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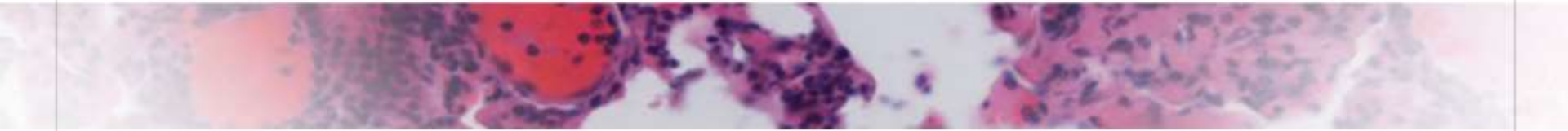


Results of a Phase 3 Study of Elderly Patients with Newly Diagnosed AML Treated with Sapacitabine and Decitabine Administered in Alternating Cycles

H Kantarjian, K Begna, J Altman, S Goldberg, MA Sekeres, S Strickland, E Rubenstein, M Arellano, D Claxton, MR Baer, M Gautier, E Berman, K Seiter, SR Solomon, G Schiller, S Luger, A Butrym, G Gaidano, X Thomas, P Montesinos, D Rizzieri, D Quick, E Agura, P Venugopal, J Subramanian, L Maness, DE Robert, Y Hicheri, T Kadia, F Ravandi, M Buyse and JH Chiao on behalf of the CYC682-12 SEAMLESS study investigators

Blood 130: abst 891; 2017

Background: AML in Elderly Patients (≥ 70 yrs)

- AML in the elderly associated with poor prognosis
- Older age = poor tolerance to intensive chemo Rx; ↑ early mortality
- Standard front-line Rx unchanged → ~40 years
- Prolonged hospitalization; severe myelosuppression
- Co-morbidities
- ↑ AHD, MDR, poor CG
- Intensive Chemo Rx—CR 40-50%; median OS < 12 mos
- Epigenetic or low-intensity Rx—CR 20-50%; median OS 8-12 mos
- Need to improve low-intensity Rx

Kantarjian. AJH 91: 131; 2017. Cancer 106: 1090; 2006. Blood 116: 4422; 2010. JCO 30: 2670; 2012

Background: Sapacitabine in AML

- **Oral nucleoside analogue; active in AML and MDS**
- **Novel mechanism of action in DNA damage and repair pathways**
- **Safety profile suitable for long-term administration**
  - **toxicity: neutropenia > thrombocytopenia**
- **Efficacy in elderly AML as front-line in alternating cycles with decitabine**
  - **CR rate: 6/25 = 24%**
  - **Median survival: 7.7 months**

Kantarjian. JCO 28: 285; 2010. Lancet Oncology 13: 1096; 2012. Ravandi. Abs. #2630, ASH 2012

Study Group

- **Randomized, open label, global study stratified by WBC, AHD and marrow blasts**
- **482 patients ≥ 70 years, not candidates for or refused intensive therapy**
- **Newly diagnosed AML by WHO – *de novo* or secondary; no restriction by peripheral WBC**

