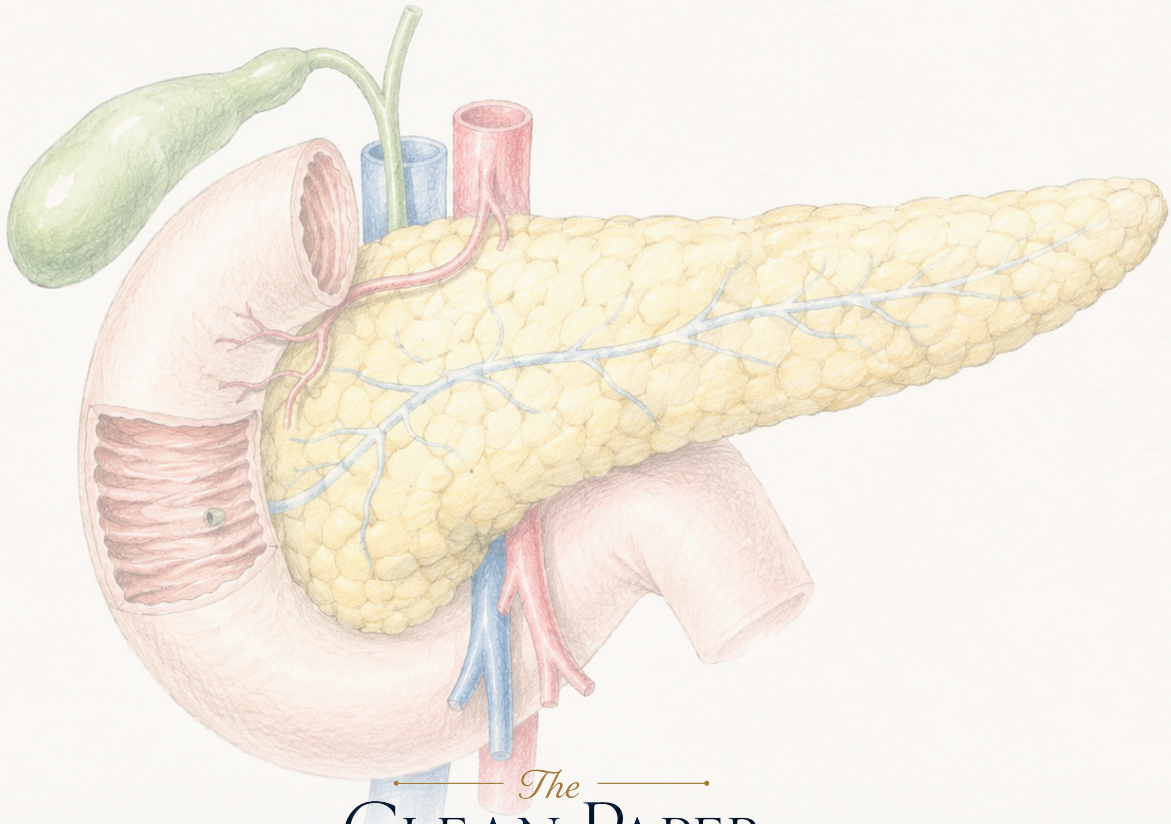

The Clean Paper

WHAT THE PAPER SAYS · WHAT IT DOESN'T · WHY IT MATTERS

KRAS vaccine ya haifar da T cell responses a 18 cikin high-risk participants 20 — ba hujjar cewa yana hana pancreatic cancer ba

Single-centre phase I trial ya gwada six-mutation KRAS peptide vaccine a mutane 20 masu inherited ko familial risk na pancreatic cancer da pancreatic cystic abnormalities. Vaccine-related adverse events sun kasance grade 1 ko 2; mahalarta 18 sun cika prespecified criterion na T cell response a jini; kuma kananan analyses sun nuna cewa wasu immune responses sun ci gaba har zuwa shekaru biyu. Babu mahalarci da ya samu pancreatic cancer a median follow-up na watanni 16.5, amma binciken open-label, non-randomized, single-arm ne kuma ba a tsara shi don gwada prevention ba. Vaccine d'in experimental ne; sakamakon yana goyon bayan larger efficacy trials, ba da'awar cewa an hana cancer ba.

