Dans une étude cas-contrôle française rétrospective, il semble que le pemetrexed soit le doublet permettant les meilleurs événements en survie chez les patients avec mutation de *BRAF* (101).

Recommandation – Cancers de stades avancés avec mutation *BRAF*

-L'association dabrafénib (150 mg x2/j) et trametinib (2 mg x 1/j) est indiqué en seconde ligne (après chimiothérapie et/ou immunothérapie) chez les patients présentant un CBNPC de stade avancé avec mutation *BRAF* V600E. Elle devrait obtenir rapidement son remboursement dans cette indication.

9. 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 présentant 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 (102). Suite à cette étude, le larotrectinib a obtenu une ATU de cohorte avec l'indication suivante « 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 ». Le traitement est à poursuivre jusqu'à progression de la maladie ou jusqu'à l'apparition d'une toxicité inacceptable. Une AMM a été obtenue en septembre 2019 et l'ATU de cohorte a pris fin en Novembre 2019. A la date de rédaction de ce document, le médicament est disponible sous le régime du post-ATU en rétrocession hospitalière, sous sa forme en solution buvable uniquement.

L'entrectinib a également été testé dans cette situation dans 2 études de phase 1 totalisant 54 patients (dont 10 atteints de cancers bronchiques) (103). Les résultats montrent un taux de réponse objective de 57% (70% pour les cancers bronchiques). Ces données ont contribué à l'obtention d'une labelisation par la FDA de ce médicament aux Etats-Unis pour les cancers avec fusion NTRK.

Recommandation – Cancers de stades avancés avec fusion *NTRK*

-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 (disponible en post-ATU en rétrocession hospitalière).

10. Mutations dans l'exon 14 de *MET*

L'étude Française ACSé crizotinib a récemment été publiée (94). Au total, 28 patients ont été traités par crizotinib dans le cadre de l'essai. Le taux de réponse objective à deux cycles était de 10,7% et le meilleur taux de réponse était de 36%. La médiane de survie sans progression dans cette cohorte s'établissait à 2.4 mois. Suite à ces résultats, une RTU est en cours d'ouverture (à la date de rédaction) pour le crizotinib, pour les mutations de *MET* exon 14. Cette demande ne concerne pas les autres altérations de *MET*.

Plus récemment, les résultats d'inhibiteurs spécifiques ont été rapportés. Ainsi, le tepotinib a été testé dans l'étude VISION auprès de 87 patients (48 avec une biopsie liquide et 51 avec une biopsie tissulaire)[17]. Le taux de

[17] Paik P.K. et al. Phase II study of tepotinib in NSCLC patients with exon 14 MET mutations. ASCO 2019, #9005.

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