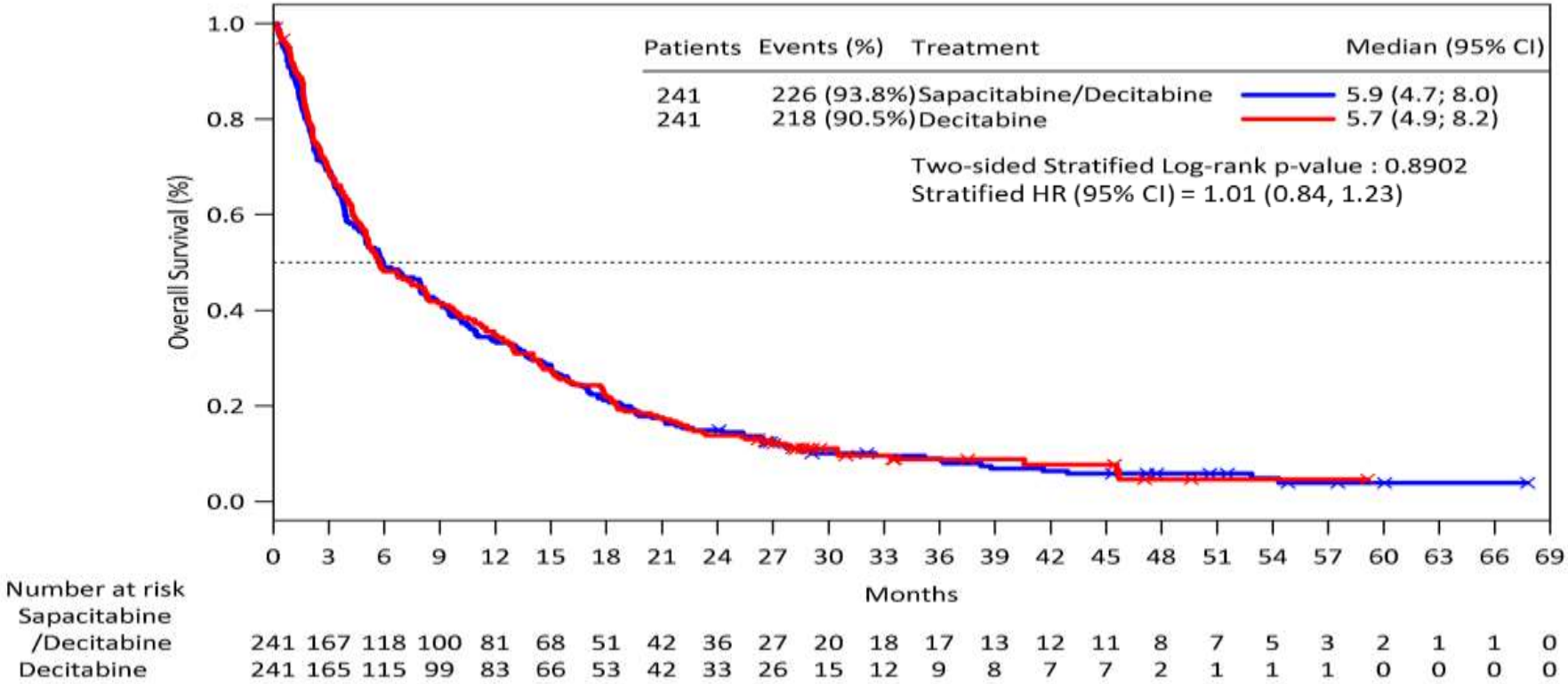
Treatment and Endpoints

- **Investigational arm**
  - **Decitabine 20 mg/m^2 x 5 days (1st and odd cycles) every 8 weeks; sapacitabine 300 mg b.i.d. x 3 consecutive days/week x 2 weeks (2nd and even cycles) every 8 weeks**
- **Control arm**
  - **Decitabine at 20 mg/m^2 x 5 days every 4 weeks**
- **Primary endpoint: overall survival at 444 deaths (92% of events)**
  - **Prespecified subgroups: AHD vs de novo; WBC ≥ 10 vs < 10 x 10^9/L; marrow blast ≥ 50% vs < 50%; unfavorable CG (SWOG) vs other**
- **Secondary endpoints: remission rates and duration; hospitalizations and transfusions; 1-year survival**

Patient and Disease Characteristics

	Sapacitabine/decitabine N=241	Decitabine N=241
Age, median: years (range)	78 (70-92)	77 (70-92)
% 70 – 79 years	61	70
% ≥ 80 years	39	30
ECOG 2, %	21	25
Physician recommended low intensity Rx, %	92	91
Physician recommended intensive Rx, patient refused, %	7	9
Type of AML, %		
De novo	68	64
Prior AHD	27	29
Rx-related	5	7
WBC ≥ 10 x 10^9/L	35	33
Marrow blasts > 50%, %	46	45
Unfavorable CG, %	41	39

