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Pharmacoepidemiology and Clinical Pharmacology

Decision-Making Throughout The Lifecycle Of Tumour Agnostic Drugs

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OBJECTIVES

The histology independent label for larotrectinib and entrectinib as granted by the European Medicines Agency announced a new era of personalized medicine in Europe. The disruption to present healthcare decision-making frameworks caused by these tumour agnostic therapies provide valuable lessons for future innovative treatments, that may contain related characteristics. This review outlines the uncertainty considerations in decision-making throughout their lifecycle.

METHODS

This documentary analysis described the full lifecycle experiences of both products, from trial design to clinical use. Uncertainty considerations for larotrectinib and entrectinib were extracted from published pivotal trials, European public assessment reports, HTA reports (Dutch, French, German, UK) and European (ESMO) clinical treatment guidelines. The PICO and procedural considerations were compared qualitatively across stakeholders.

RESULTS

Some of the considerations for tumour agnostic products were stakeholder specific, e.g. dosing strategies, orphan designation status, genetic testing strategies to identify eligible patients and comparative treatments or applying the agnostic nature to not researched tumour types. Other considerations were more universal, such as the magnitude of effect based on small sample sizes, long-term safety and heterogeneous prognoses. Some considerations were introduced by decision-making of other stakeholders, e.g. discrepancies in trial patient inclusion versus label formulation.

CONCLUSION

The introduction of disruptive therapies, such as tumour agnostics, requires flexibility of assessment frameworks (with appropriate level of scrutiny) to be able to accommodate the assessment. In turn, flexibility requires cross-stakeholder dialogue to align and prevent confusion trickling down to other stakeholders.

Want to know more?
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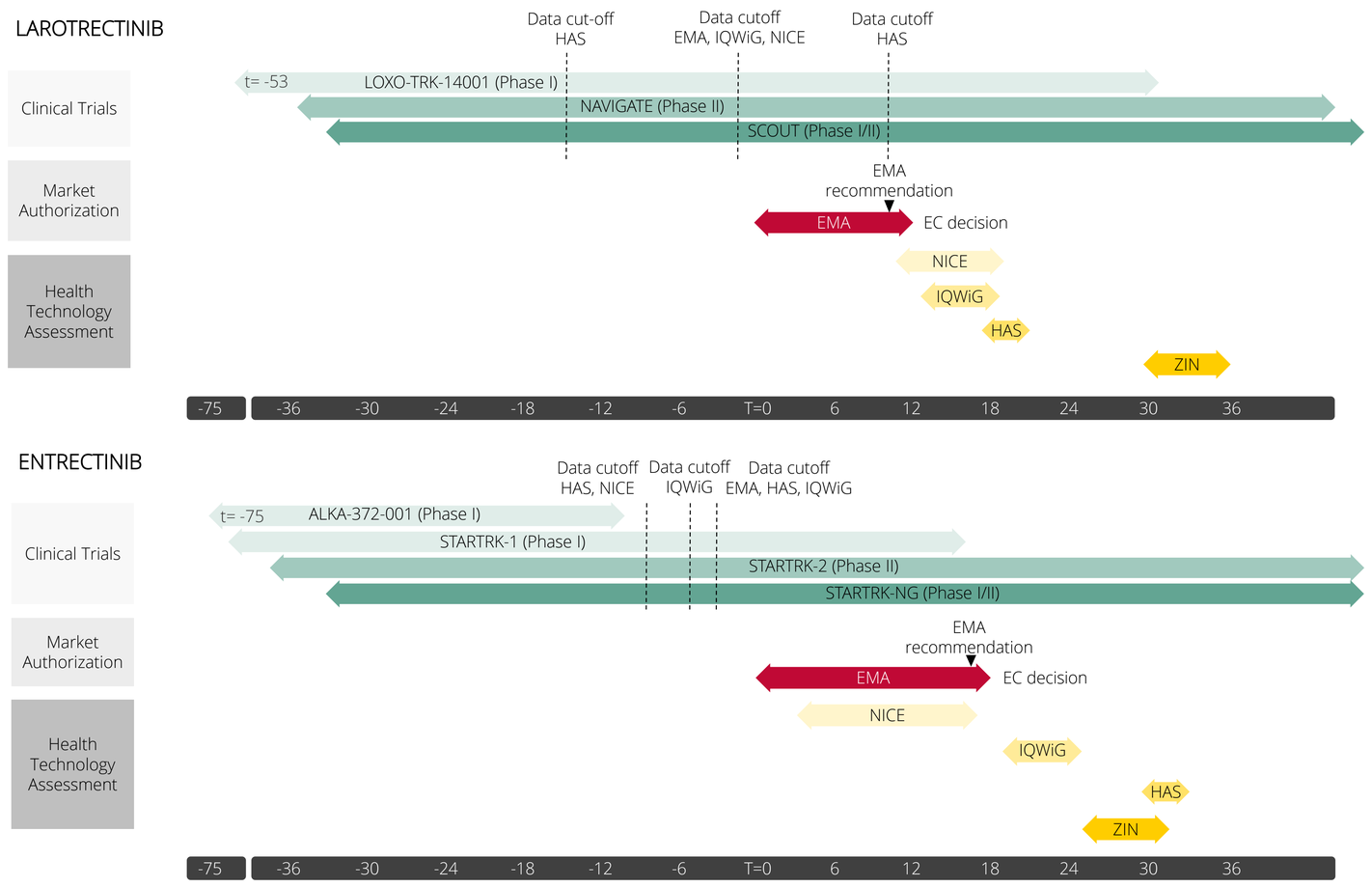
Discussion themes across stakeholders

	Population	Intervention	Comparator	Outcomes	Other
Clinical[1-8] Development	• Age • Genetic alteration • In or exclusion CNS tumours or ALK mutations • Previous NTRK	• Maximum tolerated dose • Continuous versus intermitted	• None included	• Objective Response Rate • Dose Limiting Toxicity • Quality of Life	• Trial duration • Number of participants
Market Authorisation	• Orphan designation & small sample • Paediatrics • Agnostic label • CNS & NSCLC tumours & surgically curable	• Target; NTRK as oncogenic driver • Unmet medical need for product • Modelled dose in paediatrics	n.a.	• Magnitude effect • Data immaturity • Heterogenic safety profile • Long term safety & neurological adverse events	• No accelerated Approval • Conditional approval with specific obligations • PRIME scheme & Scientific advice (1/2)
Health Technology Assessment	• Patient numbers • Generalizability (lack of common tumour types) • Label different from trial inclusion (CNS) • Heterogenic, lacking clinical characteristics	• (Previous) treatment line(s) • Unclear clinical and diagnostic pathway • Medical need for products • Target; NTRK as oncogenic driver	• Varying BSCs • Bias indirect comparison • No comparison possible • Small sample of non-responders • Substitution or addition	• Immature, short follow-up data • Magnitude effect • Long-term PFS modelling • Resistance • No OS or QoL • Poor efficacy/AE ratio • Severe AEs	• No stratification per tumour type • Stat./trial design not testing for heterogeneity • Poor NTRK characterization • CE methods • Ass. framework not suited
Clinical Guideline Development	• NTRK fusion cancer as separate tumour type	• Expert recommendation on diagnosis, emphasize agnostic nature (trial authors)	• Screening for NTRK after tumour specific treatment failure	• EMSO-MCBS = 3, based on ORR/PFS	• EMSO-MCBS accounts for rarity treatment (single-arm trials) • Prospective registry follow-up • Many not updated

Timeline of decision-making processes



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