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Paper: *First-in-human testing of a mutant KRAS vaccine for pancreatic cancer interception in high-risk cohorts*, S. Daniel Haldar, Amanda L. Huff, Hejia Henry Wang, Zirui Zhu, Maureen Berg, Jiayun Lu, Nancy Sun, Elizabeth Abou Diwan, Hassan Sinan, Christopher J. Thoburn, Matthew Z. Guo, Takeichi Yoshida, Linda C. Chu, Anna K. Ferguson, Dimitrios N. Sidiropoulos, Luciane T. Kagohara, Won Jin Ho, Katherine M. Bever, Marina Baretti, Mark Yarchoan, Daniel A. Laheru, Julie M. Nauroth, Amy M. Thomas, Hao Wang, Nilofer S. Azad, Michael G. Goggins, Elizabeth M. Jaffee, Neeha Zaidi, Cancer Discovery (2026), online ahead of print · DOI: 10.1158/2159-8290.CD-25-2245

Rigakafin ya tayar da martanin garkuwar jiki. Ko yana hana cuta kuwa har yanzu ba a sani ba

Wani experimental vaccine da aka tsara domin nau'ikan **KRAS** masu mutation guda shida da ake yawan gani — KRAS shi ne gene da yake sauyawa a yawancin pancreatic cancers — ya haifar da T-cell response da za a iya aunawa a mutane 18 daga cikin 20 da suke da inherited ko familial risk na cutar. A wannan phase I study, adverse events da aka danganta da vaccine duk grade 1 ko 2 ne a CTCAE scale na National Cancer Institute: grade 1 yawanci mild ne, grade 2 moderate, sannan scale ɗin ya ci gaba zuwa grade 3 severe, grade 4 life-threatening da grade 5 mutuwar da adverse event ya haifar. Wasu T-cell clonotypes da vaccine ya tayar har yanzu ana iya gano su bayan shekara ɗaya ko biyu. **Clonotype** lineage ne na T cells da ake gane su ta shared T-cell receptor sequence; bin clonotypes yana ba masu bincike damar tambayar ko irin waɗannan vaccine-reactive lineages suna ci gaba da kasancewa tsawon lokaci.

Waɗannan sakamako ne masu muhimmanci a matakin farko. Amma sun fi ƙanƙanta sosai fiye da cewa "rigakafi ya hana pancreatic cancer." Gwajin ƙarami ne, single-arm, open-label, kuma an tsara shi ne domin **safety da immunogenicity**, ba domin auna yawan kamuwa da cancer ba. Babu participant da ya samu pancreatic ductal adenocarcinoma (PDAC) cikin median follow-up na watanni 16.5, amma da participants 20 da aka zaɓa musamman, babu randomized control group, kuma follow-up gajere ne, wannan ba zai iya tabbatar da prevention ba.

Saboda haka fassarar da ta dace tana da ɓangarori biyu: vaccine ɗin ya nuna cewa ana iya amfani da shi kuma yana iya tayar da immune response yadda ya kamata har a cancanci manyan trials; amma ko yana ba da clinical benefit har yanzu ba a sani ba.

Waɗanne mutane suka shiga gwajin

Phase I trial na Johns Hopkins, wanda aka yi rajista da **NCT05013216 Cohort A**, ya ɗauki mutane 20 tsakanin Afrilu 2022 da Fabrairu 2026. Ba population na general screening ba ne. Kowane participant ya cika aƙalla ɗaya daga predefined high-risk criteria bisa family history ko **germline** cancer-predisposition variant — wato inherited DNA change da ke cikin jiki gaba ɗaya, ba mutation da ya taso a tumour kaɗai ba — kuma dukansu suna da wani radiographic pancreatic abnormality da aka ware a matsayin intraductal papillary mucinous neoplasm (IPMN).

