Cutaneous Melanoma: a patent on molecular markers predicting the clinical course of disease

European Patent: EP2670861
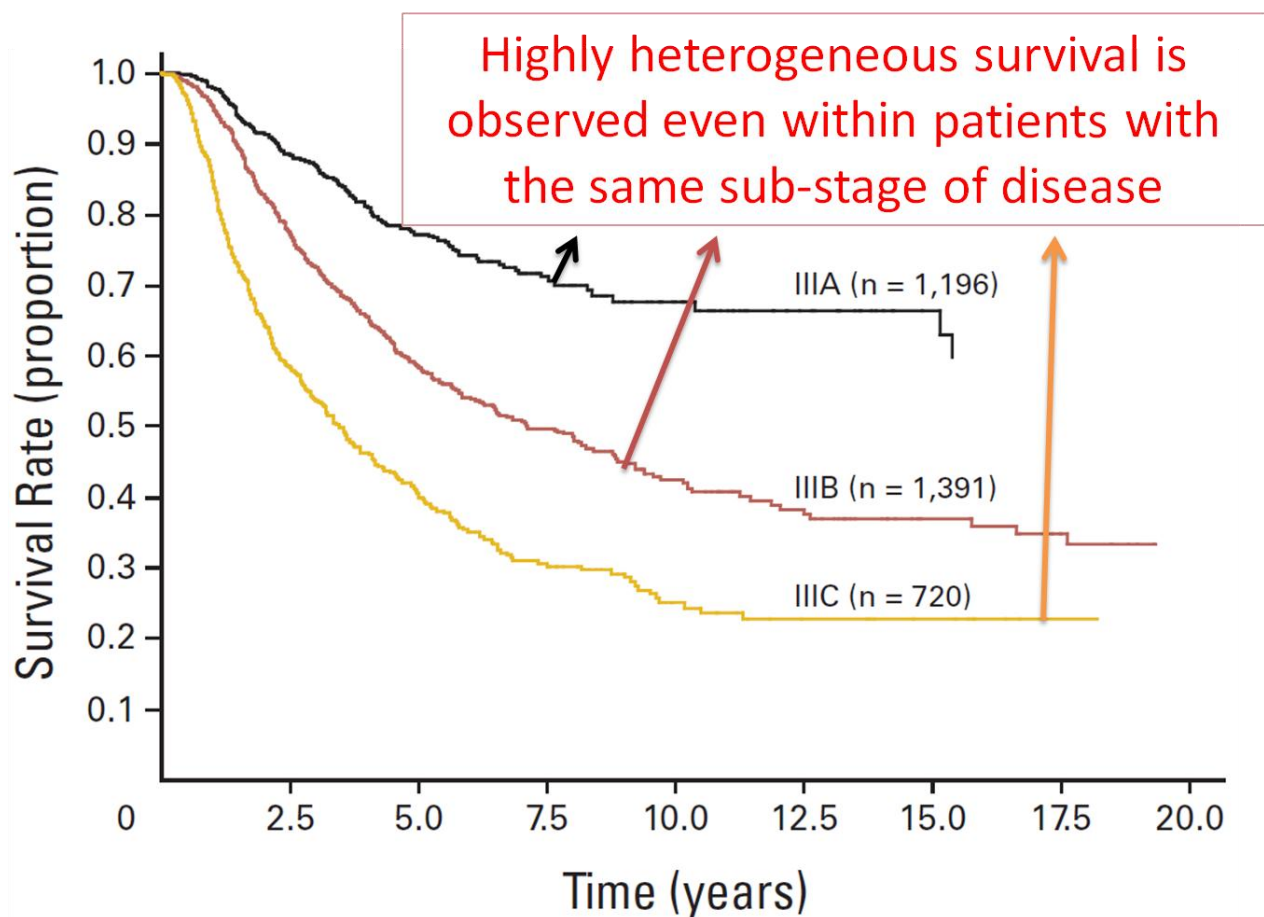
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Cutaneous Melanoma

- Increasing incidence in European Union (EU)*:

  - EU: 13.0/100000; 5-year prevalence>300000 cases (the 4-EU most affected)

