EORTC
European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

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Short Study Report to Authorities

Name of Sponsor/Company: **EORTC**	Individual study Table Referring to Part of the Dossier 06011	*(For National Authority Use Only)*
Name of the finished product	Volume:	
Name of Active Ingredient	Page	
Title of the Study	Intravenous low-dose decitabine versus supportive care in elderly patients with primary Myelodysplastic Syndrome (MDS) (>10 % blasts or high-risk cytogenetics), secondary MDS or Chronic Myelomonocytic Leukemia (CMML) who are not eligible for intensive therapy: an EORTC-German MDS Study Group randomized phase III study	
Investigators & Study Centers		

Investigator	Institution	Address	Total nr of
Aul	545.St.Johannes Duisburg (DE)	An der Abtei 7-11 DE 47166 Duisburg Germany	1
Aulitzky	504.R.Bosch Kh.Stuttgart (DE)	Auerbachstrasse 110 DE 70376 Stuttgart Germany	1
Aurer	916.Univ. Hospital Rebro (HR)	Kispaticeva 12 HR 10000 Zagreb Croatia	2
Beksac	973.Ibni Sina Hospital (TR)	SIHHIYE TR 06100 Ankara Turkey	1
Bellos	481.Univ.Klin.Heidelberg (DE)	Im Neuenheimer Feld 410 DE 69120 Heidelberg Germany	1
Blum	457.CHU Vaudois (CH)	rue du Bugnon 46 CH 1011 Lausanne Switzerland	1
Bron	101.H.Univ.Bordet-Erasme (BE)	Rue Heger-Bordet, 1 BE 1000 Brussels Belgium	2
Brossart	530.E.K.Uni.Tuebingen (DE)	Wilhelmstrasse, 35-37 DE 53111 Bonn Germany	5
Brugger	3118.Kl Villigen (DE)	Roentgenstrasse 20 DE 78054 Villingen-Schwenningen Germany	4
Cermak	931.Instit. Hematology (CZ)	U. Nemocnice 1 CZ 128 20 Prague 2 Czech Republic	4
De Valk	309.Olv Gasthuis A'Dam (NL)	Postbus 95500 - (Oosterparkstraat 9) NL 1090 HM Amsterdam OOST The Netherlands	1
Delforge	147.U.Z. Leuven (BE)	Herestraat 49 BE 3000 Leuven Belgium	6
Demuynck	1200.H.Hartzkl Roeselaere (BE)	Wilgenstraat 2 BE 8800 Roeselare Belgium	5

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Driessen	530.E.K.Uni.Tuebingen (DE)	Otfried-Mueller-Str. 10 DE 72076 Tuebingen Germany	4
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Fuchs	489.St.Antonius Eschweil (DE)	Dechant Deckersstrasse 8 DE 52249 Eschweiler Germany	1
Galm	531.Mf Aachen (DE)	Pauwelstrasse 30 DE 52074 Aachen Germany	2
Ganser	528.Med.Hochsch.Hannover (DE)	Carl-Neuberg-Str. 1 DE 30625 Hannover Germany	4
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Giagounidis	545.St.Johannes Duisburg (DE)	An der Abtei 7-11 DE 47166 Duisburg Germany	11
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Greil	902.LK Salzburg (AT)	Muellner Hauptstrasse 48 AT 5020 Salzburg Austria	4
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Indrak	1903.Univ Hosp Olomouc (CZ)	I.P. Pavlova 6 CZ 775 20 Olomouc Czech Republic	1
Labar	916.Univ. Hospital Rebro (HR)	Kispaticeva 12 HR 10000 Zagreb Croatia	12
Leone	777.A. Gemelli Roma (IT)	Largo Agostino Gemelli 8 IT 00168 Roma Italy	4
Luebbert	546.Kl.A.Ludwig Freiburg (DE)	Hugstetterstrasse 49 DE 79106 Freiburg Germany	37
Mueller	3222.Onko.Schwerpp. (DE)	Annenstrasse 11 DE 26789 Leer Germany	4
Muus	304.Radboud Univ Nijmege (NL)	P.O. Box 9101 - Geert Grooteplein 10 NL 6500 HB Nijmegen	9
Neuwirtova	961.Gen Teaching Hosp. (CZ)	U. Nemocnice 2 CZ 128 08 Prague 2 Czech Republic	1
Peschel	500.Techn Univ Muenchen (DE)	Ismaninger Strasse 22 DE 81675 Muenchen Germany	4

