Impact of cardiovascular comorbidities on bevacizumab effectiveness and safety in older patients with metastatic colorectal cancer

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ABSTRACT

Background
Older patients with cardiovascular (CV) comorbidities were under-represented in clinical trials evaluating bevacizumab in metastatic colorectal cancer (mCRC). Yet, CV comorbidities are not formal contraindications.

Objectives
To evaluate the impact of CV comorbidities on overall survival (OS) and CV safety in older mCRC patients treated with bevacizumab in first-line therapy.

Methods
A 2009-2015 cohort of mCRC patients ≥65 years initiating first-line bevacizumab was extracted from the French healthcare insurance system claims database (*Système National des Données de Santé*). At baseline, heart failure, hypertension, myocardial infarction, stroke, pulmonary embolism, and venous/arterial thrombosis have been identified using existing algorithms. 3-year OS has been described using the Kaplan-Meier method, and the impact of baseline CV comorbidities on 3-year OS evaluated using a time-dependent multivariable Cox proportional hazards model. 3-year cumulative incidence of the same CV events and the impact of baseline CV comorbidities on their 3-year occurrence have been evaluated using Fine & Gray models considering death as competing risk.

Results
9222 patients were included: 56.4% male, median age 73 years [IQR 68-78], hypertension 63.5%, heart failure 3.6%, pulmonary embolism 1.5%, stroke 1.3%, myocardial infarction 1.3%, and venous/arterial thrombosis 8.4%. At 3 years, 71.4% had died: median OS (months) was respectively 20.4 [95%CI 19.9; 21.0] and 21.8 [21.1; 22.6]; p=0.003) in patients with and without CV comorbidities. Heart failure was the comorbidity that shortened the most the median OS (-4.3 months). In multivariable analyses, none of the CV comorbidities was associated with a higher risk of death unlike age ≥75, ADL-dependency, radiotherapy and initiation of another targeted therapy during follow-up. At 3 years, CV events had occurred respectively in 60.2% [58.9; 61.4] and 44.1% [42.3; 45.9] of patients with and without CV comorbidities. Venous thrombosis at baseline was associated with a higher risk of CV events as well as female gender, >3 CV medications, initiation of another targeted therapy and >6 bevacizumab injections. When excluding hypertension from CV events, heart failure, and arterial thrombosis at baseline were also associated with a higher risk of CV events.

Conclusion
CV comorbidities before bevacizumab in older mCRC patients had a clear impact on the occurrence of CV events but few on OS. If judged beneficial, older patients with CV comorbidities should be treated with bevacizumab under a close monitoring. Attention should be paid to CV comorbidities impacting the patients' autonomy, especially heart failure.

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CONFLICT OF INTEREST STATEMENT
E Paillaud declares consulting fees or participation on advisory boards for GSK, MSD, Pfizer, and Sandoz. T Aparicio declares payment or honoraria for conferences from Amgen, Pierre Fabre, and Servier, as well as participation on advisory boards for Sirtec, Pierre Fabre, and MSD. Other authors have no conflict of interest to declare.

Cardiovascular (CV) comorbidities and overall survival

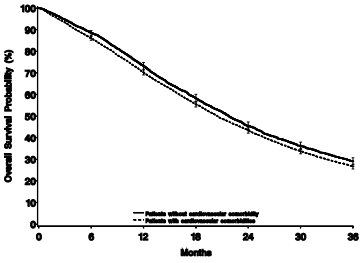

Fig 1. Overall survival during the 36 months after baseline

Median overall survival

- ✓ 20.4 months [95% CI 19.9; 21.0] in patients with CV comorbidities
- ✓ 21.8 months [21.1; 22.6] in patients without CV comorbidities

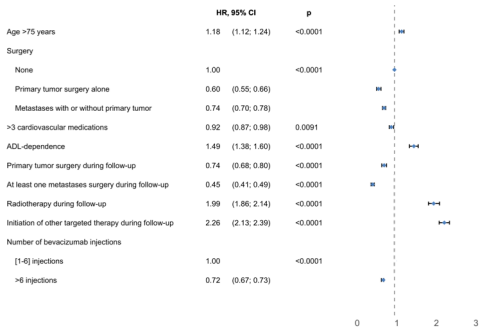

Fig 2. Factors associated with 36-month overall survival

Cardiovascular comorbidities and cardiovascular safety

Cumulative incidence of cardiovascular (CV) events

- ✓ 60.2% [58.9; 61.4] in patients with CV comorbidities
- ✓ 44.1% [42.3; 45.9] in patients without CV comorbidities

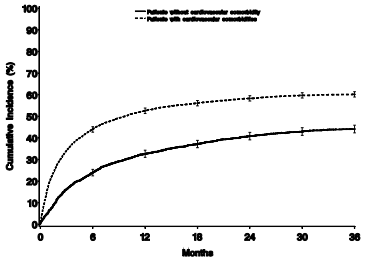

Fig 3. Cumulative incidence of serious cardiovascular events during the 36 months after baseline

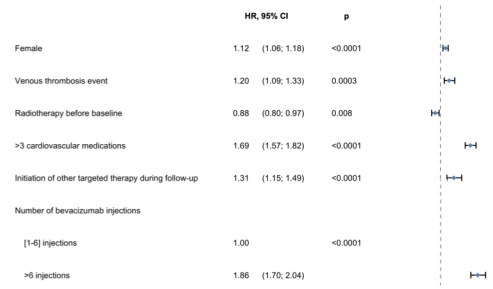

Fig 4. Factors associated with 36-month occurrence of serious cardiovascular events

TAKE HOME MESSAGES

- ✓ **Preserved benefit-risk ratio of bevacizumab in older patients with baseline cardiovascular comorbidities**
- ✓ **Attention to be paid to baseline cardiovascular comorbidities impacting functional independency (e.g. heart failure)**

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