A Randomized, Open-Label, Phase 2 Study of Selinexor Versus Physician's Choice (PC) In Older Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML)

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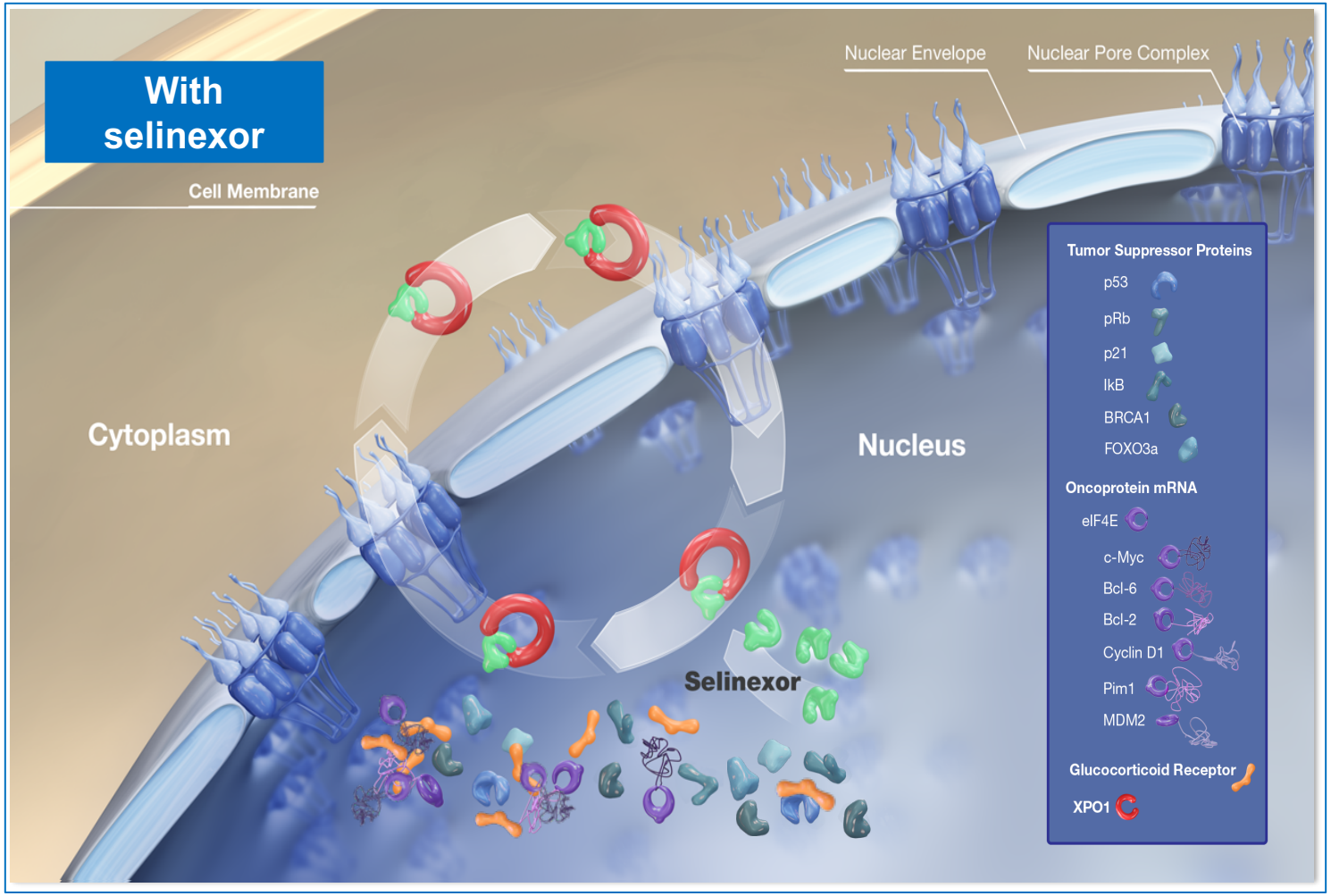
Selinexor – Mechanism of Action[1-2]