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	Platzbecker	3039.Un.C.G.Carus Dresden (DE)	Fetscherstr. 74 DE 01307 Dresden Germany	20
	Santini	762.Pol Careggi Firenze (IT)	Viale Morgagni, 85 IT 50134 Firenze Italy	2
	Schlegel	489.St.Antonius Eschweil (DE)	Dechant Deckersstrasse 8 DE 52249 Eschweiler Germany	1
	Schmielau	3163.Skh Sued Luebeck (DE)	Kronsforder Allee 71-73 DE 23560 Luebeck Germany	1
	Schouten	324.Azm/rtil Maastricht (NL)	P. Debyelaan 25 - P.O. Box 5800 NL 6202 AZ Maastricht The Netherlands	3
	Selleslag	109.A.Z. St Jan Brugge (BE)	Ruddershove 10 BE 8000 Brugge Belgium	11
	Spaeth-Schwalbe	3177.Vivantes Kl. Spandau (DE)	Neue Bergstrasse 6 DE 13585 Berlin Germany	1
	Stauder	903.Uni Kl.Innsbruck (AT)	Anichstrasse 35 AT 6020 Innsbruck Austria	3
	Visani	792.S Salvatore Pesaro (IT)	Via Lombroso IT 61100 Pesaro Italy	7
	Weissinger	3042.Med.Kl. Wuerzburg (DE)	Klinikstrasse 6-8 DE 97070 Wuerzburg Germany	2
	Wijermans	330.Haga Zkh Leyenburg (NL)	Leyweg 275 - Postbus 40551 NL 2545 CH 'S Gravenhage - Den Haag The Netherlands	21
	Willemze	310.Univ Med Ctr Leiden (NL)	Albinusdreef 2 - Postbus 9600 NL 2300 RC Leiden The Netherlands	1
	Woermann	8997.Staedt Klinikum (DE)	Celler Str. 38 DE 38114 Braunschweig Germany	2

Publication (reference)	The overall study data have not been published yet, however, publications about part of the data are: … Low Dose Decitabine Versus Best Supportive Care in Elderly Patients with Intermediate or High Risk MDS Not Eligible for Intensive Chemotherapy: Final Results of the Randomized Phase III Study (06011) of the EORTC Leukemia and German MDS Study Groups. Blood (ASH Annual Meeting Abstracts), Nov 2008; **112**: 226.
Objective(s)	To assess the efficacy, toxicity, duration of hospitalization and quality of life of low dose Decitabine versus supportive care in elderly patients with a myelodysplastic syndrome.
Methodology	Randomized open label phase III trial

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Number of patients Number planed (Statistical design) Number analyzed	 220 233	
Diagnosis and main criteria for inclusion	1) Patients aged 60 years and older with either: **primary MDS without any pretreatment** **primary MDS pretreated** with either growth factors, immunosuppressive agents or hydroxyurea. These drugs have to be stopped > 6 weeks before randomisation. **secondary MDS** (previous radio-/chemotherapy for solid tumors or lymphoma) **and** based on a BM aspiration or, in case of dry tap, on a BM biopsy, with either: Bone marrow blast count of 11-20%, Bone marrow blast count of ≤ 10% with poor cytogenetics: any numerical or structural abnormality of chromosome 7 and/or complex abnormalities (≥ 3 abnormalities)	

Cytogenetics (IPSS)	**% of BM Blasts**		
	≤ 10%	**11-20%**	**21-30%**
Good	-	+	+
Intermediate	-	+	+
Poor	+	+	+
Failure	**5-10% blasts and/or 2-3 cytopenias**	+	+

2) Absence of blast crisis of chronic myeloid leukemia.

3) Absence of t(8;21), alone or in combination with other abnormalities.

4) Absence of pretreatment for MDS or AML with chemotherapy other than hydroxyurea.

5) Absence of active malignancy in previous three years with the exception of basal or squamous cell skin cancer or cervical carcinoma *in situ* within two years of study registration.

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	6) Ineligible for intensive chemotherapy (ex: an anthracycline and Ara-C) 7) Performance status according to the WHO scale: 0, 1 or 2. 8) Adequate renal and liver function: creatinine and bilirubin < 1.5 times the upper limit of normal. 9) Absence of severe cardiovascular disease, i.e., arrhythmias requiring chronic treatment, congestive heart failure (NYHA Class III or IV) or symptomatic ischemic heart disease, where New-York Heart Association (NYHA) 10) HIV negative and HBsAg negative. 11) Absence of active uncontrolled infection. 12) No prior history or current evidence of central nervous system and psychiatric disorders requiring hospitalization. 13) Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial. 14) Signed written informed consent must be given according to ICH GCP, and national/local regulations.	

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Treatment Test product, dose and mode of administration (batch number if applicable)	Arm A: Decitabine, 45 mg/m²/day (15 mg/m² over a 4 hours period, every 8 hours) i.v. for 3 days, every 6 weeks, provided that the hematological parameters are at an acceptable level	
Duration of treatment	Maximum of 48 weeks (8 cycles)	
Reference therapy, dose and mode of administration (batch number if applicable)	Arm B: Best supportive care	
Criteria for evaluation		
Efficacy	Overall survival (principal endpoint), Time to AML transformation or death, Progression free survival, Response rate	
Safety	*Toxicity (CTC v2.0), Quality of life (QLQ-30)*	
Statistical methods	For time to event analysis: Kaplan-Meier method and Logrank test; Intent-to-treat population. Safety: descriptive. QoL: usual methods.	