Median age na cohort ya kasance shekaru 66.5. Mutane 17 daga 20 suna da first-degree relative mai PDAC, 12 suna ɗauke da germline variant, kuma largest pancreatic cyst yana da median diameter na 0.7 cm. Participants tara suna da cysts a fiye da yanki guda na pancreas.

Wannan zaɓin yana da muhimmanci. Binciken yana tambaya ko vaccination za a iya jurewa kuma ko zai iya horar da T cells a wani rukuni da ake sa ido sosai kuma risk ɗinsa ya fi na al'umma yawa. Ba ya gaya mana yadda vaccine zai yi aiki ga masu average risk, ga patients da suke da pancreatic cancer tuni, ko ga population mafi faɗi da bambanci; participants 19 daga cikin 20 White ne.

Menene mKRAS-VAX?

KRAS signalling protein ne. Mutations da ke barinsa a kunne suna daga cikin early driver events a fiye da 90% na PDACs, kuma suna yawan bayyana a precursor lesions na pancreas. **mKRAS-VAX** pooled synthetic long-peptide vaccine ne da ke rufe recurrent mutations guda shida: G12V, G12A, G12R, G12C, G12D da G13D. Peptides chains ne na amino acids, waɗanda su ne tubalan ginin proteins; a nan kowane “long” peptide wani KRAS fragment ne mai amino acids 21 da ya ƙunshi mutant site guda ɗaya. **Pooled** yana nufin an haɗa fragments shida da aka riga aka ƙera cikin vaccine guda ɗaya da za a iya amfani da shi ga mutane daban-daban, maimakon a ƙera sequence ta musamman ga kowane participant.

Participants sun karɓi vaccination rounds huɗu a makonni 1, 3, 5 da 13. Kowane round ya haɗa peptide pool da immune-stimulating adjuvant poly-ICLC, sannan aka yi injections a wurare da dama ƙarƙashin fata. **Adjuvant** wani sinadari ne mai taimaka wa vaccine ta hanyar ƙarfafa ko karkatar da immune response zuwa target; poly-ICLC kansa ba KRAS target ba ne. Manufar ba “a gane tumour na mutum guda” ba ce, sai dai “a gane wasu mutant-KRAS sequences da suke maimaituwa a pancreatic precancers da yawa.”