[1]*Ranganathan, Blood 2015,* [2]*Brunetti, Cancer Cell 2018*

Exportin 1 (XPO1) is the major nuclear exporter for:

- Tumor suppressor proteins (TSPs, e.g, p53, IκB, FOXO)
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)

Elevated XPO1 Expression:

- Enhances proto-oncoprotein translation
- Correlates with poor AML patient survival

Selinexor is an oral selective inhibitor of XPO1 that:

- Reactivates TSP's and blocks proto-oncoprotein translation
- Increases p53, reduces Flt3, c-KIT and Mcl-1 expression in AML cells
- Selectively kills AML cells but not normal hematopoietic cells

SOPRA Study Design

Selinexor in **O**lder **P**atients with **R**elapsed **A**ML (**SOPRA**): A randomized, open label, Phase 2 study of selinexor *versus* specified physician's choice (PC) in patients ≥ 60 years old with relapsed/refractory Acute Myeloid Leukemia (AML) who are ineligible for intensive chemotherapy and/or transplantation

Objectives:

- Primary Endpoint: determine the overall survival (OS) of selinexor compared to PC
- Secondary Endpoints: overall response rate (ORR), disease control rate (DCR), safety

Patient Population:

- Patients age ≥ 60 years with relapsed/refractory AML of any type except for acute promyelocytic leukemia (APL; AML M3), with relapsed or refractory AML, who have not undergone and are not eligible for stem cell transplantation, and are unfit for intensive chemotherapy

Intent to Treat (ITT) Population, Safety Population, and Randomization:

- The intent-to-treat population (ITT) will consist of all patients who are randomized, to study therapy under **Protocol Versions ≥5.0 (PV ≥5.0)**. The primary analyses of efficacy will consist of *all* patients randomized under PV ≥5.0.
- The safety population will consist of randomized patients who have received at least *one* dose of study treatment
- Patients are randomized 2:1 to selinexor versus PC

SOPRA Study Design (cont.)

Safety Analysis Only

Selinexor (PV ≤4.0)	PC (PV ≤4.0)
Randomized Treatment **55 mg/m^2 BIW** (n=71) **60 mg BIW** (n=27)	**Randomized PC** (n=44)

ITT Population – Safety & Efficacy Analyses

Selinexor (PV ≥5.0)	PC (PV ≥5.0)
Randomized Treatment **60 mg BIW** (n=118)	**Randomized PC** (n=57)

Physician's Choice Treatment Options

1. Best supportive care (BSC) including blood product transfusions, antimicrobials, growth factors as needed, and hydroxyurea; or
2. BSC + hypomethylating agent: azacitidine or decitabine; or
3. BSC + low dose cytosine arabinoside (Ara-C)

Randomization Stratification Factors – ITT Population	
Duration of First CR on Prior Therapy	≤6 months versus >6 months
Number of Prior Therapies	1 versus >1
Peripheral Leukemic Blast Count	<10,000/µL versus ≥10,000/µL

Patient Characteristics – ITT Population

Characteristic	Selinexor (N=118†)	PC (N=57†)
Age (years), median	**73**	**74**
Male : Female	72 (61%) : 46 (39%)	41 (72%) : 16 (28%)
Number of Prior Regimens, median (range)	**2 (1-8)**	**3 (1-9)**
-Chemotherapy	77 (65%)	35 (61%)
-Targeted Therapy	7 (6%)	--
-Hypomethylating Agent (HMA)	117 (99%)	55 (97%)
-Other	2 (2%)	1 (2%)
Baseline ECOG Performance Status		
-0	29 (25%)	8 (14%)
-1	67 (57%)	24 (42%)
-2	16 (14%)	11 (19%)
-Unknown	6 (5%)	14 (25%)
Baseline Disease Risk Assessment		
-Favorable	3 (3%)	1 (2%)
-Intermediate I	36 (31%)	22 (39%)
-Intermediate II	32 (27%)	12 (21%)
-Adverse	34 (29%)	17 (30%)
-Unknown	13 (11%)	5 (9%)

Patient Characteristics – ITT Population (cont.)

