A randomized phase II study of the telomerase inhibitor imetelstat as maintenance therapy for advanced non-small cell lung cancer

Chiappori A[7], Kolevska T[3], Burington B[2], Spigel DR[4], Hager S[5], Rarick M[6], Gadgeel S[8], Blais N[9], Von Pawel J[10], Hart L[11], Reck M[12], and Schiller J[1]

[1]University of Texas Southwestern Medical Center, Dallas, TX; [2]Geron Corporation, Menlo Park, CA; [3]Kaiser Permanente Medical Center, Vallejo, CA; [4]Sarah Cannon Research Institute, Nashville, TN; [5]Cancer Care Associates of Fresno Medical Group, Fresno, CA; [6]Kaiser Permanente Northwest, Portland, OR; [7]H Lee Moffitt Cancer Center, Tampa, FL; [8]Karmanos Cancer Institute, Detroit, MI; [9]CHUM-Hopital Notre-Dame, Montreal, Quebec; [10]Asklepios Fachkliniken Muenchen-Gauting, Gauting, Bayern, Germany; [11]Sarah Cannon Florida Cancer Specialists, Bonita Springs, FL; [12]Department of Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, Germany

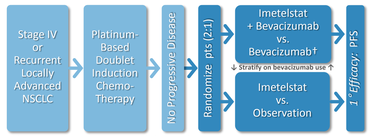
background

- Imetelstat is a 13-mer oligonucleotide which is a potent and specific telomerase inhibitor.
- Telomerase, required for indefinite replication, is upregulated in tumor progenitor cells.
- Tumor regrowth after chemotherapy may be driven by growth of tumor progenitor cells.
- Progression-free survival (PFS) and the duration of responses after 1st-line chemotherapy for non-small-cell lung cancer (NSCLC) are short, which has led to an interest in developing active maintenance therapies.
- A randomized phase II study was conducted to assess whether imetelstat, given as maintenance therapy, prolongs PFS in NSCLC.

methods

- 116 patients were enrolled between July 2010 to April 2012, with 114 completing a first visit (i.e. efficacy population).
- Patients were eligible with advanced NSCLC not progressing after completing 4-6 cycles of platinum-based doublet induction chemotherapy, any NSCLC histology, performance status (PS) ECOG 0 or 1, and not scheduled to receive maintenance with pemetrexed or erlotinib.
- Patients were randomized 2:1 to imetelstat 9.4 mg/kg (d1 and 8 of a 21d cycle) or observation until progressive disease or unacceptable toxicity and were stratified by bevacizumab continuation after induction (required if received during induction).
- The primary endpoint was PFS; safety/tolerability and objective response were secondary endpoints. Exploratory endpoints included six-month survival rate, PFS in bevacizumab subgroups and PFS in telomere length companion diagnostic subgroups (results for the exploratory telomere length analysis are reported separately).
- The protocol called for 96 patients to be enrolled and followed until 67 PFS events were available. Due to concerns about patients' stable disease status at time of enrollment and the large number of patients progressing at the first assessment, enrollment was increased to 116 and the primary analysis of PFS was conducted with 77 PFS events (9-July-2012). A retrospective review of CT scan reports identified 7 patients with RECIST PD at the time of randomization. Exclusion of these patients from the analyses did not change the results substantially. Results using only the first 67 events are similar to those reported for the 77 events (9-July-2012).
- An analysis with mature survival data was conducted with 66 OS events recorded by 11-February-2013. At this time, only 4 of 114 patients continued PFS follow up and 31 patients continued survival follow-up.
- Kaplan-Meier estimates and Cox proportional hazards models were used for analyses of PFS and OS. χ2 and Wilcoxon rank sum tests were used to test for differences in baseline characteristics.

Imetelstat maintenance study design



†Patients who received bevacizumab during induction were required to continue with bevacizumab maintenance and were stratified at randomization

baseline characteristics

	Imetelstat 76 (67%)	Control 38 (33%)	P-value
Age (Median)	63	63.5	0.200
Female	38 (50)	11 (28.9)	0.032
EGFR Mutant	8 (10.5)	3 (7.9)	0.654
KRAS Mutant	4 (5.3)	2 (5.3)	1
Induction Cycles (Median)	4	4	0.448
Induction Partial Response (vs. SD)	26 (34.2)	8 (21.1)	0.148
Weeks from End Induction to Randomization	4.5	4.9	0.667
ECOG 1 (vs. 0)	48 (64)	23 (62.2)	0.849
Baseline Measurable Disease	69 (90.1)	36 (94.7)	0.461
Squamous Histology	10 (13.2)	11 (28.9)	0.040
Bevacizumab Use	26 (34.2)	12 (31.6)	0.779

