ISRAEL SOCIETY OF HEMATOLOGY AND BLOOD TRANSFUSION

kaplan close care

Approach to the Patient with MDS Refractory to Hypomethylating Agents(HMA)

Kalman Filanovsky, MD

Kaplan Medical Center

- 74 year old man, full time working in family restaurant business
- PMH: Obesity, Hypertension, Diabetes, IHD S/P PTCA + stenting X 2 two years ago
- Progressive anemia and fatigue, required 2 units of PRBCs in last 2 months but remained active, walking daily and has good social support
- CBC: Hgb 8.6g/dL, MCV 100, WBC 9.88 K/ul, ANC 5.24 K/ul, PLT 169 K/ul, Blasts- 1%
- LDH 526 (230-480 U/L); normal ferritin, B12 and folate levels
- Bone marrow: Cellularity 60%, Trilineage dysplasia, blasts-12%: WHO 2016- **MDS-EB-2**
- Cytogenetics: 46,XY, t(1;12)(p36;p13), inv(12)(p13q15)[15]

International Prognostic Scoring System (IPSS):most widely used prognostic system

Variable	Score				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (percent)	<5	5 to 10	-	11-20	21 to 30
Karyotype*	Good	Intermediate	Poor	-	-
Cytopenias*	0-1	2/3	-	-	-

Risk group	IPSS score	Median Survival (years) without therapy
Low	0	5.7
Intermediate-1	0.5 to 1.0	3.5
Intermediate-2	1.5-2.0	1.2
High	2.5 to 3.5	0.4

Greenberg et al. Blood 1997;89(6):2079–88.

*** Karytope definitions:**
Good: Normal;-Y; del (5q); del (20q)
Poor: Complex (≥3 abnormalities); abnormal chromosome 7
Intermediate: All others

• Cytopenia definitions:
Red blood cells: Hemoglobin <10 g/dL (100 g/L)
White blood cells: Absolute neutrophil count <1800/microL
Platelets: Platelet count <100,000/microL

Revising International Prognostic Scoring System(IPSS-R)

Prognostic variable	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very Poor
Blast BM%	≤2	>2-<5	-	-	5-10	>10	-
Hb	≥10	-	8-10	<8	-	-	-
Platelets	≥100	50-<100	≤50				
Neutrophils	≥0.8	<0.8	-				

Risk Category	
Very low	≤1.5
Low	>1.5-3.0
Intermediate	>3.0-4.5
High	>4.5-6.0
Very High	>6

Table 3: IPSS-R – survival related to age

Age groups, y	IPSS-Risk categories				
	Very low	Low	Inter-mediate	High	Very high
All	8.8	5.3	3.0	1.6	0.8
≤60	NR	8.8	5.2	2.1	0.9
>60-70	10.2	6.1	3.3	1.6	0.8
>70-80	7.0	4.7	2.7	1.5	0.7
>80	5.2	3.2	1.8	1.5	0.7

Survival (Median, years)

www.ipss-r.com/

Greenberg P et al., Blood, 2012

After 6 cycles of 5-AZA

Silverman et al, Cancer. 2011; 117(12): 2697–2702.

