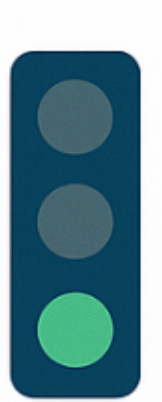
Praktisk gjennomføring



Rekruttering, samtykkeinformasjon og sikkerhetsrapportering

Forskerinitierte kliniske studier - Fra idé til publikasjon 26.11.26

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Seksjon for utprøvende kreftbehandling



nature medicine

Article

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Atezolizumab plus anthracycline-based chemotherapy in metastatic triple-negative breast cancer: t
phase 2b ALICE

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Check for updates

The prognosis for patients with metastatic triple
cer (mTNBC) is poor, with a median survival of
and the therapeutic options are limited[1]. Immu
tors (ICIs) targeting PDL/PD-L1 are effective ag
ease in many cancer forms but have limited eff

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Open access Original research

Journal for ImmunoTherapy of Cancer

Ipilimumab and nivolumab combined with anthracycline-based chemotherapy in metastatic hormone receptor-positive breast cancer: a randomized phase 2b trial

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Check for updates

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ABSTRACT

Background Immune checkpoint inhibitors have shown minimal clinical activity in hormone receptor-positive metastatic breast cancer (HR⁺mBC). Doxorubicin and low-dose cyclophosphamide are reported to induce immune responses and counter regulatory T cells (Tregs). Here, we report the efficacy and safety of combined programmed cell death protein-1/cytotoxic T-lymphocyte-associated protein 4 blockade concomitant with or after immunomodulatory chemotherapy for HR⁺mBC.

Methods Patients with HR⁺mBC starting first-/second-line chemotherapy (chemo) were randomized 2:3 to chemotherapy (pegylated liposomal doxorubicin 20 mg/m² every second week plus cyclophosphamide 50 mg by mouth/day in every other 2-week cycle) with or without concomitant ipilimumab (ipi; 1 mg/kg every sixth week) and nivolumab (nivo; 240 mg every second week). Patients in the chemo-only arm were offered cross-over to ipi/nivo without chemotherapy. Co-primary endpoints were safety in all patients starting therapy and progression-free survival (PFS) in the per-protocol (PP) population, defined as all patients evaluated for response and receiving at least two treatment cycles. Secondary endpoints included objective response rate, clinical benefit rate, Treg changes during therapy and assessment of programmed death-ligand 1 (PD-L1), mutational burden and immune gene signatures as biomarkers.

Results Eighty-two patients were randomized and received immune-chemo (N=49) or chemo-only (N=33), 16 patients continued to the ipi/nivo-only cross-over arm. Median follow-up was 41.4 months. Serious adverse events occurred in 63% in the immune-chemo arm, 39% in the chemo-only arm and 31% in the cross-over-arm. In the PP population (N=78) median PFS in the immune-chemo arm was 5.1 months, compared with 3.6 months in the chemo-only arm, with HR 0.94 (95% CI 0.59 to 1.51). Clinical benefit rates were 55% (26/47) and 48% (15/31) in the immune-chemo and chemo-only arms, respectively. In the cross-over-arm (ipi/nivo-only), objective responses were observed in 19% of patients (3/16) and clinical benefit in 25% (4/16). Treg levels in blood decreased after study chemotherapy. High-grade immune-related adverse events were associated with prolonged PFS. PD-L1 status and mutational burden were not associated with ipi/nivo benefit, whereas a numerical PFS advantage was observed for patients with a high Treg gene signature in tumor.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Therapies blocking the programmed cell death protein-1 (PD-1)-axis are approved for metastatic programmed death-ligand 1-positive triple-negative breast cancer (BC), whereas there is little knowledge on the activity of these drugs against hormone receptor-positive (HR⁺) metastatic BC. Doxorubicin and cyclophosphamide reportedly have immunostimulatory properties, but clinical data on their potential synergy with immune checkpoint blockade are lacking.

WHAT THIS STUDY ADDS

⇒ This randomized open-label trial demonstrates that the concomitant addition of PD-1/cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade to doxorubicin and cyclophosphamide increases the risk of high-grade adverse events without improving clinical activity compared with chemotherapy alone in metastatic HR⁺ BC. However, a subgroup of patients obtained clinical benefit from ipilimumab and nivolumab administered after stopping chemotherapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings provide a rationale for further trials exploring dual PD-1/CTLA-4 blockade in HR⁺ BC, but suggest that combination of these agents with chemotherapy should be sequential rather than concomitant.