Characteristic	Selinexor (N=118†)	PC (N=57†)
Prior Myelodysplastic Syndrome (MDS)	13 (11%)	3 (5%)
TP53 Mutations	14 (12%)	3 (5%)
Absolute Neutrophil Count (ANC) <0.5 x 10^9/L (Grade 4)	50 (42%)	12 (21%)
Patients Randomized but not Treated	2 (2%)	12 (21%)

†In the selinexor arm, 2 patients were not dosed and 1 patient was randomized to selinexor but received BSC excluded from the safety population. In the PC arm, 12 (21%) patients who were not dosed excluded from the safety population.

SOPRA Treatment-Emergent Adverse Events in ≥10% Patients

Preferred Term / Grade	Selinexor 60 mg (PV ≥5.0)	PC (PV ≥5.0)	Selinexor 55 mg/m^2 (PV ≤4.0)	Selinexor 60 mg (PV ≤4.0)	PC (PV ≤4.0)	Total
Hematological	**(N=115)**	**(N=45)**	**(N=71)**	**(N=27)**	**(N=39)**	**(N=297)**
Thrombocytopenia						
Grade 3	8 (7.0)	3 (6.7)	2 (2.8)	--	3 (7.7)	16 (5.4)
Grade 4	25 (21.7)	6 (13.3)	26 (36.6)	8 (29.6)	14 (35.9)	79 (26.6)
Total – (G1-4)	**39 (33.9)**	**11 (24.4)**	**29 (40.8)**	**8 (29.6)**	**18 (46.2)**	**105 (35.4)**
Anemia						
Grade 3	21 (18.3)	8 (17.8)	18 (25.4)	4 (14.8)	14 (35.9)	65 (21.9)
Grade 4	1 (0.9)	1 (2.2)	3 (4.2)	--	1 (2.6)	6 (2.0)
Total – (G1-4)	**30 (26.1)**	**12 (26.7)**	**22 (31.0)**	**7 (25.9)**	**17 (43.6)**	**88 (29.6)**
Febrile Neutropenia						
Grade 3	18 (15.7)	14 (31.1)	17 (23.9)	4 (14.8)	8 (20.5)	61 (20.5)
Grade 4	4 (3.5)	--	5 (7.0)	--	--	9 (3.0)
Grade 5	2 (1.7)	1 (2.2)	1 (1.4)	--	--	4 (1.3)
Total – (G1-5)	**25 (21.7)**	**16 (35.6)**	**24 (33.8)**	**5 (18.5)**	**10 (25.6)**	**80 (26.9)**
Neutropenia						
Grade 3	2 (1.7)	1 (2.2)	4 (5.6)	1 (3.7)	--	8 (2.7)
Grade 4	13 (11.3)	6 (13.3)	2 (2.8)	4 (14.8)	10 (25.6)	35 (11.8)
Total – (G1-4)	**18 (15.7)**	**9 (20.0)**	**6 (8.5)**	**5 (18.5)**	**10 (25.6)**	**48 (16.2)**
Gastrointestinal						
Nausea						
Grade 3	2 (1.7)	--	3 (4.2)	2 (7.4)	1 (2.6)	8 (2.7)
Total – (G1-3)	**68 (59.1)**	**8 (17.8)**	**41 (57.7)**	**16 (59.3)**	**13 (33.3)**	**146 (49.2)**
Anorexia						
Grade 3	12 (10.4)	--	10 (14.1)	3 (11.1)	1 (2.6)	26 (8.8)
Total – (G1-3)	**64 (55.7)**	**7 (15.6)**	**41 (57.7)**	**12 (44.4)**	**9 (23.1)**	**133 (44.8)**