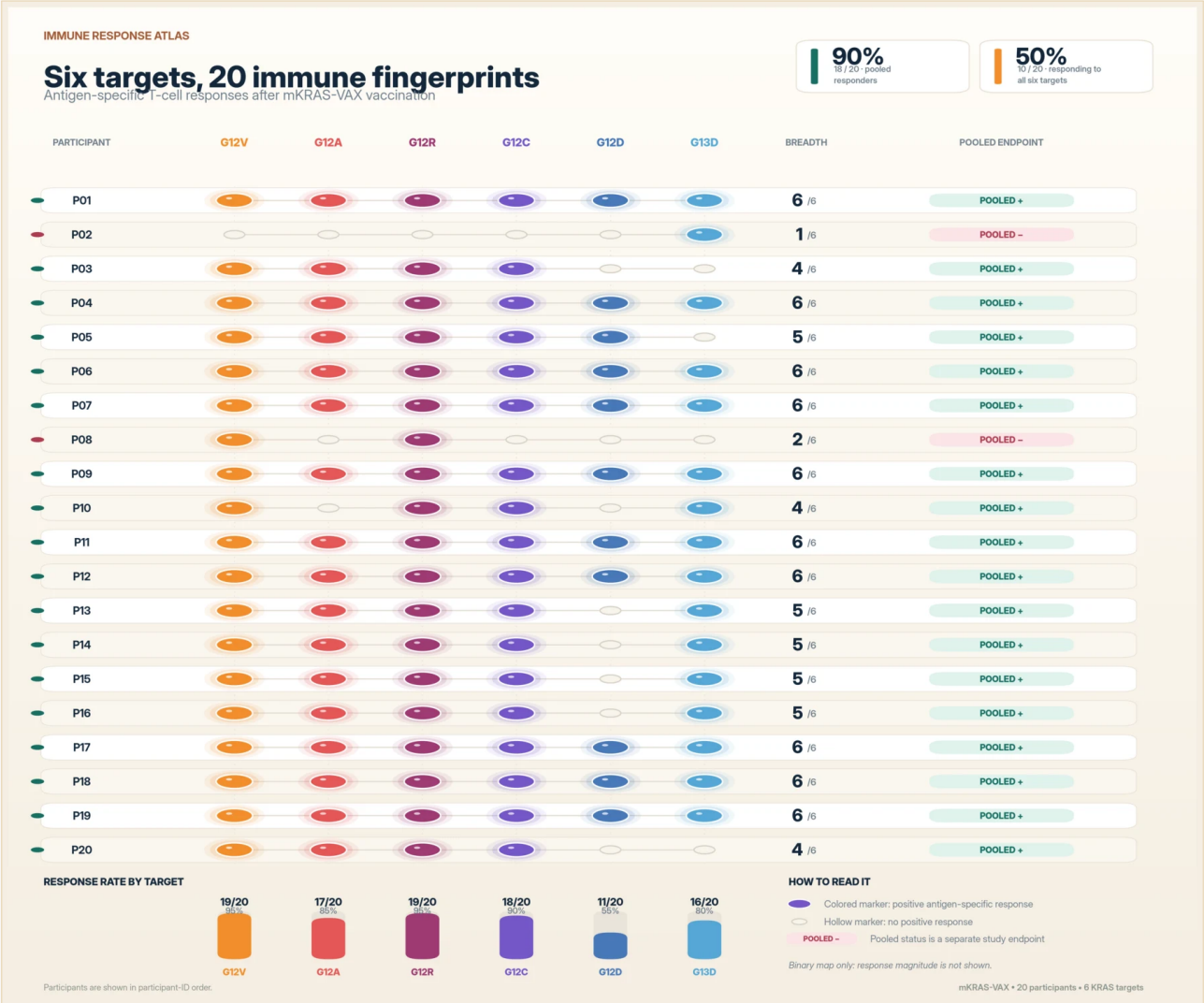
Formulation da aka tsara ya yi amfani da six-mutation non-personalized pool iri ɗaya a kowane round; ba a sake ƙera shi ga kowane mutum ko ziyara ba. Akwai manufacturing caveat guda ɗaya: an cire G12A peptide daga wasu doses, kuma takardar ba ta gano significant difference a G12A response tsakanin waɗanda suka karɓe shi a aƙalla rounds uku daga huɗu da waɗanda aka cire musu shi ba.

Co-primary endpoints na trial ɗin su ne safety da canjin mutant-KRAS-specific T-cell activity a jini cikin makonni 17. Ba a tsara trial ɗin, kuma ba shi da statistical power, domin gwada ko vaccination ya rage cancer diagnoses ko deaths.

Abin da sakamakon safety da immune response ya nuna

Ba a bayar da rahoton wani vaccine-related event da ya wuce grade 2 a participants 20 ba. Injection-site reactions sun faru a 85%, fatigue a 70%, chills a 40%, da flu-like symptoms a 40%; takardar ta ce waɗannan events sun tafi da kansu. Wannan alama ce mai kyau ta early safety, amma ba cikakken safety profile ba ne. Bincike mai mutane 20 ba zai iya gano rare ko delayed harms da kyau ba.

Domin a duba ko vaccine ya horar da T cells na jini su gane mutant KRAS, masu bincike sun fallasa blood cells da aka tattara kafin da bayan vaccination ga peptides shida, sannan suka yi amfani da IFN-gamma ELISpot assay wajen ƙirga cells da suka amsa. Participants **18 daga 20** sun cika prespecified immune-responder criterion na takardar: fiye da **2.5-fold increase** a pooled response ga KRAS antigens shida. Median pooled increase ya kai **18.2-fold**, da range daga 1.8 zuwa 167.1. Participants goma sun yi statistically significant response ga duk antigens shida; hatta participants biyun da ba su kai pooled responder threshold ba sun amsa ga selected mutations.