BMJ

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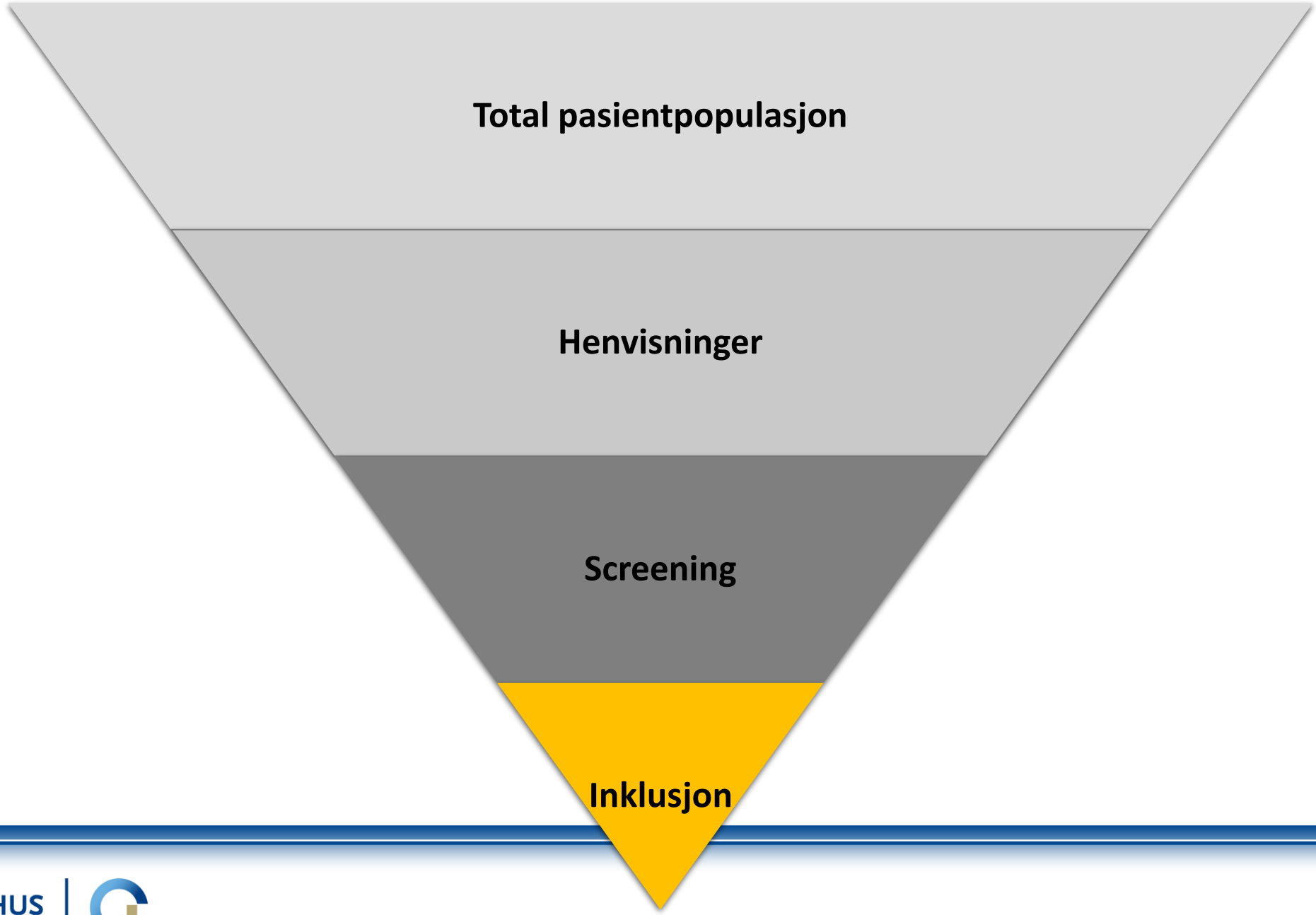
REKRUTTERING AV PASIENTER

Lasagna's Law:

The incidence of patient availability sharply decreases when a clinical trial begins and returns to its original level as soon as the trial is completed.

Louis Lasagna 1970


Total pasientpopulasjon
Henvisninger
Screening
Inklusjon

Sen rekruttering – hvor lekker det?

- Kunnskap om studien?
- Interesse?
  - Forankring i fagmiljøet?
  - Konkurrerende studier?
- Snevre inklusjons-/eksklusjonskriterier?
- Praktiske flaskehalser?

Sen rekruttering – praktiske forslag

- Forenkle inklusjons- eller eksklusjonskriterier?
- Omtale i media? Pasientorganisasjoner?
- Åpne nye sites?
- Stenge studien tidlig?

