

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 (114). Dans une autre série de 14 CBNPC (dont 10 prétraités) présentée au congrès de l'ESMO 2020, le taux de réponse était de 71 % et le taux de contrôle de 93 %²⁷. 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) (104). 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 européenne « 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 (SMR insuffisant) en Aout 2021²⁸.

Le selitrectinib (LOXO-195), ITK ciblant *NTRK* de deuxième génération a été évalué dans une étude de phase I présentée à l'ACR en 2019²⁹. 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. A compter de cette date, il n'est plus en mesure de mettre à disposition cette spécialité pour traiter de nouveaux patients, seule la poursuite des traitements déjà initiés sera assurée.

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 n'est toutefois pas remboursée en France à la date de rédaction de ce document.

²⁷ Drilon A et al. Efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (TRK) fusion lung cancer. ESMO 2020, #1289P

²⁸ https://www.has-sante.fr/jcms/p_3282231/fr/rozlytrek-entrectinib-tumeurs-solides

²⁹ 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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Cancer bronchiques non à petites cellules

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Cancer bronchiques non à petites cellules

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