  - Italy: 13.4/100000; 5-year prevalence>40000 cases

- High mortality(2,2/100.000 EU)

- Limited response to conventional therapies, except for surgery in the initial phases of the disease

- Heterogeneity in the disease course even in groups of patients with highly homogeneous clinicopathological characteristics

*Source: Eucan, 2012

Cutaneous Melanoma Prognosis

Highly heterogeneous survival is observed even within patients with the same sub-stage of disease

Cutaneous Melanoma – need for markers

- To identify patients with increased risk of bad prognosis and provide them with differentiated follow-up and therapeutic approaches vs. patients with good prognosis

- To define predictive markers of response to therapy in order to identify the most appropriate treatment for each patient, concomitantly avoiding side effects deriving from the un-necessary exposure to drugs not effective for the specific patient

Methylation statuses of melanoma cells that may influence prognosis and response to therapy

LINE-1 as a surrogate marker for global genomic methylation status

LINE1 accounts for ≈17% of the genomic DNA
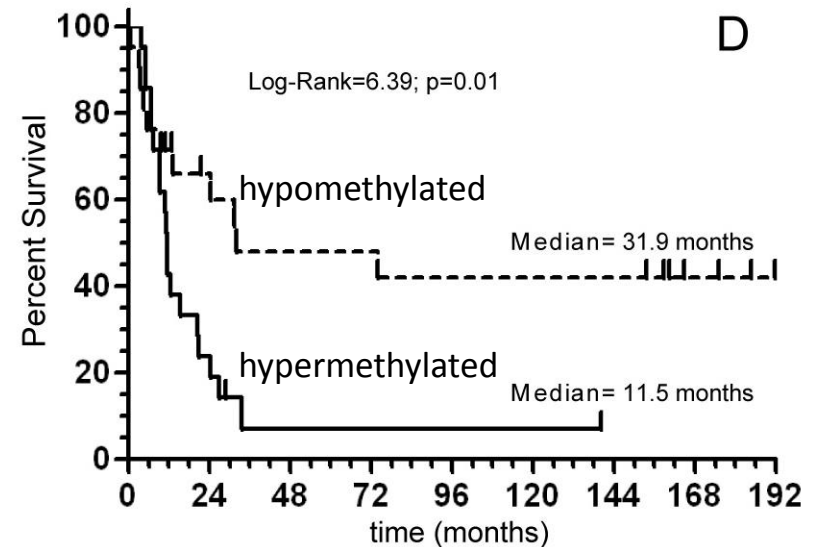
Cordaux et al, *Nat Rev Genet*, 2009
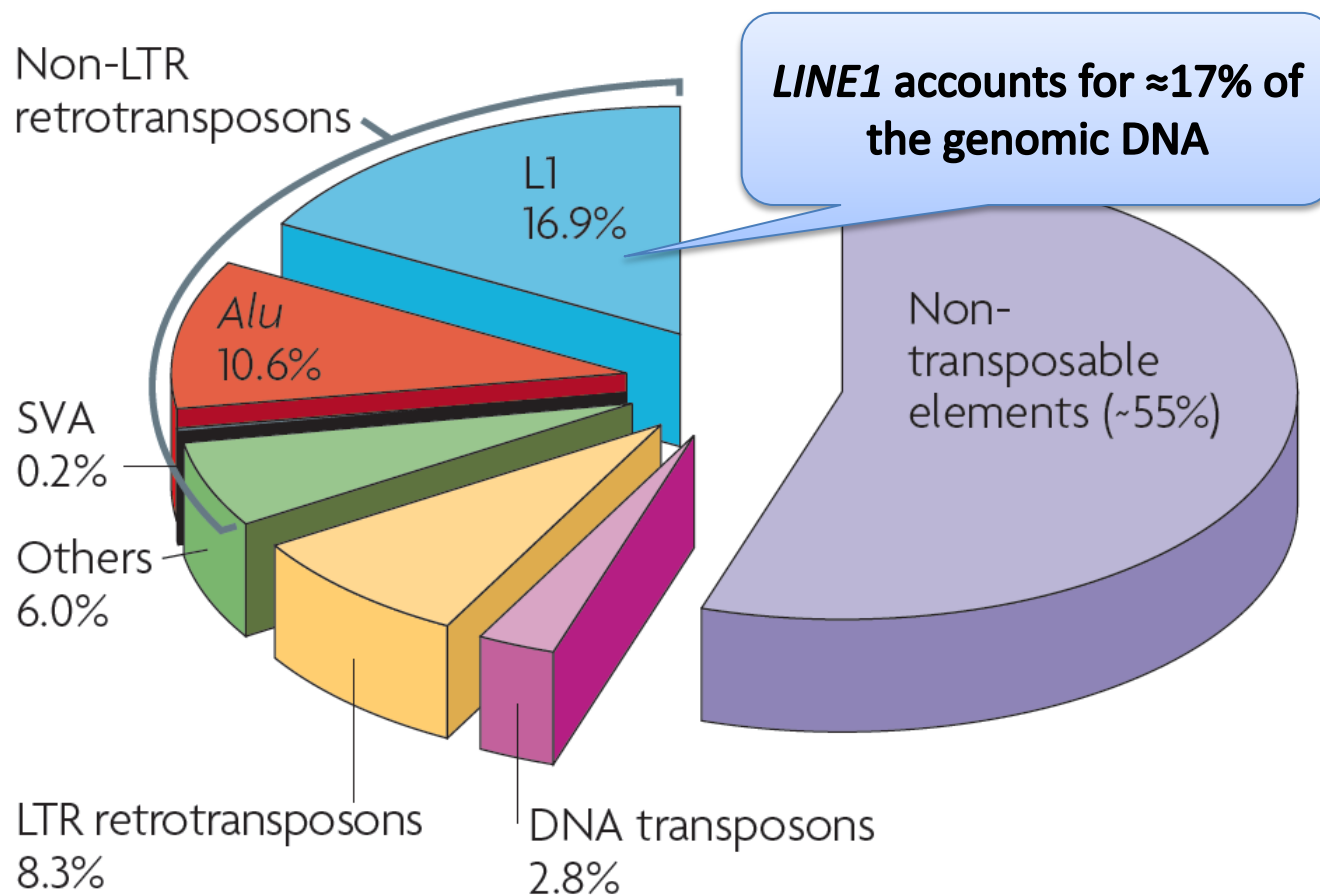
LINE-1 methylation identifies patients with different prognosis within sub-stage IIIC (indepemdent marker)