5.0 EXCLUSION CRITERIA

The subject must be excluded from participating in the trial if the subject has/is:

1. Malignancies other than breast cancer within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer)
2. Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for > ~~8~~ 2 weeks prior to randomization
3. Known CNS disease, except for ~~treated~~ asymptomatic CNS metastases, provided all of the following criteria are met:
   a. Measurable disease outside the CNS
   b. Asymptomatic for CNS disease > 4 ~~months~~weeks~~.~~
   ~~c. Only supratentorial metastases allowed~~
   ~~d. No evidence of progression after completion of CNS-directed therapy~~
   ~~c.~~c. No ongoing requirement for corticosteroids~~dexamethasone~~ as therapy for CNS disease

nature medicine

(e.g.,

Article

https://doi.org/10.1038/s41591-022-02126-1

Atezolizumab plus anthracycline-based chemotherapy in metastatic triple-negative breast cancer: the randomized, double-blind phase 2b ALICE trial

Rekruttering – nyhetsbrev?

INFORMERT SAMTYKKE

Informert samtykke

Regulert via omfattende lovverk og retningslinjer:

- Helseforskningsloven
- Forskrift om klinisk utprøvning av legemidler til mennesker → Helsinkideklarasjonen & GCP Guideline

Bygger på 4 prinsipper:

- Adekvat informasjon – et språk som er forståelig for alle
- Kompetent person som mottar informasjonen
- Fravær av påvirkning av noe slag
- Mulighet til å trekke seg når som helst i prosessen

Den skriftlige pasientinformasjonen danner grunnlaget

Informert samtykke – praktiske råd

- Skriftlig pasientinformasjon på forhånd
- Sett av god tid, også betenkningstid
- Utprøver informerer muntlig med bakgrunn i den skriftlige pasientinformasjonen
  - *Formålet med utprøvningen*
  - *Nytte og risiko*
  - *Behandlingsalternativer*
  - *Vilkår for gjennomføring*
  - *Muligheten til å trekke seg*
- Dokumenteres i journal → vurder en mal

Samtykke for deltakelse i studien

Jeg har mottatt skriftlig og muntlig informasjon om studien, spørsmålene mine er besvart, og jeg er villig til å delta i studien. Dette inkluderer samtykke til at innsamlet materiale kan benyttes til laboratorieanalyser/forskning slik som beskrevet ovenfor (kapittel A og B).

Tilleggsstudie
Samtykke til at innsamlet materiale (blod, urin, vev, avføringsprøve) kan benyttes i fremtidig forskning utover hva som er planlagt i hovedstudien, som beskrevet ovenfor (kapittel A).

☐ Ja, jeg gir mitt samtykke til at en del av innsamlet prøvemateriale også kan bli benyttet til fremtidig kreftforskning

☐ Nei, jeg gir ikke samtykke til at en del av innsamlet prøvemateriale også kan bli benyttet til fremtidig kreftforskning

_____
Deltakernavn

_____ _____
Signatur Dato

Bekreftelse på at informasjon er gitt deltakeren i studien

Pasientnr.:_____

Jeg bekrefter å ha gitt informasjon om studien.

_____
Navn på person som har informert om studien

_____ _____ _____
Signatur Rolle i studien Dato

SIKKERHETSRAPPORTERING - LEGEMIDDELSTUDIER

Adverse event (AE): Enhver uønsket medisinsk hendelse som inntreffer hos en forsøksperson som har fått et legemiddel, men som ikke nødvendigvis har en årsakssammenheng med den aktuelle behandlingen.

Adverse reaction (AR): En AR, i motsetning til en AE, kjennetegnes ved at det er mistanke om en årsakssammenheng mellom bruk av et legemiddel og en oppstått hendelse.

SIKKERHETSRAPPORTERING

- **Avklarte interne rutiner**
  → *Sikre lovpålagte krav*

- **Entydig intern rollefordeling**
  → *Medical monitor funksjonen*

- **System for kontinuerlig oversikt og rapportering**

Rapportering av alvorlige hendelser

AE alvorlig?
=Serious Adverse Event (SAE)

Relatert?
=Serious Adverse Reaction (SAR)

Uventet?

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Utprøver

«Serious» kriterier

- ❑ Død
- ❑ Livstruende
- ❑ Innleggelseskrevende
- ❑ Varig signifikant skade
- ❑ Medfødt misdannelse
- ❑ Viktig medisinsk hendelse

Rapporteres til sponsor innen 24 timer

Utprøver (& sponsor)

Kausalitetsvurdering

Sponsor

Reference safety information (RSI)

SmPC

eller

Investigators brochure (IB)

Sponsor

Rapporteres til DMP via EudraVigilance /EMA systemet

Helse Sør-Øst og Helse Nord:
SUSAR@ous-hf.no

frist:

Ved **fatal** eller **livstruende hendelse** innen 7 dager

Øvrige innen 15 dager

Takk for meg!

Anbefalt lesing:

Forside - NorCRIN

ICH TOPIC E2A

Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3) (europa.eu)