Participants goma sun nuna significant T-cell responses ga duk mutation-specific antigens shida. Participants biyun da ba su kai separate pooled-response threshold ba har yanzu sun amsa ga mutation ɗaya ko biyu.

Original chart — The Clean Paper; counts transcribed from Haldar et al., Cancer Discovery 2026, Figure 1f CC BY 4.0

Response ɗin bai yi daidai ga kowane mutation ba. G12A, G12V da G12R yawanci sun haifar da signals masu girma fiye da G12D da G13D. Binciken ya kuma ga responses a HLA types daban-daban; wannan yana goyon bayan — amma ba ya tabbatar — ra'ayin cewa shared peptide pool zai iya aiki ba tare da a ƙera vaccine daban ga kowane mutum ba.

Kalmar "durable" tana dogara da ƙananan subsets

Sakamakon persistence a takardar yana da gaske, amma yawan mutanen da ake da bayanansu yana raguwa yayin da follow-up yake tsawo.

Participants 16 sun dawo domin optional annual blood collection, kuma biyar ne kawai suka kai two-year visit kafin data cutoff. A direct ex vivo testing, 3 daga cikin 16 sun ci gaba da nuna significant pooled response, kuma 8 sun ci gaba da significant response ga aƙalla KRAS antigen ɗaya. Lokacin da masu bincike suka faɗaɗa blood

cells da KRAS peptides a lab, sun sake gano responses a duk mutane biyar da aka gwada a long-term follow-up. Wannan procedure na iya gano low-frequency memory cells, amma ba daidai yake da auna babban circulating response kai tsaye ba.

T-cell receptor sequencing ya zurfafa binciken a subsets mafi ƙanƙanta. Ga G12D da G12V, team ɗin ya ayyana **putative** vaccine-induced clonotypes ta stringent enrichment criteria kuma ya bi su a participants uku ga kowane antigen. **Putative** a nan yana nufin an infer cewa vaccine ne ya tayar da su saboda lokacin bayyana da selective expansion bayan mutant-KRAS stimulation; ba a yi direct test da ya tabbatar kowane receptor yana bind KRAS ba. Median **18.6%** na prime-phase clonotypes sun kasance reactive bayan shekara ɗaya ko biyu. Wannan yana goyon bayan cewa wani ɓangare na vaccine-linked immune memory ya dawwama; ba ya nuna cewa cells ɗin sun shiga precursor tissue na pancreas ko sun hana lesion zama cancer.

Kwatancen cyst exploratory ne, ba sakamakon efficacy ba

Bayan median watanni 16.5, babu ɗaya daga participants 20 da ya samu PDAC ko high-risk lesion da ya bukaci surgery. Wannan abin ƙarfafa gwiwa ne a gani, amma bai isa a fassara shi a matsayin prevention ba. Babu randomized control arm, cohort ɗin ƙarami ne, kuma pancreatic cancer na iya ɗaukar shekaru kafin ya bayyana.

Masu binciken sun kuma yi post hoc imaging analysis a vaccinated participants 16 da suke da follow-up scans. Small cysts uku sun bayyana sun ɓace, wasu uku kuma sun ragu da aƙalla 2 mm. Reduction-or-resolution rate na 37.5% ya fi 6.8% da aka gani a wani separately assembled unvaccinated surveillance cohort, da Fisher's exact p-value na 0.01. Fisher's exact test yana kwatanta proportions a ƙaramin count table; a ƙarƙashin model na babu difference, split da ya kai wannan rashin daidaito ko ya fi shi zai faru da chance kusan 1% na lokaci. Amma wannan ba ya gyara matsalolin post hoc da non-randomized comparison, kuma ba ya mayar da association ya zama causation. Don karin bayani kan abin da p-value zai iya da ba zai iya cewa ba, duba jagorar karanta sakamakon clinical.