SOPRA Treatment-Emergent Adverse Events in ≥10% Patients

Preferred Term / Grade	Selinexor 60 mg (PV ≥5.0)	PC (PV ≥5.0)	Selinexor 55 mg/m^2 (PV ≤4.0)	Selinexor 60 mg (PV ≤4.0)	PC (PV ≤4.0)	Total
Gastrointestinal	**(N=115)**	**(N=45)**	**(N=71)**	**(N=27)**	**(N=39)**	**(N=297)**
Diarrhea						
Grade 3	7 (6.1)	--	2 (2.8)	--	--	9 (3.0)
Grade 4	--	--	--	1 (3.7)	--	1 (0.3)
Total – (G1-4)	**46 (40.0)**	**6 (13.3)**	**18 (25.4)**	**13 (48.1)**	**8 (20.5)**	**91 (30.6)**
Constipation						
Grade 3	1 (0.9)	--	--	--	1 (2.6)	2 (0.7)
Total – (G1-3)	**25 (21.7)**	**15 (33.3)**	**20 (28.2)**	**8 (29.6)**	**16 (41.0)**	**84 (28.3)**
Vomiting						
Grade 3	3 (2.6)	--	3 (4.2)	1 (3.7)	--	7 (2.4)
Total – (G1-3)	**32 (27.8)**	**6 (13.3)**	**21 (29.6)**	**10 (37.0)**	**7 (17.9)**	**76 (25.6)**
Constitutional						
Fatigue						
Grade 3	17 (14.8)	1 (2.2)	9 (12.7)	--	3 (7.7)	30 (10.1)
Grade 4	--	--	1 (1.4)	--	--	1 (0.3)
Total – (G1-4)	**53 (46.1)**	**13 (28.9)**	**34 (47.9)**	**13 (48.1)**	**15 (38.5)**	**128 (43.1)**
Dyspnoea						
Grade 3	5 (4.3)	--	2 (2.8)	1 (3.7)	1 (2.6)	9 (3.0)
Grade 4	--	--	--	1 (3.7)	--	1 (0.3)
Total – (G1-4)	**26 (22.6)**	**10 (22.2)**	**14 (19.7)**	**6 (22.2)**	**9 (23.1)**	**65 (21.9)**
Asthenia						
Grade 3	7 (6.1)	1 (2.2)	7 (9.9)	2 (7.4)	2 (5.1)	19 (6.4)
Total – (G1-3)	**23 (20.0)**	**5 (11.1)**	**18 (25.4)**	**6 (22.2)**	**6 (15.4)**	**58 (19.5)**

SOPRA Treatment-Emergent Adverse Events in ≥10% Patients

Preferred Term / Grade	Selinexor 60 mg (PV ≥5.0)	PC (PV ≥5.0)	Selinexor 55 mg/m^2 (PV ≤4.0)	Selinexor 60 mg (PV ≤4.0)	PC (PV ≤4.0)	Total
Constitutional	**(N=115)**	**(N=45)**	**(N=71)**	**(N=27)**	**(N=39)**	**(N=297)**
Weight Loss						
Grade 3	--	--	2 (2.8)	--	--	2 (0.7)
Total – (G1-3)	**21 (18.3)**	**3 (6.7)**	**16 (22.5)**	**4 (14.8)**	**3 (7.7)**	**47 (15.8)**
Dizziness						
Grade 3	2 (1.7)	--	2 (2.8)	--	2 (5.1)	6 (2.0)
Total – (G1-3)	**18 (15.7)**	**2 (4.4)**	**13 (18.3)**	**2 (7.4)**	**8 (20.5)**	**43 (14.5)**
Other						
Pyrexia						
Grade 3	2 (1.7)	1 (2.2)	2 (2.8)	--	2 (5.1)	7 (2.4)
Grade 5	--	--	1 (1.4)	--	--	1 (0.3)
Total – (G1-5)	**32 (27.8)**	**13 (28.9)**	**12 (16.9)**	**5 (18.5)**	**15 (38.5)**	**77 (25.9)**
Hyponatraemia						
Grade 3	11 (9.6)	--	18 (25.4)	4 (14.8)	1 (2.6)	34 (11.4)
Grade 4	--	--	1 (1.4)	--	--	1 (0.3)
Total – (G1-4)	**25 (21.7)**	**1 (2.2)**	**28 (39.4)**	**6 (22.2)**	**3 (7.7)**	**63 (21.2)**
Edema Peripheral						
Grade 3	1 (0.9)	--	--	--	--	1 (0.3)
Total – (G1-3)	**21 (18.3)**	**5 (11.1)**	**17 (23.9)**	**5 (18.5)**	**10 (25.6)**	**58 (19.5)**
Epistaxis						
Grade 3	3 (2.6)	1 (2.2)	--	1 (3.7)	1 (2.6)	6 (2.0)
Total – (G1-3)	**25 (21.7)**	**8 (17.8)**	**14 (19.7)**	**3 (11.1)**	**7 (17.9)**	**57 (19.2)**