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Summary of Results

Efficacy Results

Efficacy

response		
	Trt arm	
	Supportive care (N=114)	Decitabine (N=119)
	N (%)	N (%)
Response		
Complete remission (CR)	0 (0.0)	16 (13.4)
Partial Remission (PR)	0 (0.0)	7 (5.9)
Hematological Improvement (HI	2 (1.8)	18 (15.1)
Stable disease (SD)	25 (21.9)	17 (14.3)
Progression of Disease (PD)	78 (68.4)	35 (29.4)
Hypoplasia	0 (0.0)	17 (14.3)
Inevaluable	9 (7.9)	9 (7.6)

In the decitabine arm, the median (95% CI) PFS from response for responding patients (CR+PR+HI) was 0.56 years (0.41, 0.82). The median PFS from response for CR+PR patients was 0.71 years (0.52, 1.12)

Based on the ITT principle, a significant superiority regarding PFS has been detected in favor of Decitabine and a non-significant trend towards a better outcome has been seen in terms of AML-FS and OS.

06011: PFS						
Trt arm	**Patients (N)**	**Observed Events (O)**	**Hazard Ratio (95% CI)**	**P-Value (Log-Rank)**	**Median (95% CI) (Years)**	**% at 1 Year(s) (95% CI)**
Supportive care	114	105	1.00	0.0039	0.25 (0.22, 0.35)	15.27 (9.28, 22.63)
Decitabine	119	113	0.68 (0.52, 0.88)		0.55 (0.41, 0.72)	26.89 (19.29, 35.06)

06011: AML-free survival						
Trt arm	**Patients (N)**	**Observed Events (O)**	**Hazard Ratio (95% CI)**	**P-Value (Log-Rank)**	**Median (95% CI) (Years)**	**% at 1 Year(s) (95% CI)**
Supportive care	114	99	1.00	0.2395	0.51 (0.41, 0.72)	31.58 (23.17, 40.30)
Decitabine	119	103	0.85 (0.64, 1.12)		0.73 (0.54, 1.02)	41.09 (32.20, 49.76)

06011: Survival						
Trt arm	**Patients (N)**	**Observed Events (O)**	**Hazard Ratio (95% CI)**	**P-Value (Log-Rank)**	**Median (95% CI) (Years)**	**% at 2 Year(s) (95% CI)**
Supportive care	114	96	1.00	0.3803	0.71 (0.55, 0.88)	12.80 (6.94, 20.52)
Decitabine	119	99	0.88 (0.66, 1.17)		0.84 (0.67, 1.21)	19.32 (12.20, 27.66)

Safety Results

Adverse events/Toxicity

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Maximum AE in SC or during DAC by treatment arm

	Trt arm	
	Supportive care (N=114)	Decitabine (N=114)
	N (%)	N (%)
Maximum of Hypertension		
0	85 (74.6)	69 (60.5)
1	9 (7.9)	5 (4.4)
2	7 (6.1)	12 (10.5)
3	13 (11.4)	28 (24.6)
Maximum of Fatigue		
0	41 (36.0)	39 (34.2)
1	27 (23.7)	32 (28.1)
2	30 (26.3)	33 (28.9)
3	12 (10.5)	5 (4.4)
4	4 (3.5)	5 (4.4)
Maximum of Infection with/without neutropenia		
0	45 (39.5)	37 (32.5)
1	4 (3.5)	7 (6.1)
2	8 (7.0)	4 (3.5)
3	45 (39.5)	44 (38.6)
4	12 (10.5)	22 (19.3)

QoL

Assessment time	Nb forms Received	Nb forms Expected	% compliance
baseline	140	233	60.1
wk 6	109	226	48.2
wk 12	78	206	37.9
wk 18	74	186	39.8
wk 24	49	164	29.9
wk 30	47	143	32.9
wk 36	42	129	32.6
wk 42	28	113	24.8
wk 48	28	101	27.7
Overall	595	1501	39.6

The primary analysis revealed that there was a significant treatment effect in favor of Decitabine on patient's self-reported fatigue and physical functioning.