unsorted
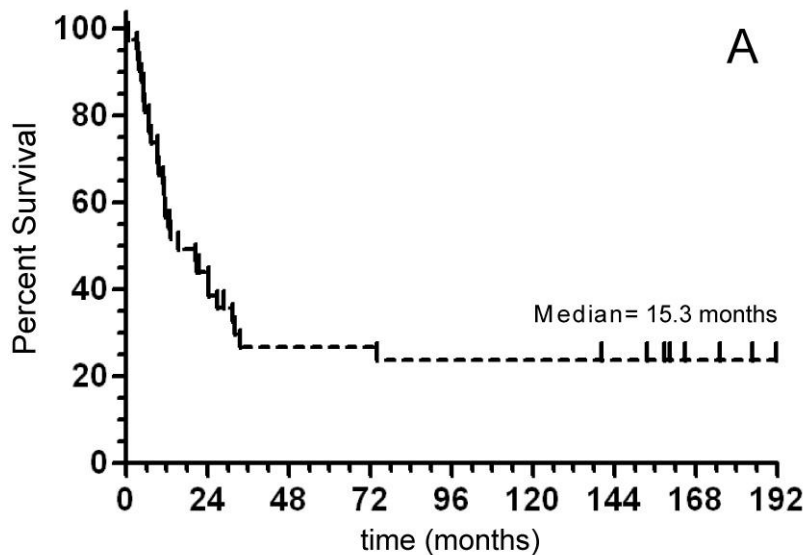
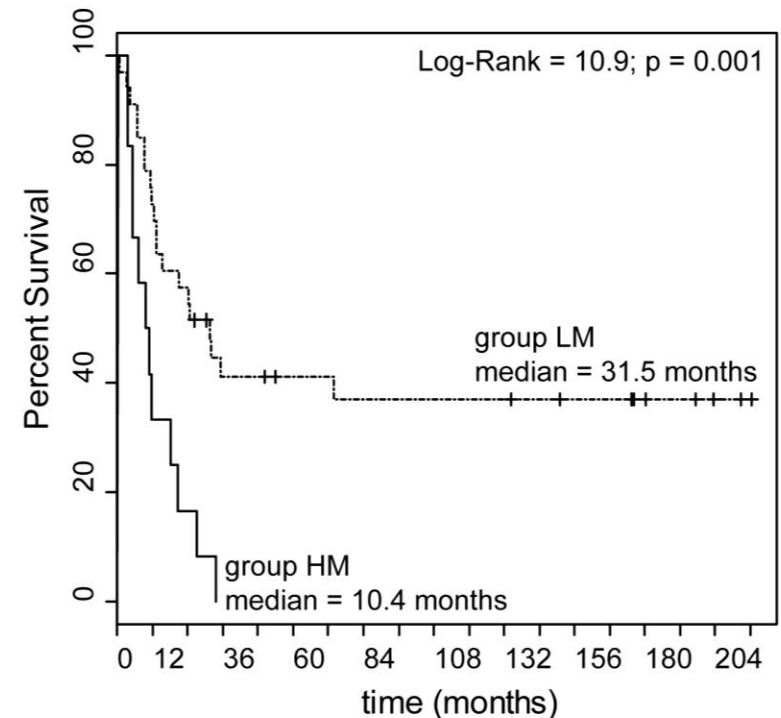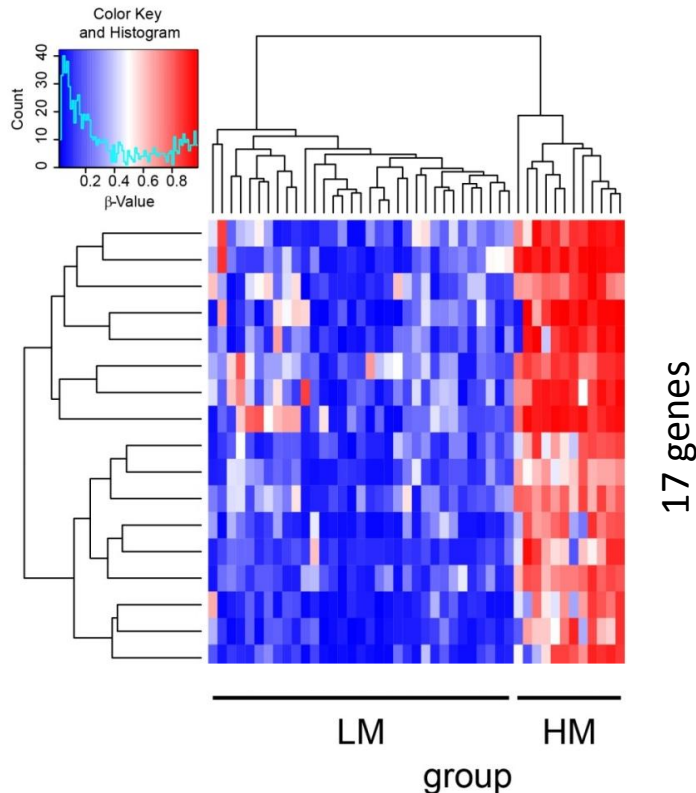sorted by *LINE-1* methylation

