Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom

Version 3.0

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INDEKSERING
DSG, sarkomer, kemoterapi, pallierende

Nyt siden sidst (ændringslog)

Nyt siden version 2.0

Retningslinjeafsnit	Beskrivelse af ændring
Titel	Forbliver det samme, version nummer opdateret
Litteratur- og evidensgennemgang	Der er foretaget en opdateret litteraturgennemgang indenfor alle anvendte behandlingsområder og nye studier er inkluderet i evidenstabellerne. Generelt gælder det, at evidensen for behandling af sarkomer ikke er høj, der er er tale om en sjælden sygdom, med mange forskellige undertyper. Der er tilføjet en ny mulig førstelinje behandling bestående af pegyleret liposomalt doxorubicin i kombination med ifosfamid. Der er tilføjet et studie, som har vist effekt af kombinationsbehandling med doxorubicin og trabectedin i første linje til patienter med leiomyosarkom efterfulgt af trabectedin vedligeholdelsesbehandling. Ligeledes er der inkluderet en udvidelse af indikationen for eribulin til også at inkludere patienter med leiomyosarkom. Trofosfamid er ligeledes inkluderet ianbefalingen. To nye stoffer til behandling af angiosarkom er inkluderet i retningslinjen.
Bemærkninger og overvejelser	Alle de nye anbefalinger omfatter stoffer som i forvejen anvendes til behandling af sarkomer. Ændringen består i, at stofferne nu kan anvendes til andre undergrupper eller i nye kombinationer.
Referencer	Alle nye studier er nu inkluderet i den opdaterede referenceliste.
Litteratursøgning	Der er foretaget en opdateret litteraturgennemgang indenfor alle anvendte behandlingsområder inkl. immunterapi, og nye studier er inkluderet i evidenstabellerne
Litteraturgennemgang	Den tidligere anvendte søgestreng er brugt, men denne gang er litteraturen gennemgået vha. programmet COVIDENCE
Formulering af anbefalinger	5 nye anbefalinger er inkluderet i retningslinjen.

Behov for yderligere forskning	Der er behov for, at der laves international forskning, for at sikre at prognosen for disse patienter bliver bedre. Det arbejdes der ihærdigt på i Dansk Sarkom Gruppe.
Bilag	Flow for nye studier er opdateret, tilføjet som en version 3, og evidenstabelbilag er opdateret. Eribulin og topotecan er flytte til evidenstabellen om med anden kemoterapi.

Indholdsfortegnelse

1. Anbefalinger (Quick guide)

Første linje behandling

1. **Enkeltstof doxorubicin (styrke B)**
2. **Kombinationsbehandling med doxorubicin og ifosfamid kan anvendes i særlige tilfælde, specielt ved histologiske subtyper følsomme for ifosfamid, hvor tumorregression kan være en særlig fordel og hos patienter som er i god performance status. (styrke A)**
3. **Kombinationsbehandling med gemcitabin og docetaxel kan være alternativ første linje behandling specielt ved uterint leiomyosarkom. (styrke C)**
4. **Kombinationsbehandling med trabectidin og doxorubicin kan anvendes ved leiomyosarkom (styrke A)**
5. **Kombinationsbehandling med doxorubicin og dacarbazin kan anvendes ved leiomyosarkom (styrke B)**
6. **Kombinationsbehandling med pegyleret liposomalt doxorubicin (PLD) og ifosfamid kan anvendes som første linje (styrke C)**

Behandlinger efter første linje

7. **Ifosfamid højdosis såfremt dette ikke er anvendt i første linje - dog ikke ved uterint leiomyosarkom (styrke C)**
8. **Trabectedin - specielt ved myxoidt liposarkom og leiomyosarkom (styrke B)**
9. **Docetaxel+gemcitabin såfremt dette ikke er anvendt i førstelinje, og kun hvis der ikke er givet gemcitabin+dacarbazin (styrke B)**
10. **Pazopanib kan anvendes ved ikke-lipogent bløddelssarkom (styrke B). Pazopanib kan dog overvejes anvendt ved dedifferentieret liposarkom (styrke C)**
11. **Eribulin kan anvendes ved liposarkom (styrke B) og viser også effekt i leiomyosarkomer (styrke B)**
12. **Eribulin kan anvendes i kombination med lenvatinib (hvis denne behandling er tilgængelig) eller i kombination med gemcitabin ved liposarkom og leiomyosarkom (styrke C)**

