9. Tumeur avec mutation de *BRAF* V600E

Chez les patients présentant une mutation *BRAF* V600E, l'association dabrafenib (ciblant BRAF, 150 mg x2/j) et trametinib (ciblant MEK, 2 mg x 1/j) a montré son efficacité (dans un essai non contrôlé) en première et en seconde ligne de traitement (96–98). Cette association est désormais disponible en France pour le traitement des patients adultes ayant un cancer bronchique non à petites cellules avancé porteur d'une mutation BRAF V600E, en 2ème ligne de traitement et plus après échec de la chimiothérapie et/ou immunothérapie.

Les résultats de la cohorte française Acsé ont également été rapportés à l'ESMO 2018 pour les mutations V600E. Il s'agissait de patients prétraités (≥1 ligne), parfois lourdement, non éligibles à des essais thérapeutiques (N=101) et traités par vemurafénib. Le taux de réponse était de 45% et la durée médiane de réponse de 6,4 mois [19]. Le vémurafénib n'a pas d'AMM dans cette indication.

En première ligne, une chimiothérapie à base de sels de platine (avec ou sans immunothérapie), en l'absence de contre-indication, doit être utilisée et obéit aux mêmes règles qu'une première ligne chez les patients non mutés. Dans une étude cas-contrôle française rétrospective, il semble que le pemetrexed soit le doublet permettant la meilleure survie chez les patients avec mutation de *BRAF* (99). L'utilisation d'un TKI après immunothérapie dans cette indication nécessite un monitorage plus strict des toxicités (100).

L'utilisation de l'immunothérapie chez ces patients peut être considérée dans les mêmes conditions que chez les patients non mutés. Dans l'étude ImmunoTarget, les patients présentant une altération de *BRAF* présentent un taux de contrôle de 54% sous immunothérapie seule en monothérapie, semblant peu impacté par le statut PDL1. Il existe toutefois une différence numérique nette entre les BRAF non V600E (médiane de survie sans progression à 4,1 mois) et les V600E (médiane de survie sans progression à 1,8 mois) (27).

Il est également souhaitable d'évaluer l'opportunité d'inclusion dans des essais thérapeutiques.

Recommandation – Cancers de stades avancés avec mutation *BRAF*

-L'association dabrafénib (150 mg x2/j) et trametinib (2 mg x 1/j) est indiquée en seconde ligne (après chimiothérapie et/ou immunothérapie) chez les patients présentant un CBNPC de stade avancé avec mutation *BRAF* V600E.

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 (101). 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 %[20]. 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.

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[19] Mazière J et al. ESMO2018 #1488P

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

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