Overall Survival – ITT Population



Additional Endpoints – ITT Population

	Sapacitabine/decitabine N=241	Decitabine N=241
CR, % [95% CI] Time to response, median (mos) Response duration, median (mos) [95% CI]	17 [12, 22] 2.6 9.5 [6.1, 13.6]	11 [17, 15] 3.4 10.4 [8.1, 14.0]
1-year survival, %	34	35
Tx-free weeks on Rx, median	13	12.3
Average number of Tx RBC and plts/wk, median	1.2	1.1
Number of hospitalized days, median	15	14
% days alive out of hospital during 360 days after randomization	88	84

Treatment Exposure

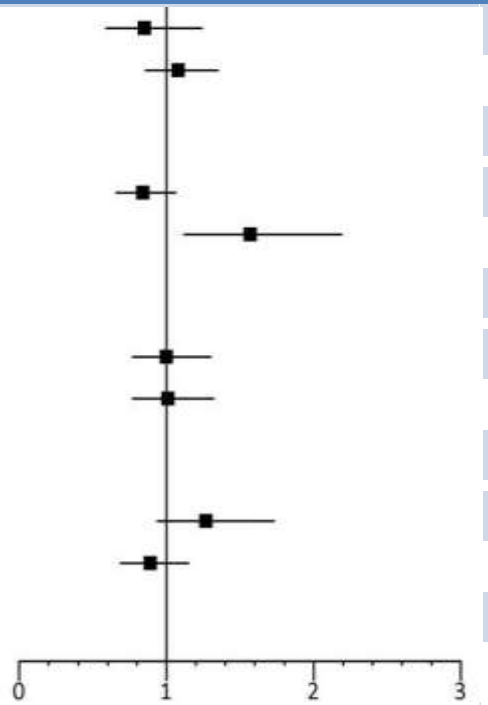
	Sapacitabine/decitabine N=236	Decitabine N=233
Total number of cycles administered	1493	1439
Number of cycles/patient, median (range)	3 (1-70)	3 (1-46)
% of patients who received:		
1 cycle (only decitabine in both arms)	23	24
2 cycles	17	18
3 cycles	14	9
4 cycles	9	11
5 or more cycles	37	37
Rx duration in mos, median (range)	3.5 (0-68)	3.3 (0-49)
% Patients with dose reduction of decitabine	8	7
% Patients with dose reduction of sapacitabine	18	-