safety

Laboratory abnormalities

	Imetelstat 76 (67%)			Control 38 (33%)		
	Grade 1	Grade 2	≥3	Grade 1	Grade 2	≥3
HEMATOLOGY						
Neutropenia	5 (6.6%)	20 (26.3%)	25 (32.9%)	0 (0.0%)	0 (0.0%)	(0.0%)
Thrombocytopenia	16 (21.1%)	14 (18.4%)	35 (46.1%)	6 (15.8%)	0 (0.0%)	(0.0%)
Anemia	41 (53.9%)	19 (25.0%)	3 (3.9%)	27 (71.1%)	2 (5.3%)	(0.0%)
LIVER FUNCTION TEST						
ALT	24 (31.6%)	1 (1.3%)	4 (5.3%)	3 (7.9%)	0 (0.0%)	(0.0%)
AST	35 (46.1%)	5 (6.6%)	0 (0.0%)	4 (10.5%)	0 (0.0%)	(0.0%)
Alkaline Phosphatase	31 (40.8%)	4 (5.3%)	0 (0.0%)	7 (18.4%)	0 (0.0%)	(0.0%)
Total Bilirubin	4 (5.3%)	7 (9.2%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	(0.0%)

Frequent non-hematologic adverse events†

	Imetelstat		Control	
	All Grades	≥3	All Grades	≥3
Fatigue	32 (42.1%)	3 (3.9%)	6 (15.8%)	1 (2.6%)
Nausea	33 (43.4%)	0 (0.0%)	5 (13.2%)	0 (0.0%)
Vomiting	19 (25.0%)	0 (0.0%)	3 (7.9%)	0 (0.0%)
Back Pain	14 (18.4%)	0 (0.0%)	3 (7.9%)	0 (0.0%)
Cough	13 (17.1%)	0 (0.0%)	4 (10.5%)	0 (0.0%)
Dizziness	14 (18.4%)	1 (1.3%)	2 (5.3%)	0 (0.0%)
Epistaxis	11 (14.5%)	2 (2.6%)	4 (10.5%)	0 (0.0%)
Headache	13 (17.1%)	0 (0.0%)	2 (5.3%)	0 (0.0%)
Hypertension	10 (13.2%)	2 (2.6%)	5 (13.2%)	2 (5.3%)
Constipation	12 (15.8%)	0 (0.0%)	2 (5.3%)	0 (0.0%)
Oedema Peripheral	13 (17.1%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Decreased Appetite	8 (10.5%)	0 (0.0%)	5 (13.2%)	1 (2.6%)
Dyspnoea	8 (10.5%)	0 (0.0%)	4 (10.5%)	0 (0.0%)
Diarrhoea	5 (6.6%)	0 (0.0%)	5 (13.2%)	0 (0.0%)
Pain in Extremity	5 (6.6%)	1 (1.3%)	5 (13.2%)	0 (0.0%)
Upper Respiratory Tract Infection	9 (11.8%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Pneumonia	6 (7.9%)	3 (3.9%)	3 (7.9%)	1 (2.6%)
Sinusitis	7 (9.2%)	0 (0.0%)	2 (5.3%)	0 (0.0%)
Urinary Tract Infection	9 (11.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

†Includes AEs with total frequency ≥10 and infections with total frequency ≥9

Infusion reactions†

	Imetelstat		Control	
	All Grades	≥3	All Grades	≥3
Any IRR	12 (15.8%)	2 (2.6%)	0 (0.0%)	0 (0.0%)
SYMPTOMS				
Rash	4 (5.3%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Burning Sensation	3 (3.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chest Discomfort	3 (3.9%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Dyspnoea	3 (3.9%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Chest Pain	2 (2.6%)	1 (1.3%)	0 (0.0%)	0 (0.0%)
Nausea	2 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Urticaria	2 (2.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

†Includes infusion reaction symptoms with total frequency ≥2

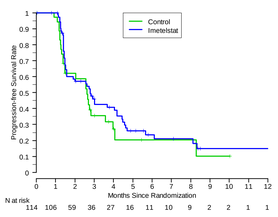
Fatal adverse events

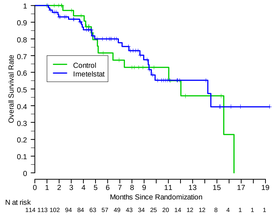
	Cause	Imetelstat Related (Y/N)	Bevacizumab Related (Y/N)
Imetelstat + Bevacizumab (N=24)	2 x Disease Progression	N	N
Bevacizumab Only (N=12)	No Fatal AEs		
Imetelstat Only (N=52)	2 x Disease Progression	N	
	Intracranial Haemorrhage	N	
	Sepsis†	N	
Observation (N=26)	Pneumonia		

† Patient had previous grade 4 thrombocytopenia and resolving grade 4 hepatic failure attributed to imetelstat.

primary analysis of PFS (july 9, 2012)

- Imetelstat demonstrated minimal activity for PFS
- OS was immature at this time



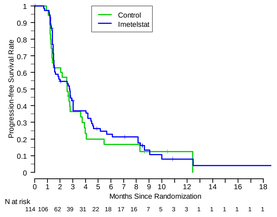


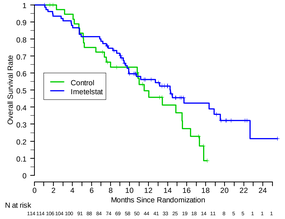
PFS Results (N=114, Events=77, Median FU 2.8mn)	
Control Median (95% CI)	2.63 (1.38, 3.59)
Imetelstat Median (95% CI)	2.80 (1.58, 4.18)
Hazard Ratio (95% CI)	0.77 (0.48, 1.25)
P-value (Score Test)	0.295

