8. Réarrangements de *ROS1*

Le crizotinib a une AMM non remboursée en première ligne et remboursée en 2ème ligne en cas de réarrangement de *ROS1*[21] (102). Les données Françaises de l'étude ACSé confirment son efficacité (103).

Lors de la progression, il est conseillé de rechercher les mécanismes de résistance sur ADN circulant ou re-biopsie tissulaire.

L'entrectinib a été évalué dans trois études de phase 1-2, avec un taux de réponse objective de 77 % et une durée médiane de réponse de 24,6 mois chez 53 patients naïfs d'ITK (104). Il dispose d'une AMM européénne dans cette indication[22] mais d'un avis d'éfavorable de la HAS[23]. Le ceritinib a une efficacité dans les réarrangements de *ROS1* chez les patients non traités par ITK antérieurement mais ne dispose pas d'AMM dans cette indication (105).

Le lorlatinib a été évalué dans une étude de phase 1/2 chez 69 patients *ROS1* dont 21 étaient naïfs de tout traitement par ITK (106). Le taux de réponse objective est de 62% chez les ITK-naïfs et 35% chez les antérieurement traités (taux de contrôle de la maladie de 91% et 75% respectivement). Le temps médian de réponse est de 25,3 mois et 13,8 mois respectivement. Cette molécule n'est pas disponible en France dans cette indication à l'heure de la rédaction de ce document.

Le brigatinib a été testé en seconde ligne (après crizotinib) chez 19 patients. Le taux de réponse objective était de 26,3% (IC 95% 9,2-48,6), le taux de contrôle de 57,9% (IC 95% 33,5-79,7%). Le taux de SSP a un an était de 26,9% (9,2-48,6%), témoignant d'une activité modeste dans cette indication[24]. Des données similaires ont été retrouvées dans un étude rétrospective (107). La molécule est désormais en phase 2 en première ligne.

Le repotrectinib, un pan-ITK (ROS1/TRK/ALK) de nouvelle génération, donne des résultats intéréssant dans des modèles précliniques, dont en cas de mutation G2032R (108). Dans l'étude TRIDENT-1, le taux de réponse objective chez les patients naïfs de tout traitement est de 91% (71-99) chez 22 patients [25].

Une chimiothérapie, si elle est réalisée, doit l'être par un doublet à base de pemetrexed.

Recommandation – Cancers de stades avancés avec réarrangement *ROS1*

- Le traitement de 1ère ligne repose sur une thérapie ciblée orale par crizotinib (250mg x 2/j).

[21] https://www.has-sante.fr/upload/docs/evamed/CT-18042_XALKORI_ROS1_PIC_REEV_AvisDef_CT18042.pdf
[22] https://www.ema.europa.eu/en/documents/product-information/rozlytrek-epar-product-information_fr.pdf
[23] https://www.has-sante.fr/jcms/p_3282234/fr/rozlytrek-entrectinib-cpnpc
[24] Daga H et al. Phase II study of brigatinib in ROS1 positive non-small cell lung cancer (NSCLC) patients previously treated with crizotinib: Barossa cohort 2. ASCO 2021, #9040.
[25] Cho et al. Phase 1/2 TRIDENT-1 Study of Repotrectinib in Patients with ROS1+ or NTRK+ Advanced Solid Tumors. WCLC 2021, #3255

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