|	# events/ # patients	% methylation	Median OS (95%CI)	HR (95%CI; P)	5-year OS (%)
LINE-1	11/21	<40.46	31.9 (13.1-inf)	1	48
methylation	19/21	≥40.46	11.5 (9.2-20.6)	2.52 (1.21-5.26)	7

Specific methylation profiles define survival of sub-stage IIIC melanoma patients (independent marker)

Group	# events/ # patients	Median OS (95%CI)	HR (95% CI; P)	5-year OS (%)
LM	20/33	31.5 (13.12-inf)	1	41.2
HM	12/12	10.4 (5.29-inf)	3.30 (1.56-6.99; p=0.001)	0

Prognostic value of the methylation of selected genes taken from the identified methylation signatures
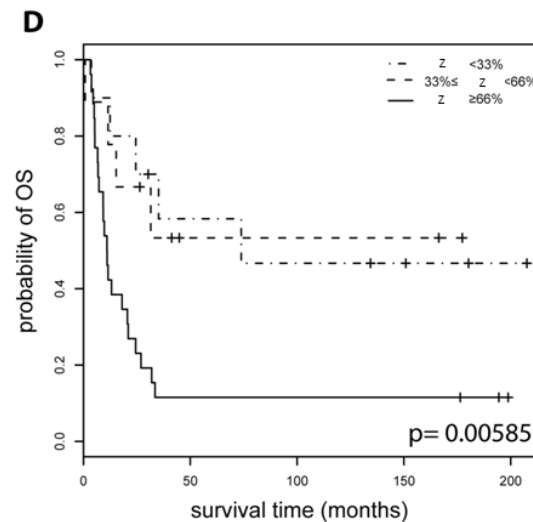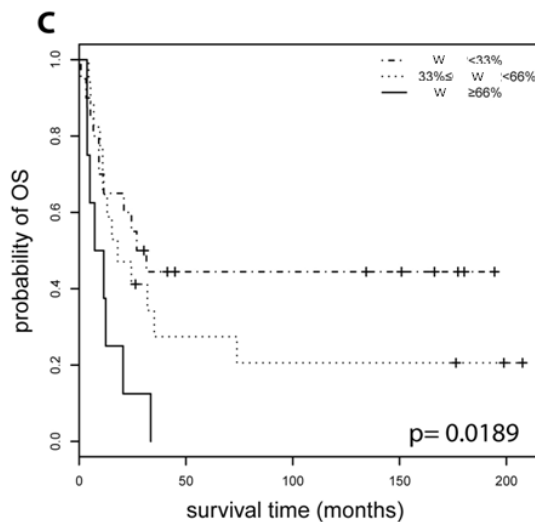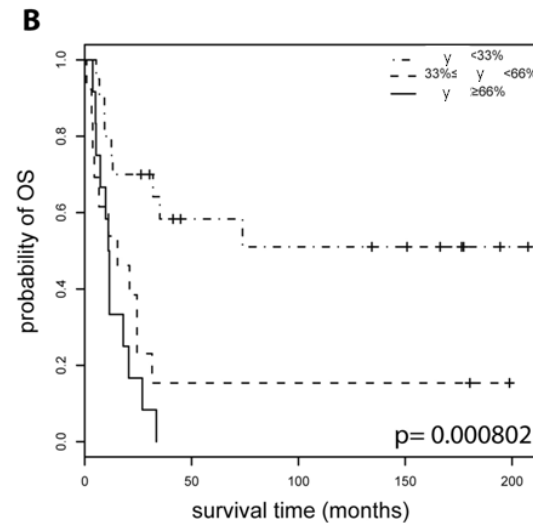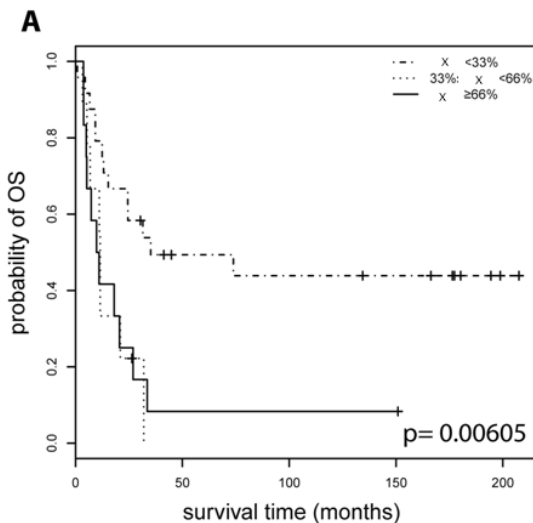
LINE-1 methylation inversely correlates with the number and level of expression of CTA target of immunotherapy
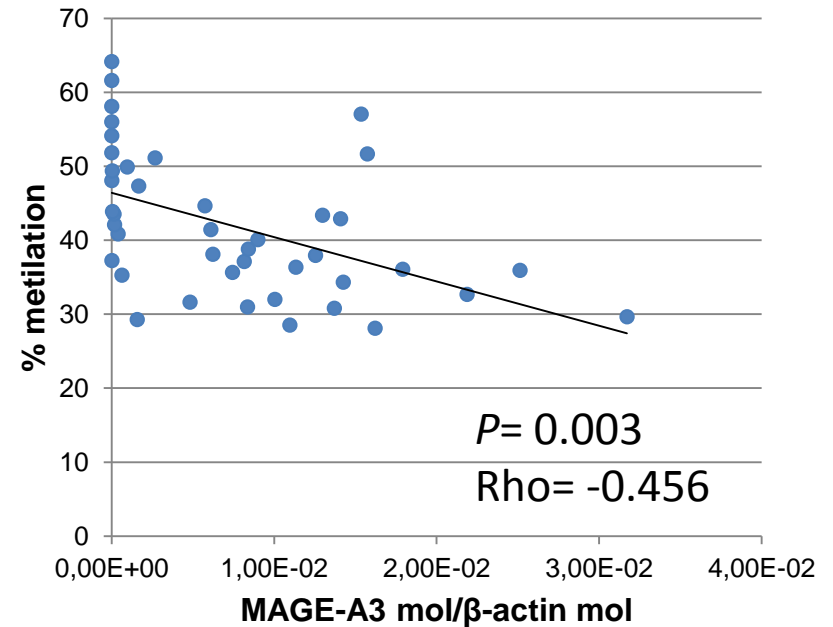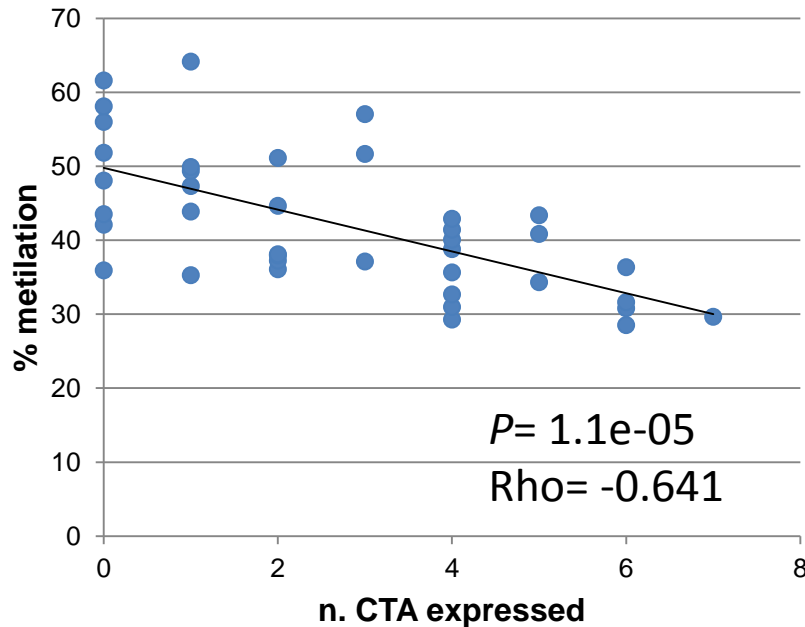
Summary of the results

- Methylation markers are able to independently define prognosis of melanoma patients within the same sub-stage of disease

- The prognostic value is maintained by methylation signatures composed of a limited number of genes (e.g., 17) and even by single selected genes

- Methylation markers potentially represent markers of response to therapy (e.g., immunotherapy)

ADVANTAGES

- Far superior stability of DNA methylation markers in clinical samples as compared to RNA-based markers

- Applicability to different types of biological samples, including archival FFPE tissues

- High sensitivity of the assays

- Potentially evaluable in serum/plasma to allow easy to run routine screenings.

- Robust technology

APPLICATIONS

- Defining differentiated follow-up and therapeutic procedures according to the predicted prognosis/response to therapy of patients (increased efficiency of health care)

- Identifying patients candidates to personalized therapies (e.g., hypomethylating drugs, immunotherapies, targeted therapies…)

- Improving staging of melanoma patients

- Providing a strong parameter for the stratification and/or the randomization of patients included in clinical trials

- Providing the basis for designing companion tests for new drugs