Safety Profile

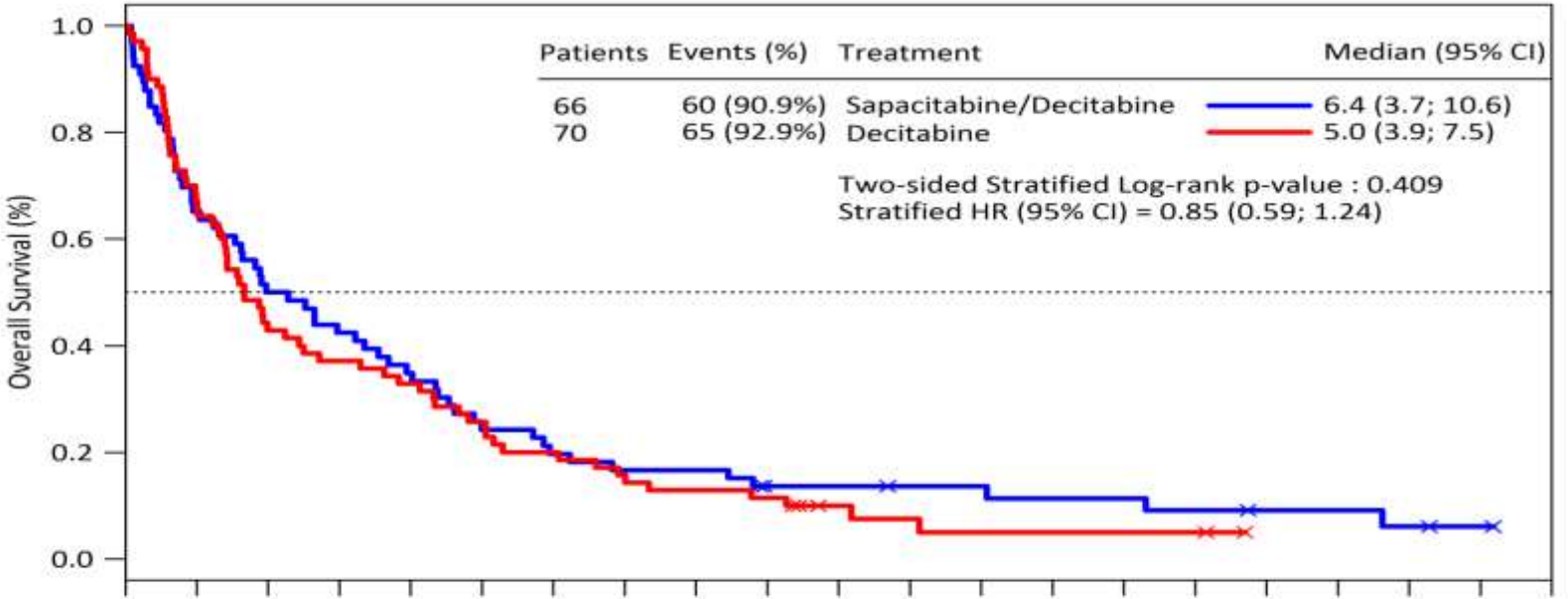
Grade 3/4 Emergent AE in >10%, regardless of causality, %	Sapacitabine/decitabine N=236	Decitabine N=233
Anemia	48	44
Neutropenia	44	37
Thrombocytopenia	52	51
Febrile neutropenia	26	27
Pneumonia	27	29
Sepsis or septic shock	8	11
Hyponatremia	6	11
Number of patients with at least 1 serious AE, regardless of causality, %	84 (19% only decitabine as 1st course)	81
AE with outcome of death, regardless of causality, %	36 (13% only decitabine as 1st course)	24