Wannan comparison yana haifar da hypothesis ne; ba ya tabbatar da vaccine efficacy. Allocation ba randomized ba ne, analysis post hoc ne, follow-up imaging bai samu ga vaccinated participants huɗu ba, kuma cysts da suka ɓace kusan 4 mm ne — ƙanana har measurement da imaging variability za su iya yin tasiri. Marubutan kansu sun ce ba za su iya kawar da technical imaging effects ba kuma sample da follow-up ba su isa a haɗa immune responses da cyst stability ko PDAC incidence ba. PanIN lesions, waɗanda su ne mafi yawan precursors, yawanci ba a ganin su a routine imaging kuma ba a auna su kai tsaye ba.

Menene phase I da immunogenicity a nan?

Phase I yana nufin wannan early human study ce da aka fi mayar da hankali kan tolerability, feasibility da biological activity. Ba wannan ne matakin trial da ke tabbatar da prevention ba.
Immunogenicity yana nufin vaccine ya haifar da measurable immune response ga targets ɗinsa. T-cell response mataki ne da wannan strategy take buƙata, amma laboratory surrogate result ne, ba hujjar cewa cancer risk ya ragu ba.
Interception yana nufin ƙoƙarin dakatar da cancer a high-risk ko precancerous state. A nan manufar research programme ce, ba outcome da wannan trial ya tabbatar ba.

Abin da wannan bai tabbatar ba

- Bai nuna cewa mKRAS-VAX yana hana pancreatic cancer ba. Ba a kafa efficacy endpoint ba, babu randomized control arm, kuma watanni 16.5 gajere ne idan aka kwatanta da natural history na PDAC.
- Bai nuna cewa rashin samun PDAC a participants ya faru ne saboda vaccination ba. A participants 20 masu high risk, ba a san tabbas cancers nawa ake sa ran su bayyana cikin wannan gajeren lokaci ba, kuma adadin na iya zama kaɗan ko da babu treatment.
- Bai nuna cewa vaccine ya rage ko ya kawar da precancerous cysts ba. Kwatancen post hoc ne, non-randomized, kuma an yi shi da separately assembled surveillance cohort; participants huɗu ba su da follow-up imaging; cysts ɗin kuma ƙanana ne, kusan 4 mm, har measurement variability za ta iya tasiri.
- Wannan ba approved vaccine ba ne. mKRAS-VAX har yanzu experimental ne kuma an gwada shi a centre guda cikin selected cohort.
- Bai tabbatar da benefit ga average-risk people, patients da active PDAC, ko duk hereditary-risk groups ba.
- Bai nuna cewa T cells na jini sun shiga pancreas, sun gane precursor cells a tissue ko su ne suka haifar da canjin cysts ba. Wani separate window-of-opportunity cohort ne aka tsara domin tambayar tissue-level questions.
- Bai warware long-term safety ko durability ba. Rare harms suna buƙatar manyan cohorts, kuma mafi ƙarfan analyses na shekara ɗaya zuwa biyu sun yi amfani da ƙananan subsets da laboratory expansion.

Yaya ƙarfin shaidar yake?

Shaidar tana da kyau ga narrow phase I conclusions: takardar ta bayar da short-term safety data na participants 20, 18 sun cika prespecified blood-based immune-response criterion, kuma assays iri-iri sun goyi bayan kasancewa da persistence na mutant-KRAS-reactive T cells.

Shaidar clinical benefit kuwa tana da rauni, domin trial ɗin ba a gina shi domin auna hakan ba. Success criteria ɗinsa safety ne da canjin blood immune marker. Safety endpoint yana magana ne kan short-term tolerability, immunogenicity kuma surrogate ce ta clinical benefit; babu ɗayansu da ke tabbatar da cancer prevention. Rashin PDAC, cyst comparison da kalmar “interception” ya kamata a ɗauke su a matsayin dalilan yin controlled, longer studies — ba madadin irin waɗannan studies ba. Binciken investigator-initiated ne a centre guda, kuma wasu immunologic experiments sun yi amfani da participants uku zuwa biyar kawai.

