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

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Background: Sapacitabine is a novel oral nucleoside analogue with a unique ability to induce single-strand DNA breaks after incorporation into DNA, leading to production of double-strand DNA breaks and/or G2 cell cycle arrest. In AML cell lines, the active metabolite of sapacitabine, CNDAC, is synergistic with hypomethylating agents (HMAs) particularly when treated with HMAs first. In a pilot study, there were 6 CRs and 2 PRs in 25 patients treated with sapacitabine in alternating cycles with decitabine. This global randomized phase 3 study evaluated the survival benefit of this treatment strategy vs. decitabine monotherapy. *Methods:* Decitabine 20 mg/m^2 was administered intravenously daily x 5 days of a 4-week cycle (for the control arm and odd cycles of the study arm) alternating with sapacitabine 300 mg p.o. *b.i.d.* x 3 days/week x 2 weeks of a 4-week cycle (even cycles of the study arm). The safety of these doses was further evaluated in the lead-in phase of the phase 3 study to confirm the findings from the pilot study. Eligible patients were ≥70 years with untreated AML and unsuitable for or unwilling to receive standard induction chemotherapy. Patients who had received HMAs for prior MDS or MPD were excluded. *Results:* For 482 patients randomized to receive decitabine/sapacitabine (n=241) vs. decitabine only (n=241), randomization was stratified by the presence of antecedent MDS or MPN, peripheral white blood cell count (WBC <10,000 vs. ≥10,000) and bone marrow blast percentage (≥50% vs. < 50%). Median age was 77 years (range 70-90), and 317 patients had *de novo* AML (66%), 165 secondary AML (34%). WBC was ≥10,000 in 161 patients (33%) and >40,000 in 59 patients (12%); 194 patients (40%) had unfavorable cytogenetic risk by SWOG criteria. Disease

characteristics were well balanced in both arms. In total, 13.7% of patients achieved CR, more on the study arm vs. control (16.6% vs. 10.8%). A total of 37.3% treated patients received ≥5 cycles of treatment, similar on both arms, as were 30- and 60-day death rates. Median overall survival was 5.9 months on the study arm vs. 5.7 months on control arm, which did not reach a statistically significant difference. In the subgroup of patients with <10,000 WBC (n=321), median overall survival was higher on the study arm vs. control arm (8.0 months vs. 5.8 months), as was CR rate (21.5% vs. 8.6%). Grade 3 or higher adverse events (regardless of causality) that occurred in >10% patients were thrombocytopenia, anemia, neutropenia, pneumonia, febrile neutropenia, sepsis, and disease progression. *Conclusion:* The regimen of sapacitabine administered in alternating cycles with decitabine was active and well tolerated but it did not significantly improve overall survival as compared to decitabine monotherapy. Further analyses are being conducted to characterize the subgroups of patients who appeared to have benefited from this treatment regimen and the potential cost savings associated with the use of an oral drug.

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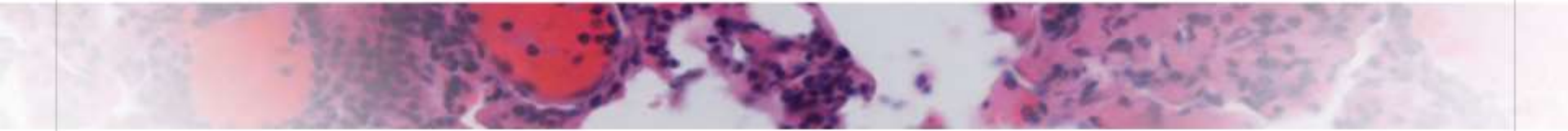