Survival - Subgroup Analysis

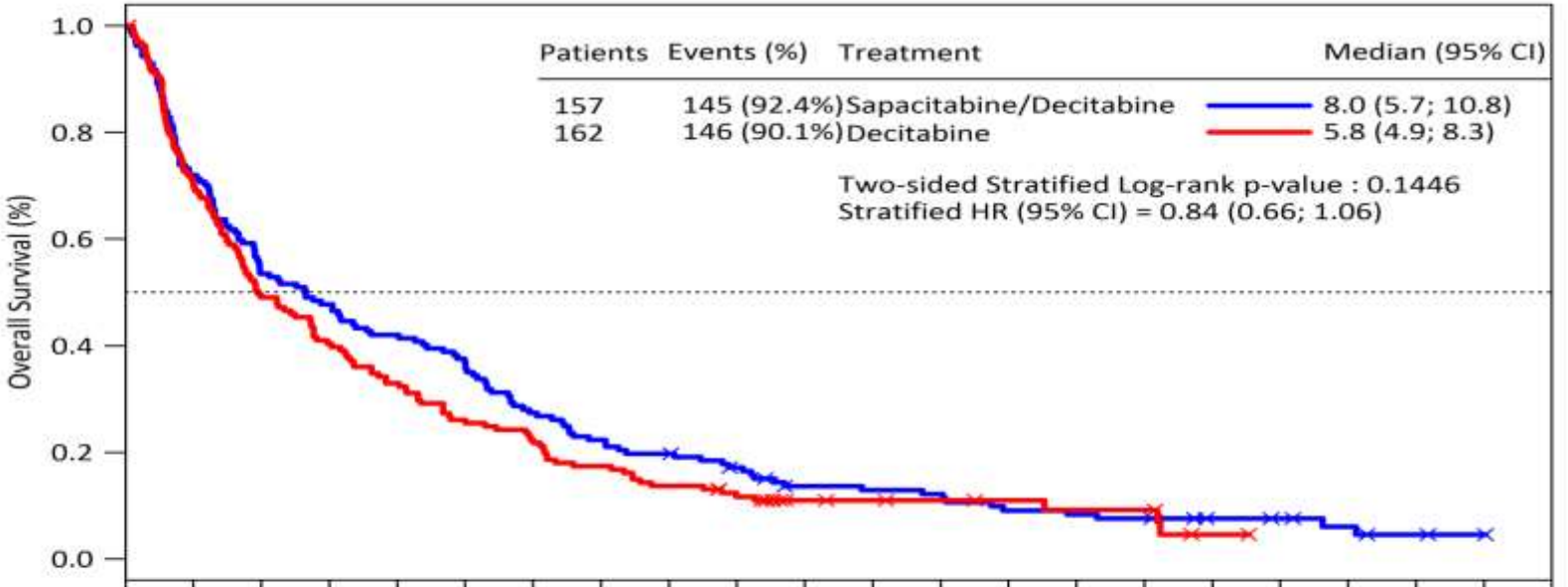
Exploratory Subgroup	Stratified HR [95% CI]	Sap/Dec better ← → Decitabine better	Sap/Dec Event/ N	Sap/Dec Median, mos	Decitabine Event/ N	Decitabine Median, mos	P
Antecedent MDS/MPD	0.85 [0.59, 1.24]		60/66	6.4	65/70	5.0	0.409
De novo / Rx-related	1.08 [0.86, 1.35]		166/175	5.9	153/171	6.7	0.515
Interaction test	*P=0.396*						
WBC <10,000	0.84 [0.66, 1.06]		145/157	8.0	146/162	5.8	0.145
WBC ≥10,000	1.57 [1.12, 2.19]		81/84	3.8	72/79	5.5	0.007
Interaction test	*P=0.011*						
BM Blasts <50%	1.00 [0.77, 1.30]		113/123	9.5	114/131	9.8	0.986
BM Blasts ≥50%	1.01 [0.77, 1.32]		113/118	3.9	104/110	3.9	0.957
Interaction test	*P=0.885*						
CG unfavorable	1.27 [0.94, 1.73]		97/100	3.8	87/94	5.7	0.116
CG other	0.89 [0.69, 1.15]		129/141	8.2	131/147	5.7	0.377
Interaction test	*P=0.142*						



