In summary, the involvement of RET in the pathogenesis of BC and in the development of ERα+ tumors is confirmed by several independent studies and a strong body of evidence confirms that RET might be an effective target to enhance sensitivity of BC to antitumoral therapy and to overcome drug resistance.

CONCLUSION

Improved knowledge around BC and persisting unsolved aspects of its biology, does suggest we keep on current research strategies: (1) patient stratification, according to gene expression patterns[141], distinct response to treatments, recurrence and survival[87,142,143], will result useful to search for further suitable markers; (2) around 40%-50% of BC patients develop endocrine-resistant BC[144], thus disclosing the mechanism of HR has become a priority in reducing the BC mortality; (3) RTKs have emerged as promising therapeutic targets to modulate the response to therapy in BCs, mostly mediated by their amplification or overexpression. Unfortunately, thus far, there is no evidence for the direct involvement of amplification or overexpression of RTK in ER+ disease, a circumstance explaining why no RTKi has been approved yet; (4) *RET* has emerged as driving oncogenesis not only in thyroid tumors but also in lung cancers as well as in other epithelial tumors (e.g., ERα+ BC)[79]. The development of new biomarkers and drugs will require a better understanding of RET-mediated signaling pathways and their crosstalk with ERα signaling; (5) inhibitors actually found to also hit RET in screenings designed to target other RTKs have revealed the emerging role of RET as a potential druggable target. Nevertheless, no RET-specific inhibitor has been developed thus far; and (6) as downstream RET pathways modulating ER activity are shared with other RTKs, combining endocrine therapies with inhibitors targeting shared signaling components has been proposed as a promising approach in ER- and RTK signaling-positive patients[145]. Indeed, combination approaches will allow larger subsets of patients to become eligible for trials, besides preventing secondary resistance in highly mutable tumors.

DECLARATIONS

Authors' contributions

Conception and design, literature review: Lo Nigro C
Data analysis: Lo Nigro C, Ceccherini I
Figure drawing: Rusmini M
Comments and conclusion of the review, revision and editing of the manuscript: all authors

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All authors declared that there are no conflicts of interest.

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