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Blood 130: abst 891; 2017

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**

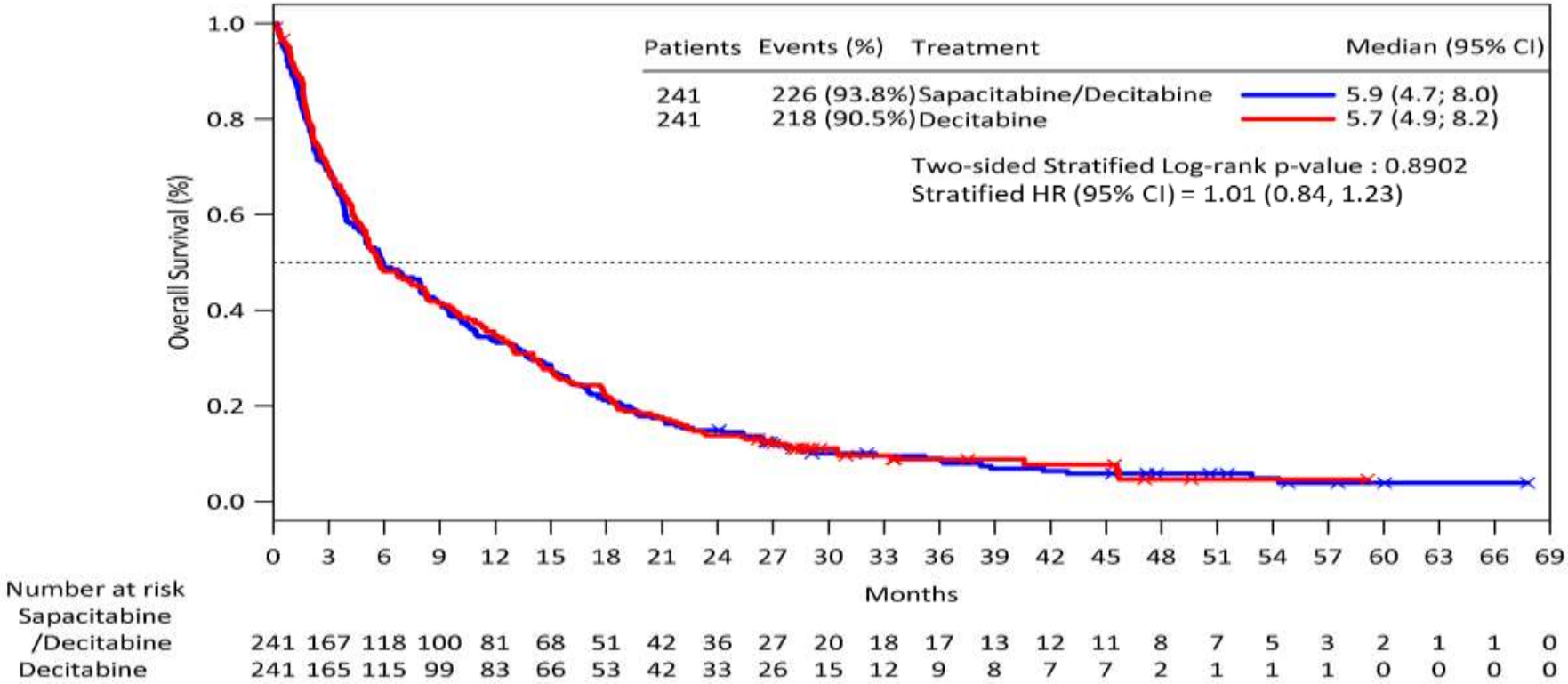
Treatment and Endpoints

- **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

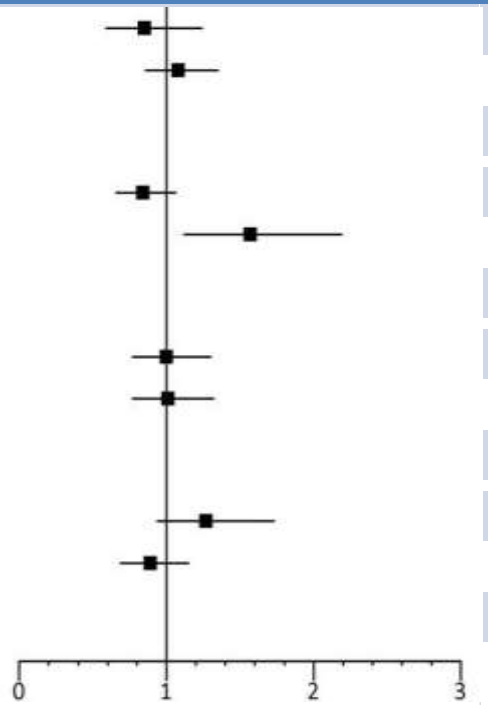
	Sapacitabine/decitabine N=236	Decitabine N=233
Total number of cycles administered	1493	1439
Number of cycles/patient, median (range)	3 (1-70)	3 (1-46)
% of patients who received:		
1 cycle (only decitabine in both arms)	23	24
2 cycles	17	18
3 cycles	14	9
4 cycles	9	11
5 or more cycles	37	37
Rx duration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

