10. Fusion de *NTRK*

Une étude groupée de trois études de phase 1 et 2, totalisant 55 patients (adultes et enfants) avec une tumeur solide présentant une fusion de NTRK (*Neurotrophic Tyrosine Receptor Kinase*) traités par Larotrectinib, a été publiée en 2018. Dans cette étude, 4 patients présentaient un cancer du poumon ; 4 patients étaient PS 2 ; 1 patient présentait des métastases cérébrales ; et 27 patients n'avaient reçu aucune ligne ou seulement une préalablement. Le taux de réponse objective était de 75% (taux de contrôle 88%). La médiane de survie sans progression n'était pas atteinte après un suivi médian de 9,9 mois (181). Dans une autre série de 14 CBNPC (dont 10 prétraités), le taux de réponse était de 71 % et le taux de contrôle de 93 % (182). Le larotrectinib (100 mg x 2/j) est indiqué en monothérapie dans le traitement des patients atteints de tumeurs solides localement avancées ou métastatiques présentant une fusion *NTRK* lorsqu'il n'existe aucune option thérapeutique satisfaisante (AMM). Néanmoins, l'avis de la commission de transparence du 10 juillet 2020 préconise son remboursement uniquement pour les formes pédiatriques. Les formes adultes disposent donc d'une AMM mais pas de remboursement en France.

L'entrectinib a également été testé dans cette situation dans 2 études de phase 1 totalisant 54 patients (dont 10 atteints de cancers bronchiques) (170). Les résultats montrent un taux de réponse objective de 57% (70% pour les cancers bronchiques). Ces données ont contribué à l'obtention d'une AMM européénne « en monothérapie chez les patients adultes et pédiatriques âgés de 12 ans et plus, atteints de tumeurs solides exprimant une fusion du gène NTRK : ayant une maladie au stade localement avancé ou métastatique ou pour laquelle une résection chirurgicale risquerait d'entraîner une morbidité sévère et, non précédemment traités par un inhibiteur NTRK lorsqu'il n'existe aucune option thérapeutique satisfaisante ». L'HAS a émis un avis défavorable au remboursement (SMR insuffisant) en Aout 2021[36].

Le selitrectinib (LOXO-195), ITK ciblant NTRK de deuxième génération a été évalué dans une étude de phase I[37] . Chez 29 patients atteints de cancer préalablement traités par un autre ITK, le taux de réponse était de 34 %. En date du 02/08/2021, le laboratoire Bayer a informé l'ANSM de l'arrêt de développement du Selitrectinib.

Par conséquent, à la date de rédaction de ce document, malgré des données cliniques encourageante dans cette forme rare de CBNPC, et malgré la présence d'AMM, de manière surprenante, la HAS a refusé l'accès précoce de toutes les alternatives thérapeutiques ciblées existantes (chez l'adulte).

Recommandation – Cancers de stades avancés avec fusion *NTRK*

-L'inclusion en essai clinique est à privilégier.

-Le larotrectinib (100 mg x 2/j) est indiqué en monothérapie dans le traitement des patients adultes et pédiatriques à partir d'un mois, atteints de tumeurs solides localement avancées ou métastatiques présentant une fusion *NTRK*, réfractaires aux traitements standards ou en l'absence d'alternative thérapeutique appropriée. Cette spécialité dispose d'une AMM mais n'est remboursée que chez l'enfant dans cette indication.

[36] https://www.has-sante.fr/jcms/p_3282231/fr/rozlytrek-entrectinib-tumeurs-solides

[37] Hyman D, et al. Phase I and expanded access experience of LOXO-195 (BAY 2731954), a selective next-generation TRK inhibitor (TRKi). AACR 2019, #CT127

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