Survival - Prior AHD



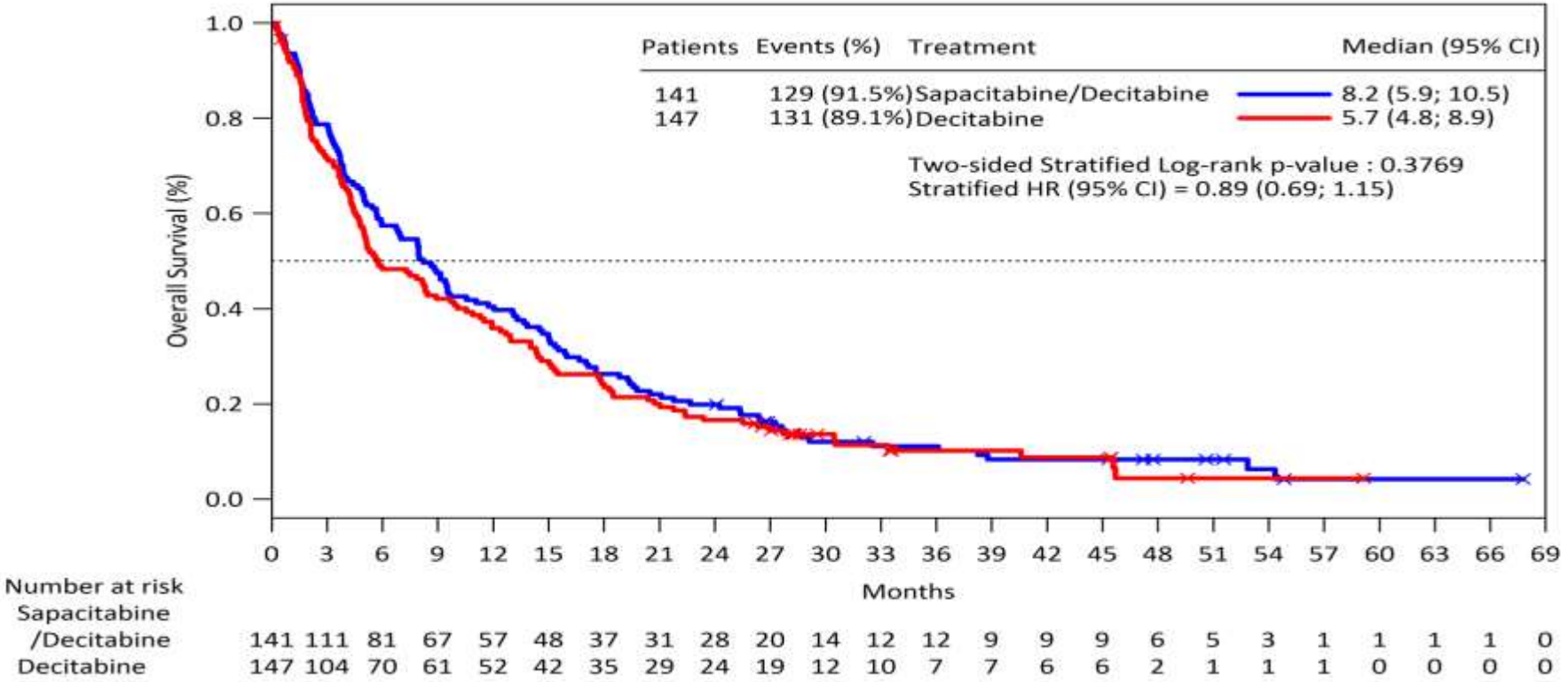
Survival - Baseline WBC <10,000



Number at risk

Sapacitabine /Decitabine	157	113	84	75	66	58	43	35	31	25	18	17	16	12	11	10	7	6	4	2	1	0
Decitabine	162	113	79	65	53	42	36	28	22	17	9	8	7	6	5	5	1	0	0	0	0	0

Survival - CG not Unfavorable



Subgroup Analyses: CR and Durations

	Sapacitabine/decitabine	Decitabine	Sapacitabine/decitabine	Decitabine
	Antecedent MDS/MPD – Yes		*Antecedent MDS/MPD – No*	
Patients (N)	*66*	*70*	*175*	*171*
CR	16.7% (p=0.0398)	5.7%	16.6%	12.9%
CRD median (mos)	9.5	7.1	8.5	10.4
	WBC <10,000		*WBC ≥ 10,000*	
Patients (N)	*157*	*162*	*84*	*79*
CR	21.0% (p=0.0017)	8.6%	8.3%	15.2% (p=0.1819)
CRD median (mos)	12.9	10.4	4.7	10.1
	CG other than unfavorable		*Unfavorable CG*	
Patients (N)	*141*	*147*	*100*	*94*
CR	19.9% (p=0.1622)	11.6%	12.0%	9.6%
CRD median (mos)	9.5	12.1	9.7	10.4

