

13. Mutations G12C de KRAS

Les mutations KRAS concernent 35% des CBNPC dont 40% de mutation G12C.

Récemment, plusieurs inhibiteurs spécifiques pour les mutations de KRAS G12C ont émergé.

Le sotorasib (AMG-510) a été évalué dans une étude de phase 2 CodeBreak 100 rapporte sur 172 patients évaluable multi pré-traités, avec un suivi médian de 24,9 mois, un taux de réponse de 41%, une durée de réponse médiane de 12,3 mois, une survie à 1 an de 50%, à 2 ans de 32.5%, une médiane de survie sans progression de 6,3 mois, et une médiane de survie globale de 12,5 mois (192). L'essai de phase III CodeBreak 200 compare le sotorasib au docétaxel en 2ème ligne et plus et portait sur 345 patients. La médiane de survie sans progression est de 5,6 mois vs 4,3 mois (HR 0,66 [IC95% 0,51-0,86] p=0.002) avec un bénéfice également sur les métastases cérébrales, un taux de réponse objective à 28,1% contre 13,2%, une durée de réponse de 8.6 mois vs 6.8 mois, un taux de survie à 1 an de 24,8% vs 10,1%, et une médiane de survie globale de 11,3 mois vs 10,6 mois (HR 1,01 [IC95% 0,77-1,33] p=0.53) avec un taux de cross-over important (36% dans le bras sotorasib et 35,4% dans le bras contrôle) (193). Cette spécialité est actuellement disponible en accès précoce en seconde ligne et vient de bénéficier d'un avis favorable au remboursement.

L'adagrasib (MRTX-849) est un autre inhibiteur irréversible sélectif de KRAS G12C. L'essai de phase 2 multi-cohorte KRYSTAL 1 rapporte sur 112 patients évaluable multi pré-traités avec un suivi médian de 12,5 mois, un taux de réponse de 43%, un taux de contrôle de la maladie de 80%, une durée de réponse médiane de 8,5 mois, une médiane de survie sans progression de 6,5 mois, et une médiane de survie globale de 12,6 mois. Il existe une bonne pénétration intra-cranienne (194). Une étude de phase 3 (contre docétaxel) est en cours (KRYSTAL 12, NCT04685135).

Recommandation – Cancers de stades avancés avec mutation G12C de KRAS

-Le sotorasib est indiqué en seconde ligne après chimiothérapie, dans le cadre d'un dispositif d'accès précoce post-AMM.

-Dans les autres circonstances, les patients doivent être orientés vers des essais cliniques, notamment en première ligne.

14. Mutation HER2 (mutation ou insertion dans l'exon 20)

Plusieurs molécules ont démontrées leur intérêt dans cette indication.

L'anticorps conjugué trastuzumab-deruxtecan a montré un taux de contrôle à 84% et une médiane de durée de réponse à 9,3 mois dans l'essai DESTINY-Lung01 (195). L'essai de phase 2 DESTINY-Lung 02 a permis de déterminer la dose dans le cancer du poumon à 5,4mg/Kg. Il y a une moindre toxicité, notamment pulmonaire à cette dose.

Le poziotinib a montré des résultats préliminaires intéressants (étude ZENITH 20) (196).

En revanche, l'association Traztuzumab + Pertuzumab + docetaxel (essai IFCT R2D2) est décevante (197).

OPTION : Les patients présentant une mutation ou une insertion dans l'exon 20 de HER2 doivent être orientés vers des essais cliniques.

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