Recommandations – Cancers de stades avancés avec réarrangement *ALK (quel que soit le statut de PDL1)*

-Le traitement de 1ère ligne est l'alectinib (600 mg x 2/j) ou le brigatinib (90mg x1/j 7j puis 180mg x1/j, lorsqu'il sera remboursé).
-Le traitement de seconde ligne repose

- **sur un autre ITK anti-ALK adapté au profil moléculaire à la progression,**
- **ou un autre ITK (non utilisé au préalable) choisi parmi l'alectinib, le brigatinib, ou le ceritinib (450mg/j au cours du repas), ou le lorlatinib (100mg x1/j).**

-Le traitement de 3ème ligne et plus repose sur un ITK anti-ALK adapté au profil moléculaire à la progression, l'utilisation séquentielle des différents ITK disponibles, et/ou inclusion dans des essais thérapeutiques ou une chimiothérapie (doublet platine et pemetrexed +/- bevacizumab).
-En cas d'échec des ITK, il est recommandé d'utiliser un doublet de chimiothérapie à base de pemetrexed +/- associé au bevacizumab. L'association à l'immunothérapie n'est pas indiquée.

OPTION : Recherche des mutations de résistance aux ITK d'ALK sur re-biopsie tissulaire ou ADN tumoral circulant. En cas de mise en évidence d'une mutation de résistance, le dossier doit être discuté en RCP pour inclusion dans un essai si disponible ou traitement par un autre ITK auquel la tumeur est sensible.

8. Réarrangements de *ROS1*

Le crizotinib a une AMM dès la première ligne en cas de réarrangement de *ROS1* et dispose désormais d'un remboursement dans cette indication à la date de rédaction de ce document[18] (91). Les données Françaises de l'étude ACSé confirment son efficacité (92).
Lors de la progression, il est conseillé de rechercher les mécanismes de résistance sur ADN circulant ou re-biopsie tissulaire.
L'entrectinib a été évalué dans trois études de phase 1-2, avec un taux de réponse objective de 77 % et une durée médiane de réponse de 24,6 mois chez 53 patients naïfs d'ITK (93). Il ne dispose pas d'AMM dans cette indication.
Le ceritinib a une efficacité dans les réarrangements de *ROS1* chez les patients non traités par ITK antérieurement mais ne dispose pas d'AMM dans cette indication (94).
Le lorlatinib a été évalué dans une étude de phase 1/2 chez 69 patients *ROS1* dont 21 étaient naïfs de tout traitement par ITK (95). Le taux de réponse objective est de 62% chez les ITK-naïfs et 35% chez les antérieurement traités (taux de contrôle de la maladie de 91% et 75% respectivement). Le temps médian de réponse est de 25,3 mois et 13,8 mois respectivement. Cette molécule n'est pas disponible en France dans cette indication à l'heure de la rédaction de ce document.
Une chimiothérapie, si elle est réalisée, doit être par un doublet à base de pemetrexed.

Recommandation – Cancers de stades avancés avec réarrangement *ROS1*

- Le traitement de 1ère ligne repose sur une thérapie ciblée orale par crizotinib (250mg x 2/j).

[18] https://www.has-sante.fr/upload/docs/evamed/CT-18042_XALKORI_ROS1_PIC_REEV_AvisDef_CT18042.pdf

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