Treatment-Emergent Adverse Events as of February 8, 2018

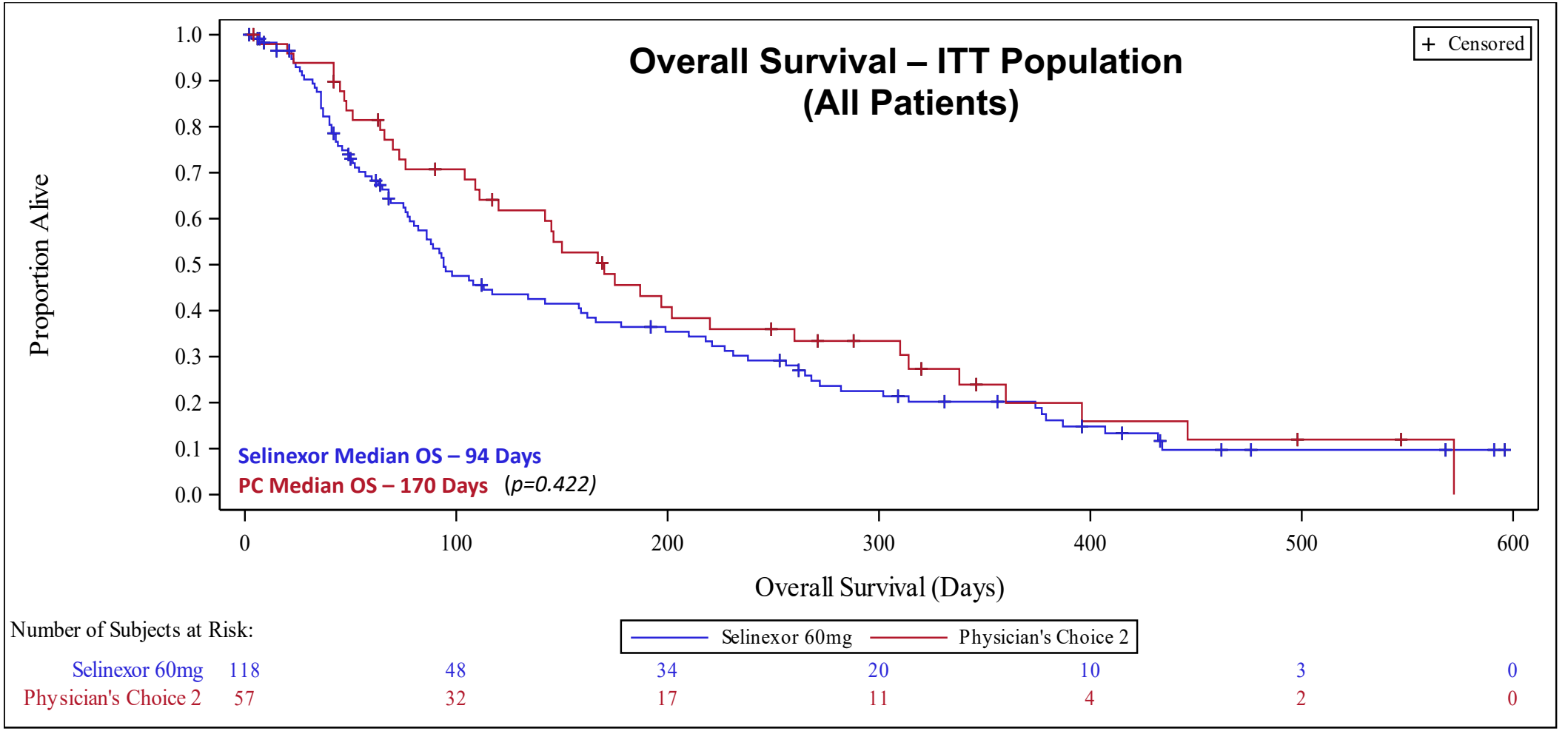
SOPRA Treatment-Emergent Adverse Events in ≥10% Patients