- CBC: Hgb 8.8 g/dL, WBC 10.6K/ul ANC 5.9K/ul, PLT 152K/ul

  Peripheral blood smear- 6% blasts

- BM: Cellularity 90%, **Blasts-20%**

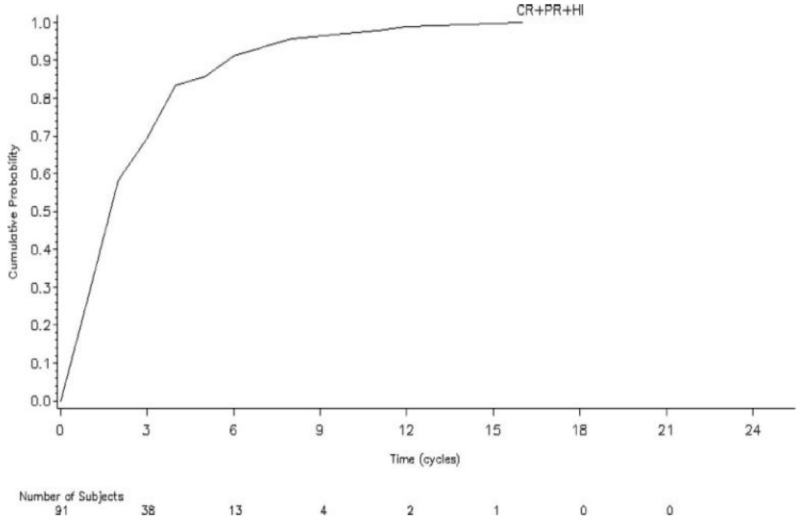


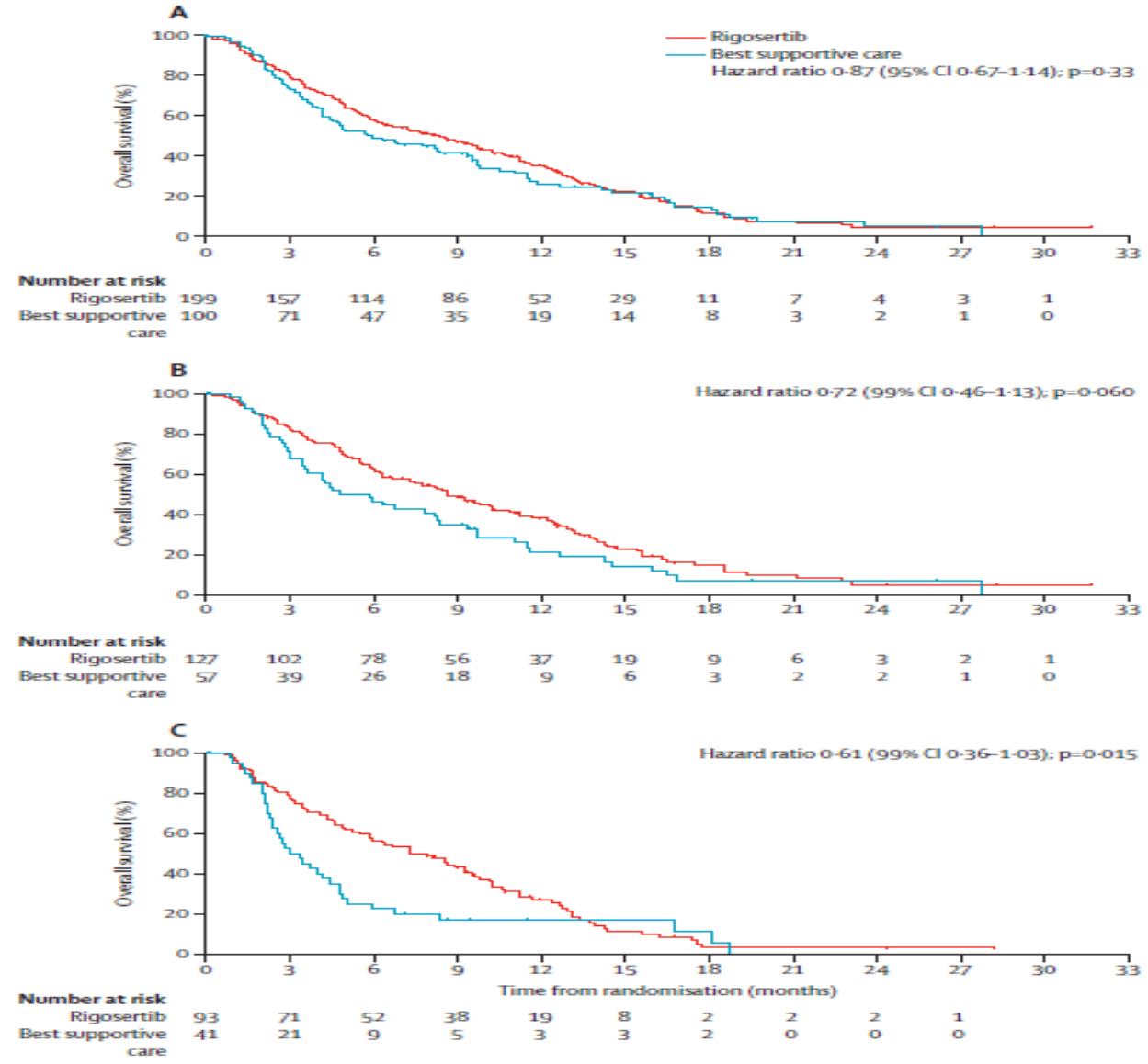
Figure 1.
Time to first response (complete response [CR], partial response [PR], or hematological improvement [HI]) in patients who achieved a response during treatment with azacitidine is shown.

- Cytogenetics: 46,XY,t(1;12)(p36;p13),inv(12)(p13q15)[9]46,**idem,t(13;17)(q14;q21)[6] del7[3]**

Patient with MDS and Complex Karyotype, refractory to HMA with increased blasts.

Still with good performance status

Our second line treatment after HMA failure: Clinical trial (Rigosertib)



erall survival curves for the rigosertib group and best supportive care group
(A) For the intention-to-treat population, (B) patients with primary hypomethylating drug failure, and (C) patient with IPSS-R very high risk. IPSS-R=Revised International Prognostic Scoring System.

Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial

8 week on Rigosertib - Progressive disease

FLT3 TKD- mutated

IDH1/IDH2/FLT3 ITD--WT

Garcia-Manero G et al. Lancet Oncol. 2016

Q: What is your optimal treatment strategy in 2020 for High risk MDS primary refractory to HMA?

1. **Clinical trial**

2. **Intensive chemotherapy followed by hematopoietic stem cell transplantation**

3. **Venetoclax ± HMA (other HMA?)**

4. **Targeting therapy: IDH1/IDH2 or FLT3 inhibitors if mutated (not approved in Israel for this indication)**

5. **Best supportive care**