Treatment comparison	Num DF	Den DF	F Value	P-value
Fatigue	1	389	8.57	0.0036

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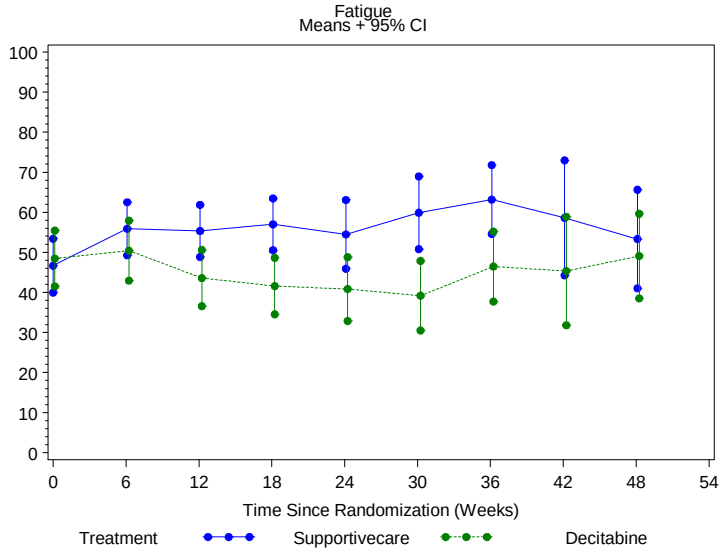
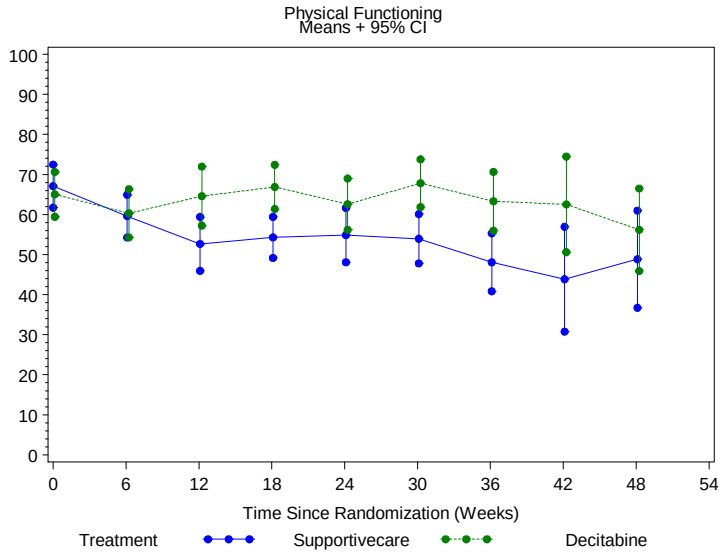


Treatment comparison	Num DF	Den DF	F Value	P-value
Physical Functioning	1	383	8.29	0.0042



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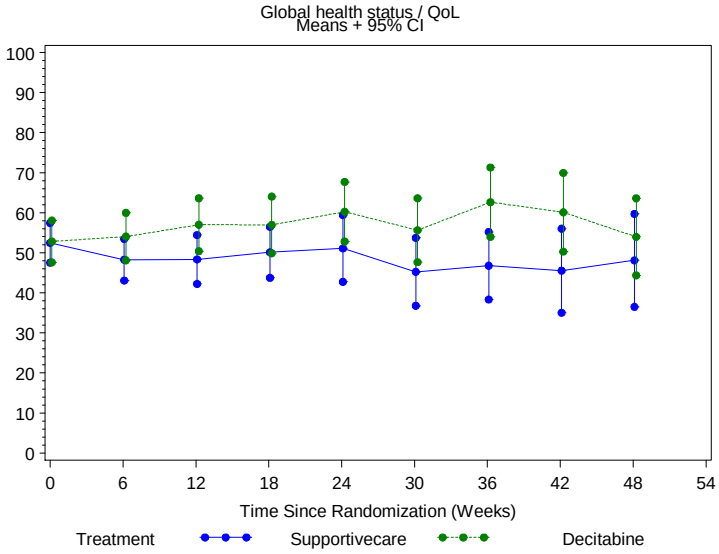
A borderline effect on Global Health Status was observed, while the treatment had apparently no effect on dyspnoea.

Treatment comparison	Num DF	Den DF	F Value	P-value
Global health status / QoL	1	384	3.29	0.0706



Supportive analysis revealed that for most other HRQoL scales, the trend was in favor of the Decitabine treatment.

Conclusions

Response rate points towards a clear activity of Decitabine in this patient population. This is in line with the results published by Wijermans and Lubert, in large phase II trials, in similar patient populations.

PFS was significantly (P=0.004) longer (HR=0.68) in the decitabine arm vs Observation; AML-free survival was not significantly (P=0.24) longer (HR=0.85) in the Decitabine arm as compared to Supportive care, as was the overall survival (main endpoint): HR=0.88, P=0.38. The "reduced" treatment difference in terms of survival might be explained by the post-protocol treatment, which contained AML-salvage, transplantation, etc.

Date of Report	*3rd of December, 2008*