

Circulating tumour DNA and melanoma survival: a systematic literature review and meta-analysis

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Introduction

Circulating tumour DNA (ctDNA) has been studied in several articles in recent years for its potential use in clinical practice as a prognostic biomarker for melanoma patients. Here, we present the results of a systematic literature review and meta-analysis of the available evidence on the association between ctDNA levels and survival of melanoma patients.

Flow-chart of the selection process for the studies included in the literature review and meta-analysis on the association between circulating tumour DNA and survival of melanoma patients.



Methods and Materials

We searched studies published until December 2019 in MEDLINE and EMBASE. We used random effects meta-analysis models to calculate summary hazard ratio (SHR) and 95% confidence intervals (CI) for the association between ctDNA (measured before any treatment was started or in the follow-up) and the survival of melanoma patients, and quantified the betweenestimates heterogeneity using the I2 statistics.

free survival of melanoma patients.

Gonzalez Cao, 2015 Gray, Target Therapy, 2015 Gray, Immunotherapy, 2015 Santiago Walker, BREAK-2, 2016 Santiago Walker, BREAK-3, 2016 Santiago Walker, BREAK-MB, 2016 Santiago Walker, BREAK-MB, 2016 Lee, 2017 Mc Evoy, 2017 Gonzalez Cao, 2018 Herbreteau, 2018 Mc Evoy, 2018 Salemi, 2018 Tang, 2018 Board, 2019 Forthun, 2019 Long, 2019 Seremet, 2019 Tan, Australia, 2019 Tan, UK, 2019	
nary HR=2.47 (1.85-3.29), I ² =30%	
0.4 0.6 0.8	

Fig. 1. Forest plot for the association between ctDNA levels measured before treatment and progression-



Results

We included 26 studies published between 200 and 2019 for over 2,000 melanoma patients: mo stage III-IV. BRAF-mutant ctDNA was searched most studies, while somatic mutations of other genes were searched in the minority of studies. Melanoma patients with detectable ctDNA before treatment had worse progression-free survival ((SHR 2.47, 95%CI 1.85-3.29, Fig 1) and overall survival (OS) (SHR 2.98, 95%CI 2.26-3.92, Fig compared to patients with undetectable ctDNA, no significant difference by tumour stage. ctDN/ detectability during follow-up was also associate with poorer patients' PFS (SHR 4.27, 95%CI 2.1 6.63; fig 3) and OS (SHR 3.91, 95%CI 1.97-7.7) Fig. 4); in the latter case, association of ctDNA outcome was stronger (p=0.01) for stage IV vs. melanomas. Between-estimates heterogeneity low for all pooled estimates.

Fig. 2 Forest plot for the association between ctDNA levels m before treatment and overall survival of melanoma patients



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	Conclusion
9 ostly in	ctDNA is a strong prognostic biomarker for advanced-stage cutaneous melanoma patients, robust across a wide range of tumour (e.g. genomic profile) and patients (e.g. systemic therapy) characteristics.
re PFS) 2)	Fig. 3 Forest plot for the association between ctDNA levels measured during treatment and progression-fre survival of melanoma patients.
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Δ	Lee, 2017
	Louveau, 2017
20 75	Lee, 2018
()- 0	Tan Australia 2019
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was	Summary HR=4.27 (2.75-6.63), I ² =0%
easured	0.6 0.8 1.0 1.5 2.0 2.5 5.0 7.0 10.0 17.0 23.
easured	Fig. 4 Forest plot for the association between ctDN levels measured during treatment and overa survival of melanoma patients.
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easured	Fig. 4 Forest plot for the association between ctDN levels measured during treatment and overa survival of melanoma patients. Lee, Australia, 2017 Lee, UK, 2018 Forthun, 2019 Seremet, 2019 Tan, 2019 Summary HR=3.91 (1.97-7.78), I ² =25%