before and after transplant
- More convenient regimens

Courtesy of Andrew H Wei, MBBS, PhD

Future directions

- More intensive combinations
- Combinations with targeted therapies
  - Targeted drugs
  - Immunotherapy
- Maintenance therapy
- More convenient regimens- with CC-486, ASTX727 (decitabine + cedazuridine)

Courtesy of Andrew H Wei, MBBS, PhD

Optimal duration of therapy with venetoclax in patients with AML experiencing a sustained clinical response

- 77yo man
- Dec 2016: AML 64% blasts (NK, no mutations)
  - Rx AZA + VEN → CRi
  - Flow MRD <0.1%
  - After 4 cycles, chest pain and SOB
  - Critical thoracic aortic aneurysm
  - Patient refused operation
- Patient monitored
  - After 2.5 years
  - Progressive AML with 22% blasts
  - Retreated with AZA-VEN→ MLFS
  - Deconditioning
  - Patient refused further therapy

Learning points

- Risk for further therapy
- Durable remission despite minimal therapy
- Relapsing disease may be sensitive to retreatment
- Advancing age makes salvage therapy with myelosuppressive therapy difficult in this population

Courtesy of Andrew H Wei, MBBS, PhD

Optimal duration of therapy with venetoclax in patients with AML experiencing a sustained clinical response

- 78yo lady
- Dec 2014: AML 34% blasts (IDH2 R140Q)
  - Rx LDAC + VEN → CR
  - Ceased in July 2016 (15 cycles)
  - IDH2 R140Q still present
- Jan 2020: Relapse 51% blasts (IDH2 R140Q, new SRSF2)
  - Rx enasidenib → MLFS EOC4 2% blasts
- FLT3-ITD relapse
  - Rx gilteritinib

Learning points
- Patient able to cease therapy
- Relapse 3.5 years after ceasing therapy
- Important to look for targetable causes of clonal evolution with targeted therapy

Courtesy of Andrew H Wei, MBBS, PhD