Interim analysis of survival outcomes in a prospective multicenter cohort evaluating a prognostic 31-gene expression profile (GEP) test for melanoma

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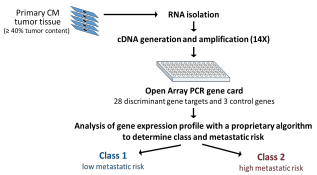
Background

- A prognostic gene expression profile (GEP) test that predicts metastatic risk has been previously validated in three studies.[1-3]
- The test evaluates the expression of 31 genes in primary melanoma tumor to provide a binary classification (low risk Class 1 or high risk Class 2) of metastasis risk.
- To date, 782 cases have been accrued in retrospective cohorts; 26% (201/782) of these are sentinel lymph node (SLN) positive.
- This study reports the prognostic accuracy of the GEP test in an interim analysis of a *prospective, multi-center* registry cohort.

Methods

- Eleven U.S. dermatologic and surgical centers participated in two IRB-approved registry protocols. Physicians enrolled CM pts who were ≥16 years old and had successful GEP test results.
- Endpoints of recurrence-free (RFS), distant metastasis-free (DMFS) and overall survival (OS) were assessed using Kaplan-Meier and Cox regression analysis.
- As an interim analysis at year 3 of an expected 5-year study, the critical alpha level (p value) was 0.01.

Figure 1. Schematic of the GEP test workflow



Results

Table 1. Demographic information for this prospective cohort.

	All cases (n=322)	Class 1 (n=248)	Class 2 (n=74)	p value
Age, median (range)	58 (18-87)	57 (18-87)	65 (23-85)	0.003
Gender				
Female	146 (45%)	123 (50%)	23 (31%)	0.005
Male	176 (55%)	125 (50%)	51 (69%)	
Breslow thickness, median (range)	1.2 (0.2-12.0)	1.0 (0.2-7.0)	2.5 (0.4-12.0)	<0.001
Ulceration				
Absent	238 (74%)	204 (82%)	34 (46%)	<0.001
Present	58 (18%)	23 (9%)	35 (47%)	
Unknown	26 (8%)	21 (9%)	5 (7%)	
Mitotic rate				
≤1/mm²	222 (69%)	176 (71%)	46 (62%)	0.151
>1/mm²	100 (31%)	72 (29%)	28 (38%)	
Node status				
Negative	201 (85%)	155 (89%)	46 (74%)	0.007
Positive	36 (15%)	20 (11%)	16 (26%)	
Primary tumor location				
Extremity	178 (55%)	133 (54%)	45 (61%)	0.547
Head and neck	58 (18%)	46 (19%)	12 (16%)	
Trunk	86 (27%)	69 (28%)	17 (23%)	
AJCC stage				
None	3 (1%)	3 (1%)	0 (0%)	<0.001
I	209 (65%)	192 (77%)	17 (23%)	
II	73 (23%)	32 (13%)	41 (55%)	
III	36 (11%)	20 (8%)	16 (22%)	
IV	1 (0%)	1 (0%)	0 (0%)	

Figure 3. Kaplan-Meier survival analysis to compare prospective and retrospective cohorts. Class 1 (blue) and Class 2 (red) RFS rates from the prospective (solid lines; n=322) and retrospective (dashed lines; n=782) studies of the GEP test. GEP class is a significant predictor of RFS in both cohorts.
Note: 11% (36 of 322) of the cases in the prospective cohort were sentinel lymph node positive, compared to 26% (201/782) of the cases in the retrospective cohort.

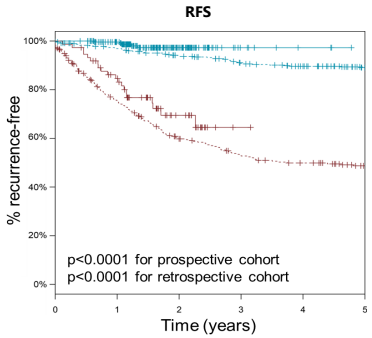


Figure 2. Survival curves for GEP groups. RFS, DMFS and OS rates, associated 95% confidence intervals (CI) and number of events for Class 1 and Class 2 groups are shown. Median follow-up time was 1.5 years for event-free subjects.

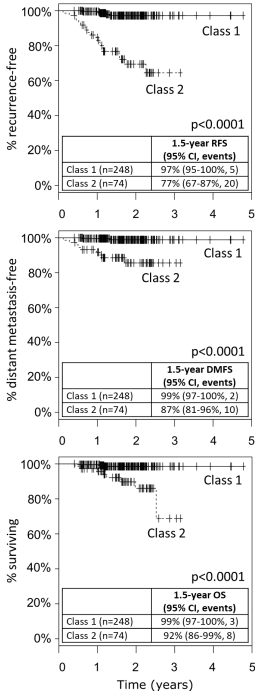


Table 3. Cox regression analysis for recurrence of disease. Hazard ratios (HR) for each clinical factor considered in the Cox multivariate analysis are shown with 95% confidence intervals (CI). Breslow thickness, mitotic rate, and GEP class were considered significant. 296 complete cases were used in these analyses.

	RFS	
	HR (95% CI)	p value
Mitotic rate	1.05 (1.01-1.08)	**0.005**
Ulceration present	1.89 (0.75-4.72)	0.17
Breslow thickness	1.43 (1.18-1.73)	**0.001**
SLN positivity	2.46 (1.07-5.68)	0.035
GEP Class 2	7.15 (1.99-25.8)	**0.003**

Table 2. Correlation of outcomes with prognostic factors. Outcome events (recurrence, distant metastasis or death) in the 322-patient prospective cohort and correlation with GEP Class, SLN status, and ulceration.

	RFS n (rate of recurrences)	DMFS n (rate of DM)	OS n (rate of deaths)
Class 1 (n=248)	5 (2%)	2 (0.4%)	3 (1%)
Class 2 (n=74)	20 (27%)	10 (14%)	8 (11%)
p-value	<0.0001	<0.0001	<0.001
SLN- (n=286)	15 (5%)	6 (2%)	10 (3%)
SLN+ (n=36)	10 (28%)	6 (17%)	1 (3%)
p-value	<0.0001	<0.001	1
Ulceration- (n=264)	10 (4%)	3 (1%)	6 (2%)
Ulceration+ (n=58)	15 (26%)	9 (16%)	5 (9%)
p-value	<0.0001	<0.0001	0.04

Conclusions

- This interim analysis of a **prospective, multicenter study** confirms the association between GEP class and outcomes (p<0.0001).
- Consistent with prior results, Class 1 cases have significantly better recurrence-free, distant-metastasis-free and overall survival compared to Class 2 cases (p<0.0001).
- In this study, 83% (10 of 12) of patients who developed distant metastases were identified as high risk by the GEP test, compared to 50% (6 of 12) who had a SLN-positive result indicating that the GEP test can improve the identification of high-risk CM patients.
- While these results are from an interim analysis of this study cohort, the consistency with prior retrospective and prospective single center studies of the GEP test confirms that molecular profiling of melanoma tumors with the 31-gene GEP test offers the opportunity for accurate identification of high-risk tumors.
- Considering the rapid time to event and the accuracy of risk prediction by the GEP test, increased surveillance with imaging for Class 2 patients may be warranted.

Limitations

A limitation of the study is the median follow-up time of 1.5 years. However, prior studies have shown that the GEP test identifies tumors at high risk for near-term metastasis (e.g., median time to recurrence for Class 2 cases is 1.1 years). Thus, this interim analysis is based on greater than 50% of events that are expected in this cohort, the majority of which occur in the Class 2 population.

References

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Disclosures

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