Overall Survival Results (N=114, Events=38, Median FU 6.3mn)		
	IMETELSTAT	CONTROL
Median (95% CI)	14.2 (9.3, NA)	12.0 (6.5, NA)
6-Month Survival Rate	80%	72%
Hazard Ratio (95% CI)	0.86 (0.44, 1.66)	
P-value (Score Test)	0.64	

mature survival analysis (february 11, 2013)

- An improvement in OS was evident, though not statistically significant, and there was minimal to no improvement in PFS



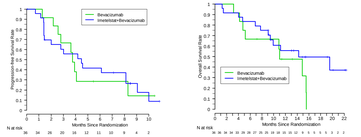


PFS Results (N=114, Events=92, Median FU 2.6mn)	
Control Median (95% CI)	2.57 (1.41, 3.62)
Imetelstat Median (95% CI)	2.76 (1.58, 3.03)
Hazard Ratio (95% CI)	0.84 (0.54, 1.31)
P-value (Score Test)	0.446

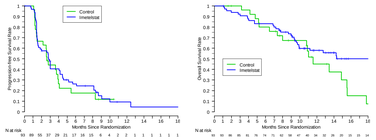
Overall Survival Results (N=114, Events=66, Median FU 10.5mn)		
	IMETELSTAT	CONTROL
Median (95% CI)	14.3 (9.9, 18.9)	11.5 (7.6, 15.5)
6-Month Survival Rate	81%	75%
Hazard Ratio (95% CI)	0.68 (0.41, 1.12)	
P-value (Score Test)	0.129	

sub-group analysis (february 11, 2013)

- Imetelstat improved OS when added to bevacizumab, but the effect was not statistically significant
- Best sub-population is non-squamous +/- bevacizumab

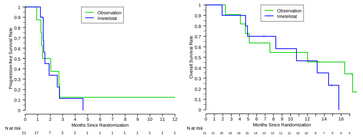


	PFS Results N=36, Events=27	OS Results N=36, Events=21
Control Median (95% CI)	3.75 (2.17, 8.29)	11.02 (4.18, 15.53)
Imetelstat Median (95% CI)	4.47 (1.45, 8.12)	14.24 (9.08, NA)
Hazard Ratio (95% CI)	0.95 (0.42, 2.14)	0.54 (0.22, 1.31)
P-value (Score Test)	0.907	0.167



	PFS Results N=93, Events=75	OS Results N=93, Events=50
Control Median (95% CI)	2.63 (1.41, 3.91)	11.55 (7.37, 15.53)
Imetelstat Median (95% CI)	2.83 (1.58, 4.18)	18.36 (9.9, 22.66)
Hazard Ratio (95% CI)	0.86 (0.52, 1.41)	0.60 (0.33, 1.09)
P-value (Score Test)	0.54	0.092

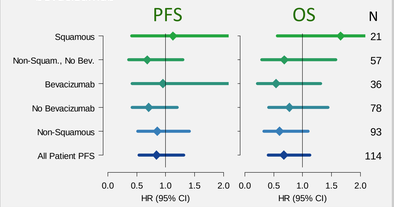
- No activity evident in squamous subpopulation



	PFS Results N=21, Events=17	OS Results N=21, Events=16
Control Median (95% CI)	1.71 (0.92, 2.76)	12.04 (4.08, 17.34)
Imetelstat Median (95% CI)	1.58 (1.22, 2.73)	10.72 (1.91, NA)
Hazard Ratio (95% CI)	1.13 (0.41, 3.07)	1.66 (0.57, 4.85)
P-value (Score Test)	0.816	0.351

Sub-group Hazard Ratios

- OS benefit is greater than PFS in all patients and with bevacizumab



conclusions

- No clinically meaningful trend toward PFS benefit was seen for imetelstat as maintenance therapy in patients with NSCLC (HR = 0.84, P=0.446).
- An improvement in OS was evident, but was not statistically significant (HR=0.68, P=0.129).
- In combination with bevacizumab, imetelstat improved OS, but the improvement fell short of statistical significance (HR=0.54, P=0.167).
- No activity in the squamous histology subpopulation was evident.
- A pre-specified exploratory subgroup analysis of PFS by tumor telomere length is reported separately (AACR 2013 Abstract # 2376).
- Imetelstat was generally well tolerated. The most frequent increased toxicities in the imetelstat arm were hematologic, predominantly neutropenia and thrombocytopenia. Constitutional symptoms (e.g. fatigue, dizziness), GI symptoms (e.g. nausea, vomiting), low-grade infections and biochemical liver function tests were also increased in the imetelstat arm.

AACR abstract #4660

We thank all of the patients, caregivers, principal investigators and staff who have participated in this study.

This study was sponsored by Geron Corporation

geron