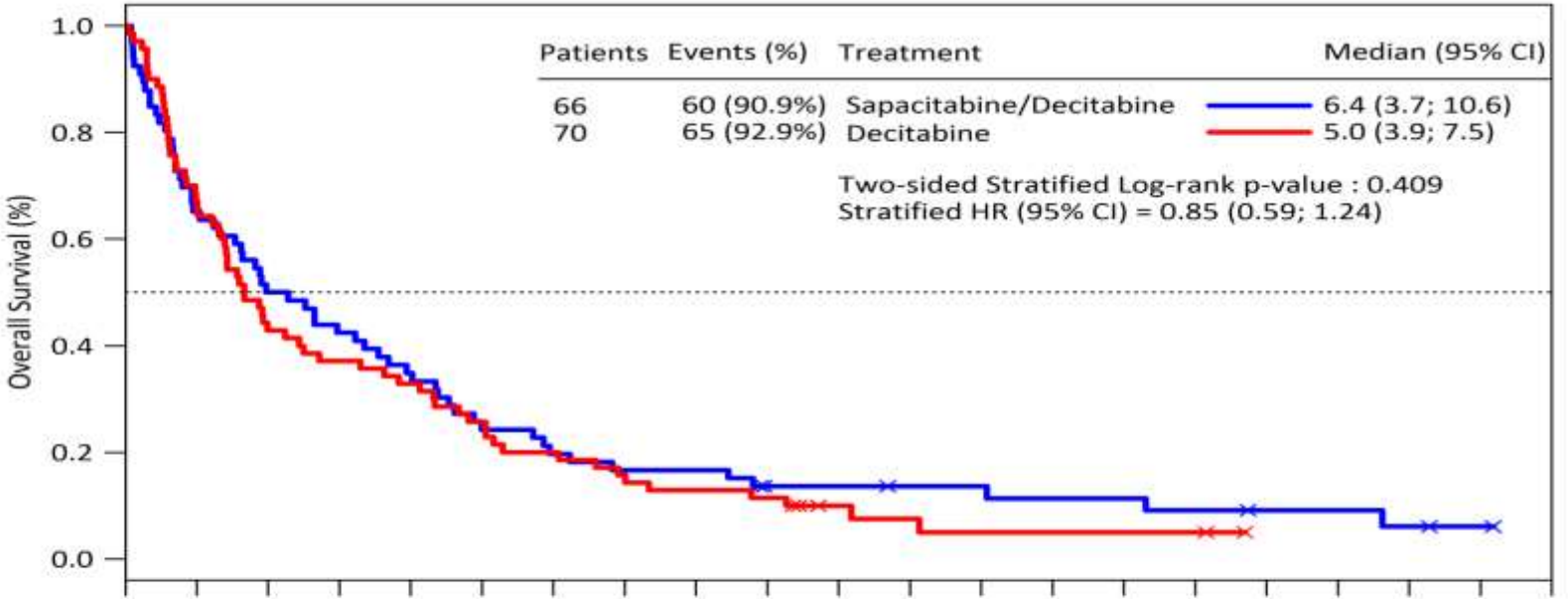
Grade 3/4 Emergent AE in >10%, regardless of causality, %	Sapacitabine/decitabine N=236	Decitabine N=233
Anemia	48	44
Neutropenia	44	37
Thrombocytopenia	52	51
Febrile neutropenia	26	27
Pneumonia	27	29
Sepsis or septic shock	8	11
Hyponatremia	6	11
Number of patients with at least 1 serious AE, regardless 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

