12. Réarrangement de *RET*

On estime que 1 à 2% des CBNPC présentent une fusion dans *RET* (103,104). Dans une méta-analyse récente, il semble que les caractéristiques cliniques des patients présentant ce type d'anomalie soient le sexe féminin et le jeune âge (<60 ans), sans impact évident du statut tabagique (105).

Le pralsetinib (BLU-667) est un inhibiteur avec une haute affinité pour *RET* (106). A l'ASCO 2019, Gainor a rapporté les premiers résultats de l'étude ARROW évaluant le Pralsetinib (400mg x 1/j) chez des patients avec un cancer broncho-pulmonaire présentant un réarrangement *RET* avant 1ère ligne par sel de platine (N=40) ; ou progressant après une première ligne de platine (N=80)[24]. Le taux de réponse objective de l'ensemble de la population était de 58% (taux de contrôle à 96%) sur les 58 patients évaluables (réponse objective à 60% et taux de contrôle à 100% chez les 35 patients préalablement traités par sels de platine et évaluables).

Le selpercatinib (LOXO-292) est également un inhibiteur de RET. Il a montré son intérêt dans le CBNPC dans l'étude LIBRETTO. Le taux de réponse objective était de 70% (taux de contrôle à 95%) avec une médiane de survie sans progression de 18,4 mois chez 105 patients prétraités par une chimiothérapie à base de platine ; chez 39 patients naïfs de traitement : taux de réponse objective à 90%, taux de contrôle à 92% et une médiane de survie sans progression non atteinte (107).

OPTION : Les patients présentant un réarrangement de *RET* doivent être orientés vers des essais cliniques. Alternativement, une ATU nominative pour du Pralsetinib ou du Selpercatinib peut être demandée à partir de la seconde ligne.

13. Mutations G12C de *KRAS*

Récemment, plusieurs inhibiteurs spécifiques pour les mutations de *KRAS* G12C ont émergé, en particulier le sotorasib (AMG-510) qui devrait faire l'objet d'une ATU courant 2021. Dans une étude de phase I de 59 CBNPC lourdement prétraités, le taux de réponse était de 32,2 %, le taux de contrôle de 88,1 % et la médiane de survie sans progression de 6,3 mois (108).

L'adagrasib (MRTX-849) semble également intéressant dans les études de phase 1/2[25].

Les essais en cours concernent la seconde ligne, tandis que les essais de première ligne devraient débuter en 2021.

OPTION : Les patients présentant une mutation KRAS G12C doivent être orientés vers des essais cliniques.

14. Autres altérations oncogéniques cliniquement pertinentes

Les dossiers des patients présentant une altération oncogénique cliniquement pertinente (mutations *HER2*, autres altérations de *MET*, réarrangements *NRG1*) doivent être discutés dans des RCP intégrant des biologistes moléculaires en vue d'inclusion en essais cliniques notamment.

Concernant les amplifications de MET (≥6 copies), 25 patients ont été traités par crizotinib dans la cohorte ACSé. Les résultats étaient décevants avec un taux de réponse objective à deux cycles de 16%, un taux de contrôle de la maladie à 4 cycles de 52% et une médiane de survie sans progression de 3,2 mois (92).

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