Treatment-Emergent Adverse Events

- Of the 317 randomized patients, 297 patients received at least 1 dose of study drug and were included in the safety population
- When the selinexor dose was changed to a fixed dose of 60 mg from 55 mg/m^2, the frequencies of common TEAEs were reduced
- For the ITT (PV ≥5.0) safety population, among the 115 patients in the selinexor 60 mg dose group, the most common TEAEs included nausea, anorexia, fatigue, diarrhea, thrombocytopenia, vomiting, and pyrexia
- Among the 45 patients in the PC (PV ≥5.0) group, the most common TEAEs included febrile neutropenia, constipation, fatigue, pyrexia, anemia, thrombocytopenia, and dyspnea.

Selinexor *vs.* PC Overall Survival

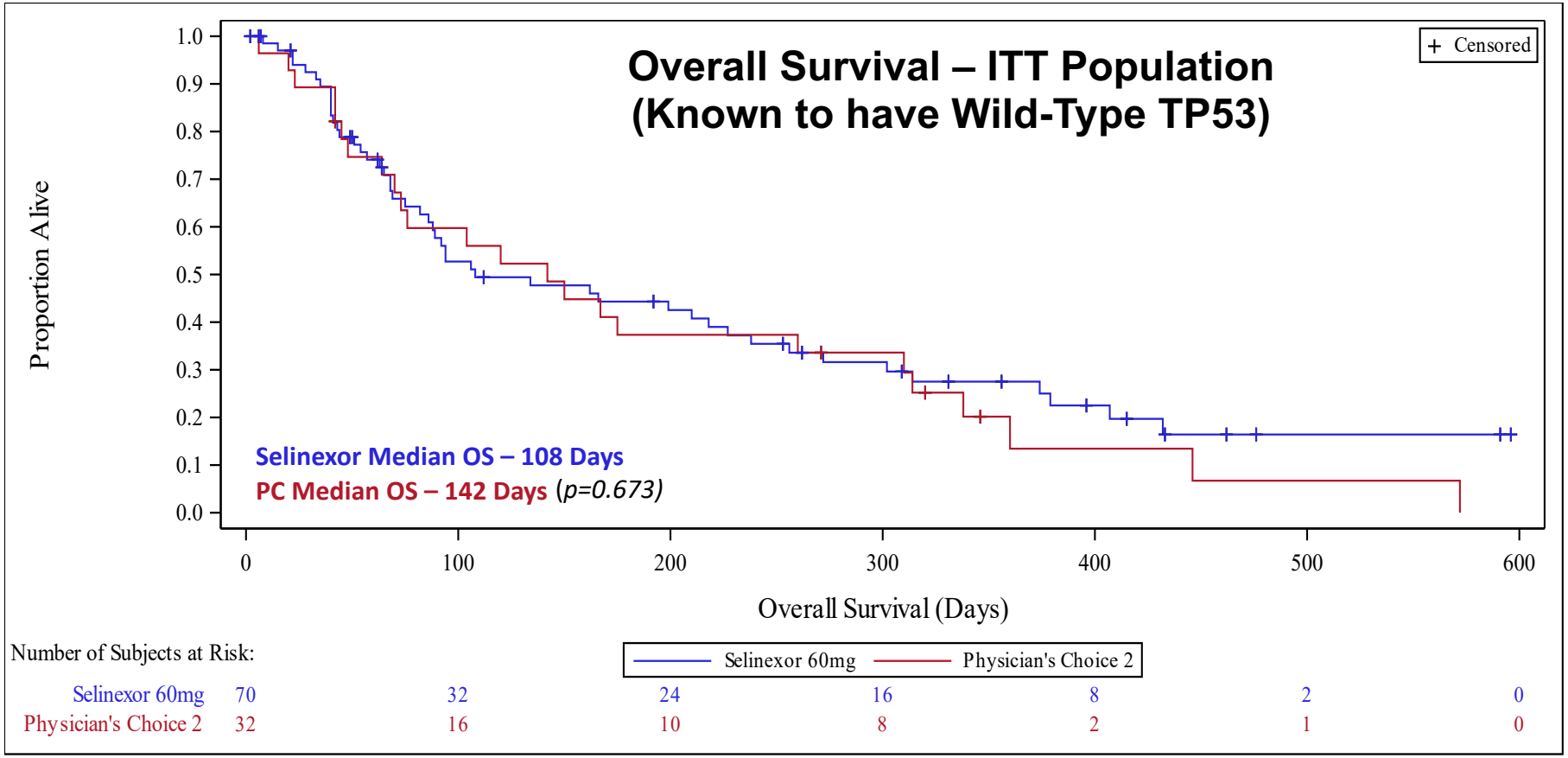
A



Median overall survival analyzed in the ITT population (PV ≥5.0) was not significantly different in patients treated with selinexor (**94** days) compared to patients treated with PC (**170** days) (*p=0.422)*; stratified log-rank test. The hazard ratio was **1.18** with a 95% CI (0.79, 1.75).

Selinexor *vs.* PC Overall Survival (TP53 Mutation Status)

B



Patients randomized to selinexor had a numerically higher percentage of patients with TP53 abnormalities (12%) compared to the PC arm (5%). TP53 mutation or TP53 deletion correlates with significantly inferior complete remission duration and OS in patients with AML (*Kadia 2016*). For this reason an ad-hoc analysis of OS in patients with known wild-type TP53 (no mutations) was performed, 70 patients on the selinexor arm and 32 patients on the PC arm, demonstrated similar survival in selinexor and PC arms (median OS of **108** and **142** days, respectively); the hazard ratio was **0.89** with a 95% CI (0.53, 1.51), (*p=0.673)*; stratified log-rank test.