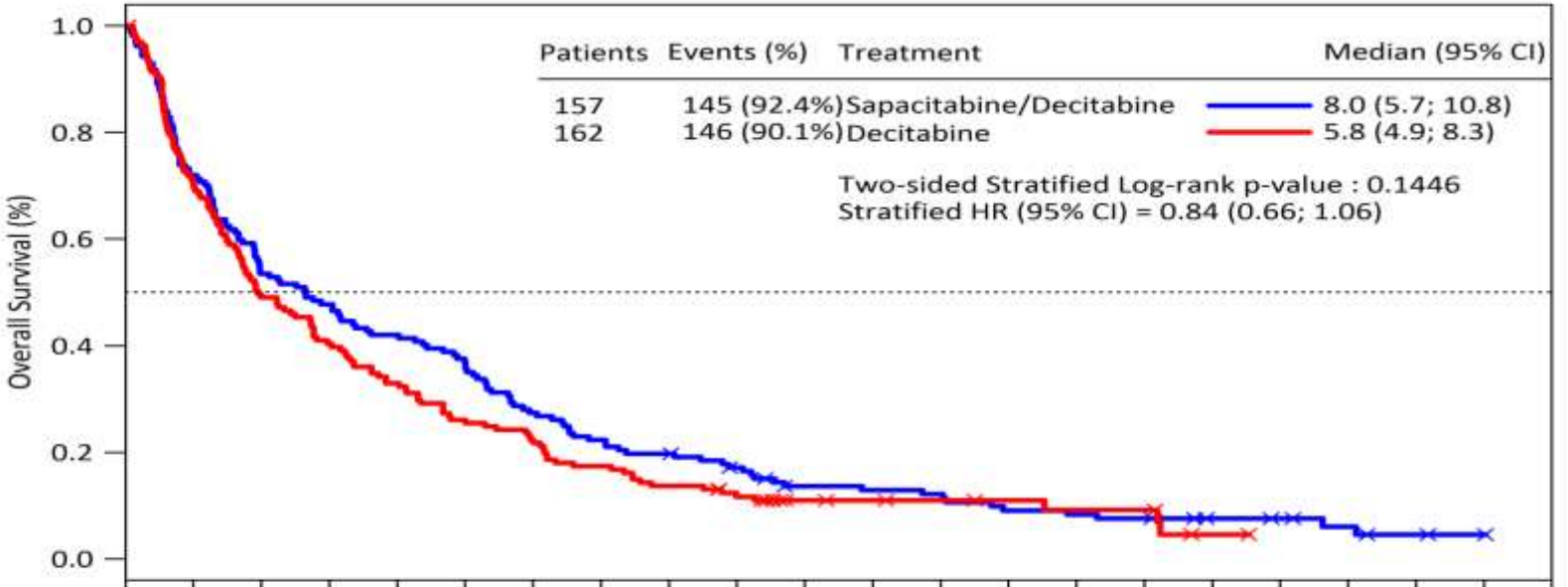
Exploratory Subgroup	Stratified HR [95% CI]	Sap/Dec better ← → Decitabine better	Sap/Dec Event/ N	Sap/Dec Median, mos	Decitabine Event/ N	Decitabine Median, mos	P
Antecedent MDS/MPD	0.85 [0.59, 1.24]		60/66	6.4	65/70	5.0	0.409
De novo / Rx-related	1.08 [0.86, 1.35]		166/175	5.9	153/171	6.7	0.515
Interaction 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



