Interacties: Sotorasib + PD-(L)1-remmers M8568

Conclusie

Een signaal is nodig bij een te kort interval tussen de behandelingen; waarschuwen om geen sotorasib te starten binnen 6 weken na de laatste gift van een PD(L)-1-remmer, gezien de vergrote kans op het ontwikkelen van (verlate) immunotherapie-gerelateerde hepatotoxiciteit. Bij het ontstaan van degelijke hepatotoxiciteit is de behandeling in principe hetzelfde als bij andere immunogerelateerde toxiciteiten (bv prednison). Koppelen PD-1 & PD-L1-remmers.

Overige opmerkingen

PD = programmed cell death 1-receptor
PD-1-remmers: oa pembrolizumab, nivolumab, cemiplimab, dostarlimab
PD-L1-remmers: durvalumab, atezolizumab, avelumab

Werkgroep Interacties Oncologische middelen: discussie of de studies onderbouwend zijn voor 'interactie', maar ze geven wel genoeg aanleiding voor een signaal.

	Interactie	Actie	Datum
Beslissing werkgroep OncoIA	Ja	Ja	25-6-2025

Literatuur

Onderbouwend	Stof	Effect	Code
Ernst SM. EBioMedicine 2024 Apr;102:105074.	Sotorasib + PD-(L)1-remmers	Prior anti-PD-(L)1 and prior immune-related hepatotoxicity were associated with a higher incidence of severe hepatotoxicity (35% vs 0%, p = 0.016 resp. 75% vs 31%, p = 0.019). Patients with an interval of ≤6 weeks between anti-PD-(L)1 and sotorasib (n = 18) had a significantly higher incidence of severe hepatotoxicity than those with a 6-12 week (n = 24) and ≥12 week (n = 38) interval (83% vs 33% vs 13%, respectively, p < 0.0001). Sotorasib trough concentrations did not differ significantly between those with or without severe hepatotoxicity (106 vs 126 ng/mL, p = 0.16). Pembrolizumab concentrations were higher in those with severe hepatotoxicity vs those without (25.6 vs 6.1 µg/mL, p < 0.0001). Methods: patients with KRASG12C-mutated NSCLC treated with sotorasib were prospectively enrolled in our biomarker cohort study (NCT05221372). Plasma samples were collected prior and during sotorasib treatment for anti-PD-1 and sotorasib concentrations. ALT/AST/ALP/GGT increases were collected prospectively and graded according to CTCAEv5.0. Severe hepatotoxicity was defined as grade ≥3 ALT/AST/ ALP/GGT increase. 80 of the 91 included patients (88%) received prior anti-PD-(L)1. Interpretation: in this preliminary prospective study, sotorasib after PD-(L)1 blockade was associated with severe hepatotoxicity, especially in patients with a short interval between treatments, prior immune-related hepatitis and higher anti-PD-1 plasma concentrations. Our results suggest	(3?)

		a minimum interval of 6 weeks between anti-PD-(L)1 and sotorasib to minimize the risk of hepatotoxicity.	
Chour A. J Thorac Oncol 2023;18:1408-15. KRASG12C inhibitor sotorasib may trigger severe immune-mediated hepatotoxicity when used in sequence or in combination with anti-PD-(L)1. Gelsomino F. J Thorac Oncol 2023;18:e112-3. = commentaar op Chour A. Die reageert daar weer weer op: Chour A. J Thorac Oncol 2023;18:e114-e5. GIC: gaat erg ver, niet uitgewerkt.	Sotorasib + PD-(L)1-remmers	severe sotorasib-related AEs were significantly more frequent in the sequence group compared with those in the control group (50% vs 13%, p < 0.001); severe sotorasib-related AEs occurred in 24 patients (24 of 48, 50%) in the sequence group, and among them 16 (67%) experienced a severe sotorasib-related hepatotoxicity. Severe sotorasib-related hepatotoxicity was 3-fold more frequent in the sequence group compared with that in the control group (33% vs 11%, p = 0.006). No fatal sotorasib-related hepatotoxicity was reported. Non-liver severe sotorasib-related AEs were significantly more frequent in the sequence group (27% vs 4%, p < 0.001). Severe sotorasib-related AEs typically occurred in patients who received last anti-PD-(L)1 infusion within 30 days before sotorasib initiation. Methods: retrospective study of consecutive advanced KRASG12C-mutant NSCLC treated with sotorasib outside clinical trials; patient records were reviewed to identify sotorasib-related AEs (National Cancer Institute Common Classification Criteria for Adverse Events-Version 5.0). Grade 3 and higher AE was considered as severe. Sequence group: pat. who received an anti-PD-(L)1 as last line of treatment before sotorasib initiation (n=48 (47%)). Control group: pat. who did not receive an anti-PD-(L)1 treatment before sotorasib (n=54 (53%)); control pat. received an anti-PD-(L)1 followed by at least one treatment regimen before sotorasib in 87% of the cases or did not receive an anti-PD-(L)1 at any time before sotorasib in 13% of the cases. Conclusions: sequential anti-PD-(L)1 and sotorasib therapy are associated with a significantly increased risk of severe sotorasib-related hepatotoxicity and severe non-liver AEs. We suggest avoiding starting sotorasib within 30 days from the last anti-PD-(L)1 infusion.	(3?)

Overig	**Stof**	**Effect**
SPC Lumykras	Sotorasib + PD-(L)1-remmers	Sotorasib kan hepatotoxiciteit veroorzaken. Het is in verband gebracht met een tijdelijke verhoging van ALAT, ASAT, alkalische fosfatase en totaal bilirubine in klinische onderzoeken met 960 mg als monotherapie. Bij in totaal 740 patiënten met een solide tumor met KRAS G12C-mutatie die dagelijks 960 mg Lumykras kregen als monotherapie, is de incidentie van hepatotoxiciteit het hoogst in de subgroep van patiënten die recent (≤ 3 maanden geleden) immuun-therapie kregen (38%) voordat werd gestart met Lumykras, vergeleken met degenen die meer dan 3 maanden na de laatste dosis immuuntherapie met Lumykras waren gestart (17%) en degenen die nooit immuuntherapie kregen (22%). Ongeacht het moment van de eerdere immuuntherapie verbeterde of verdween 87% van de verhogingen bij een onderbreking van de behandeling met Lumykras en een behandeling met corticosteroïden.
	sotorasib	Bij stijging van ALAT en/of ASAT graad 2 met symptomen, of stijging van ALAT en/of ASAT graad 3 of hoger, de behandeling onderbreken tot herstel tot graad 1 of lager.

		Bij stijging van ALAT en/of ASAT >3x ULN en stijging van bilirubine >2x ULN de behandeling permanent staken.

Zoektermen Pubmed

Datum: jan 2025

Search #	“geneesmiddel A” AND “geneesmiddel B” AND (“drug interaction” OR "Drug Interactions"[MeSH Terms])
#1	Sotorasib and Anti–PD-(L)1 and hepatotoxicity