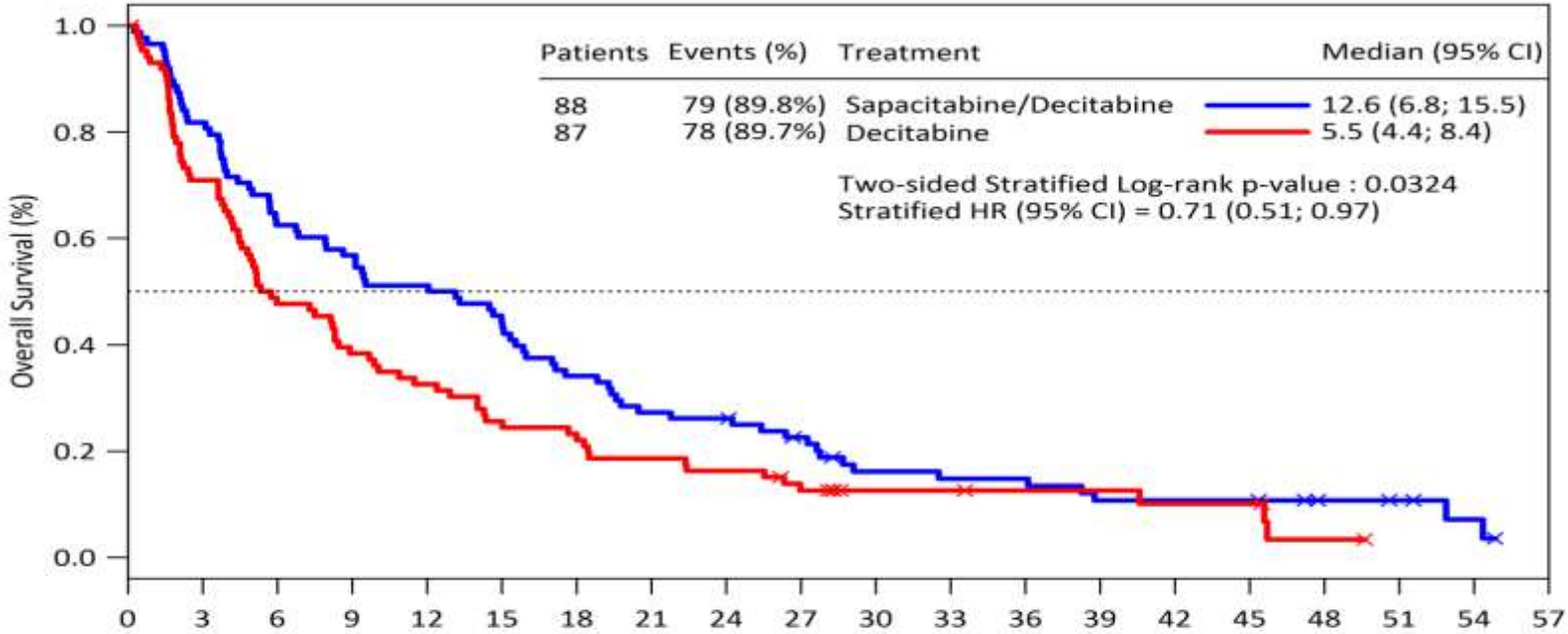
Summary

- **Sapacitabine administered in alternating cycles with decitabine did not improve overall survival**
- **Stratified subgroup analyses suggested that sapacitabine/decitabine regimen may have clinically relevant benefit in patients with baseline WBC <10,000**
  - **median OS: 8.0 vs 5.8 months; HR 0.84 (p=0.14)**
  - **CR rates: 21% vs 8.6% (p=0.0017); durable responses**

Summary *(cont.)*

- **Clinically relevant benefit in baseline WBC <10,000:**
  - **Plausible; high WBC carries poor prognosis; all phase 3 hypomethylating agent studies excluded patients with high WBC**
  - **Addresses AML heterogeneity**
  - **Improves outcome of low-intensity Rx of decitabine**
  - **Oral sapacitabine more convenient in elderly with similar safety profile**
  - **Statistical robustness of subgroup results currently being investigated**
  - **Ongoing analysis to identify optimal cut-off point of baseline WBC for best treatment effect**

Survival - Baseline WBC <10,000 & CG not Unfavorable



Number at risk																			
Sapacitabine /Decitabine	88	72	55	50	45	39	30	24	23	18	12	11	11	8	8	8	5	4	2	0
Decitabine	87	61	41	33	28	22	20	16	14	10	6	6	5	5	4	4	1	0	0	0