SOPRA Best Overall Responses

Response	Selinexor (N=118)	PC (N=57)
CR	6 (5.1%)	--
CRi	8 (6.8%)	2 (3.5%)
PR	2 (1.7%)	3 (5.3%)
ORR	16 (13.6%)	5 (8.8%)
DCR	60 (50.8%)	23 (40.4%)
SD	44 (37.3%)	18 (31.6%)
PD	12 (10.2%)	6 (10.5%)
NE*	46 (38.9%)	28 (49.1%)

Responses as of February 8, 2018 as assessed by local investigators according to International Working Group (IWG) criteria. CR=complete remission; CRi=complete remission with incomplete recovery; ORR=overall response rate (CR+CRi+PR); DCR= disease control rate (CR+CRi+PR+SD); PR=partial remission; SD=stable disease; PD=progressive disease; NE=non-evaluable for response. *NE patients include patients randomized but not treated, patients who did not have a post-baseline assessment, and patients who were not assessed a response by their local investigator.

Conclusions

- The primary endpoint was not met and selinexor treatment did not show a significant difference in median OS compared to treatment with physician's choice (PC)
- The numerical imbalances between the two treatment arms indicated that patients in the selinexor group had more adverse risk factors than those in the PC group: higher level of prior MDS and TP53 mutations, lower starting ANC levels
  - In addition, higher numbers of patients randomized to the PC arm withdrew consent prior to receiving therapy (21% *vs* 2% on selinexor)
- There were **11.9%** CR/CRi in patients treated with selinexor versus **3.5%** on PC
  - Patients on selinexor with CR/CRi also showed improved survival (median OS of 397 days, not shown) versus the overall selinexor or PC arms
- Additional studies of selinexor in combination with other therapies in the relapsed/refractory AML setting, as well as in front-line treatment, have shown promising efficacy