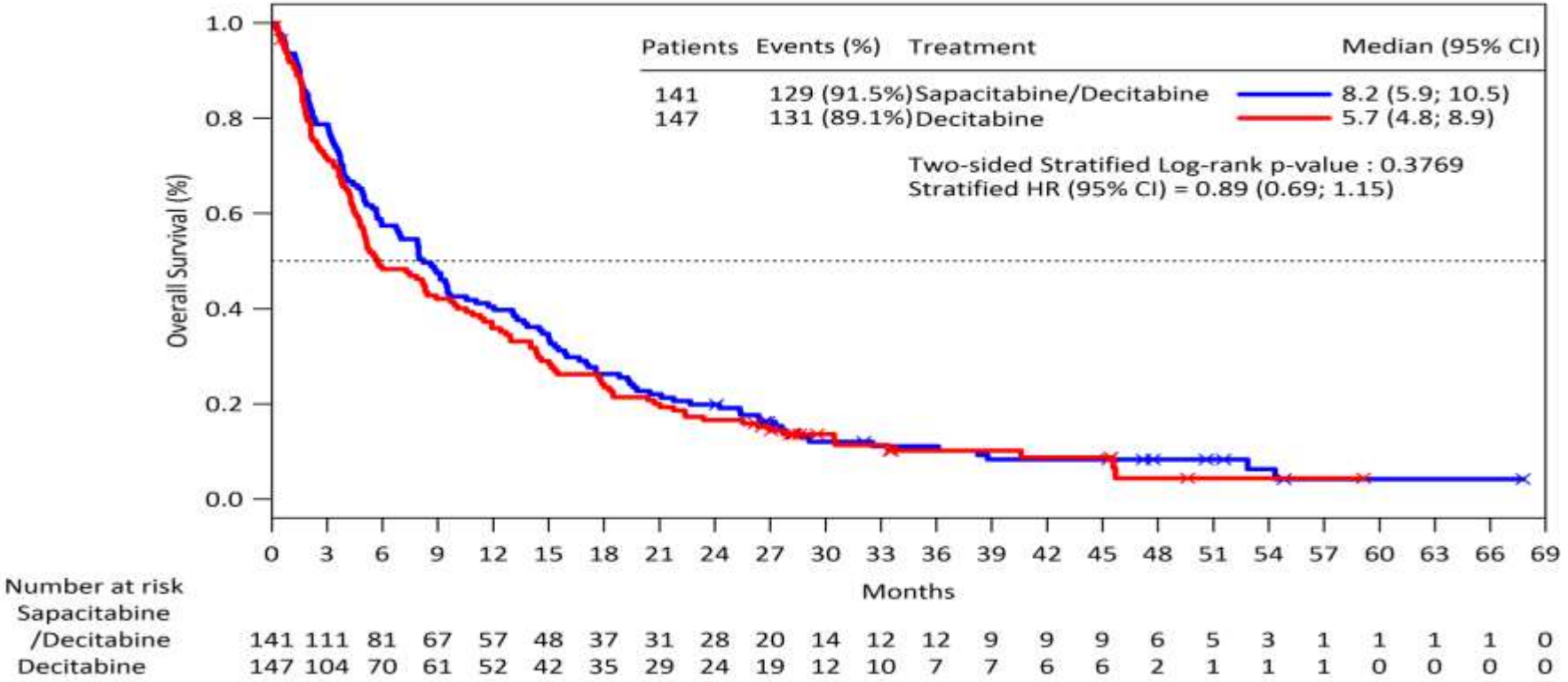
Survival - Baseline WBC <10,000



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

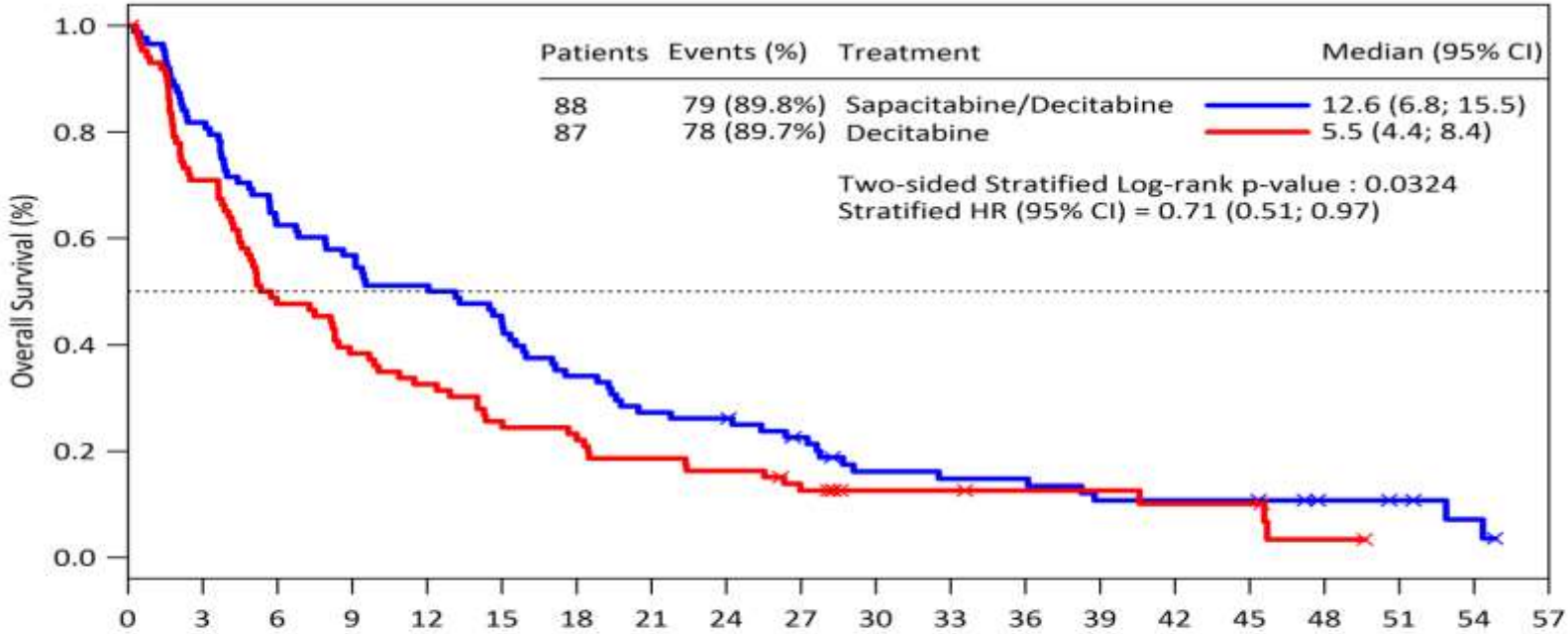
Summary

- **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