Second-line treatment has recently been dramatically modified by the report of two large phase III trials showing improvement in OS with nivolumab [an anti-programmed death 1 (PD-1) inhibitor] and cabozantinib [38–40] over everolimus. Both trials showed very significant improvement in OS and response rate, while PFS was improved only in the cabozantinib trial. In both trials, patients could be treated after either one or two TKIs.

• Obviously, availability of these two drugs is still very limited, and several situations should be differentiated:
  – Only nivolumab is available: It should be recommended [Level of evidence (LOE) I; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.0 score: 5].
  – Nivolumab and cabozantinib are both available: either drug is recommended. The ESMO-MCBS score associated with nivolumab is 5, while that of cabozantinib is 3.
  – Neither of these drugs is available: either everolimus [II, B] or axitinib [II, B] can be used.

The combination of lenvatinib and everolimus has recently been approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) based on a small, phase II, randomised study of 150 patients, showing PFS and OS benefit over everolimus [LOE II; ESMO-MCBS v1.0 score: 4] [41]. It is the opinion of the ESMO Guidelines Committee that the encouraging positive findings of the phase II study require verification in an adequately powered phase III study.
References