Ya dace kuma conflicts of interest su kasance bayyane. Wasu authors sun bayar da rahoton filed patents da suka shafi KRAS peptides ko T-cell receptors, sannan wasu sun bayar da consulting, research ko sauran alaƙa da biotech da pharmaceutical companies, ciki har da Adventris. Wannan ba ya soke measurements, amma yana ƙara muhimmancin independent replication da controlled efficacy trials.

Me ya sa wannan yake da muhimmanci

Pancreatic cancer sau da yawa ana ganinsa ne bayan ya yi nisa har curative treatment ya yi wahala. KRAS mutations suna tasowa da wuri kuma suna maimaituwa a precursor lesions da yawa, saboda haka target ne mai jan hankali ga wani “off-the-shelf” immune strategy kafin invasive cancer ya bayyana. Wannan trial ya tsallake wani early hurdle:

a ƙaramin high-risk cohort, peptide pool bai haifar da severe vaccine-related toxicity ba kuma yawanci ya samar da T-cell signal da ake nema.

Mataki na gaba ya fi wahala sosai. Masu bincike dole su nuna cewa response ɗin yana kai wa pancreatic tissue da ya dace, yana dawwama cikin aminci, kuma yana canza clinically meaningful outcomes a manyan populations da suke da controls masu dacewa. Har sai an nuna hakan, wannan promising immune-engineering result ne, ba prevention result ba.

Taƙaitaccen bayani

Single-centre phase I trial ya ba mutane 20 masu familial ko germline pancreatic-cancer risk da pancreatic cystic abnormalities wani six-mutation KRAS peptide vaccine. Vaccine-related adverse events duk grade 1 ko 2 ne, kuma participants 18 sun cika prespecified mutant-KRAS-specific T-cell response criterion. Ƙananan follow-up analyses sun gano persistent responses ko putative vaccine-induced clonotypes a wasu participants har zuwa shekara biyu. Babu participant da ya samu PDAC cikin median watanni 16.5, amma trial ɗin single-arm, non-randomized ne kuma ba a tsara shi domin gwada prevention ba. Vaccine ɗin experimental ne; binciken yana goyon bayan manyan efficacy trials, ba ikirarin cewa an hana pancreatic cancer ba.

Bincike ba tare da ƙarin gishiri ba

Abin da takardar ta nuna: A participants 20 da aka zaɓa saboda high risk, ba a bayar da rahoton vaccine-related event sama da grade 2 ba, kuma mKRAS-VAX ya haifar da prespecified blood T-cell response a 18 daga 20. Wasu immune responses da putative vaccine-induced clonotypes sun ci gaba da kasancewa a later visits.

Abin da yake da alƙawari amma ba a tabbatar ba: Waɗannan T cells na iya samar da useful immune surveillance ga pancreatic precursor lesions kuma wata rana su rage PDAC incidence.

Abin da ba ta nuna ba: Prevention na pancreatic cancer; clinical efficacy; approval; benefit ga general population; tissue-level killing na precancer cells; ko long-term safety a babban population.

Manyan iyakoki: Participants 20; centre guda; open-label, non-randomized da single-arm; short median follow-up; babu efficacy endpoint; post hoc cyst analysis da non-randomized comparator; optional long-term visits da ƙananan immune-analysis subsets; yawancin measurements daga peripheral blood ne.

Yawan amincewar da ya dace: Matsakaicin zuwa babban amincewa cewa vaccine ɗin ya kasance tolerable kuma immunogenic a wannan ƙaramin cohort. Amma amincewa cewa yana hana pancreatic cancer ta yi ƙasa sosai, domin wannan study ba ta gwada wannan tambayar da tsarin da zai iya ba da amsa ba.

Majiyoyi

Haldar et al., First-in-human testing of a mutant KRAS vaccine for pancreatic cancer interception in high-risk cohorts, Cancer Discovery (2026)
https://doi.org/10.1158/2159-8290.CD-25-2245

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