13. **Regorafenib kan anvendes ved ikke-lipogent bløddelssarkom herunder angiosarkom og Ewing-lignende tumorer (styrke C)**

14. **Dacarbazin monoterapi kan anvendes til patienter med leiomyosarkom, hvis dette ikke er givet som førstelinje behandling (styrke B)**

15. **Check-point hæmmere kan anvendes til patienter med udifferentieret pleomorft sarkom, alveolar soft part sarkom og angiosarkom. Herudover kan check-point hæmmere evt. anvendes ved sjældne typer af sarkomer, hvor case-studier har vist en behandlingseffekt (styrke C).**

16. **Generelt skal patienter, der er progredieret på antracyklinbaseret kemoterapi indgå i kliniske forsøg, såfremt disse er tilgængelige for inklusion. Dette gælder også forsøg, som er baseret på genetiske forandringer (styrke C).**

17. **Trofosfamid kan anvendes (styrke B) evt i kombination med etoposid (styrke C)**

Pallierende behandling af specifikke histologiske subtyper

Angiosarkom

18. **Ugentlig paclitaxel til patienter med angiosarkom er doxorubicin overlegen som føste linje behandling ved response rate og OS angår (styrke B)**

19. **Angiosarkom kan behandles med taxaner eksempelvis ugentlig paclitaxel (styrke B). Gemcitabin enkelstof (styrke C) evt. i kombination med docetaxel (styrke D). PLD samt pazopanib kan ligeledes anvendes på indikationen (styrke C)**

20. **Angiosarkom kan behandles med regorafenib (styrke C)**

21. **Angiosarkom kan behandles med pembrolizumab (styrke C)**

2. Introduktion

Bløddelssarkomer er en heterogen gruppe af tumorer udgående fra kroppens bindevæv. Der findes mere end 50 forskellige histologiske undergrupper(1)(1). Patienter i alle aldersgrupper diagnosticeres med bløddelssarkom.
Bløddelssarkomer er sjældne tumorer med en estimeret incidens på 4-5/100.000 om året i Europa. I Danmark diagnosticeres ca. 250 nye tilfælde om året(2, 3)(2, 3). Den 5-års sygdomsspecifikke overlevelse er omkring 75% for patienter med lokaliseret sygdom. På diagnosetidspunktet har ca. 12% af patienterne metastatisk sygdom(4), patienter med dissemineret sygdom har en yderst dårlig prognose(5).

Formål

Det overordnede formål med retningslinjen er at understøtte en evidensbaseret kræftindsats af høj og ensartet kvalitet på tværs af Danmark. Da sarkomer udgør en sjælden og heterogen sygdomsgruppe, er nationalt og internationalt samarbejde afgørende i forhold til udarbejdelse af kliniske retningslinjer for behandling og udvikling af kliniske studier.

Patientgruppe

Retningslinjen dækker patienter med bløddelssarkom, hvor kurativ intenderet behandling ikke er mulig. Retningslinjen dækker kun voksne sarkompatienter, dvs. patienter over 18 år, og den inkluderer ikke patienter med Kaposis sarkom, solitære fibrøse tumorer, uterint endometrielt stromalt sarkom (ESS), udifferentieret endometrielt sarkom (UES), Gastro Intestinal Stromal Tumor (GIST), ekstraskeletalt Ewings sarkom, Ewing-lignende sarkomer samt embryonale/alveolære rhabdomyosarkomer.

Målgruppe for brug af retningslinjen

Denne retningslinje skal primært understøtte det kliniske arbejde og udviklingen af den kliniske kvalitet, hvorfor den primære målgruppe er klinisk arbejdende sundhedsprofessionelle i det danske sundhedsvæsen. Retningslinjen er vejledende og må aldrig træde i stedet for en individualiseret lægelig vurdering. Da behandlingen af sarkomer er centraliseret til 2 nationale centre, er denne retningslinje primært udarbejdet til sundhedspersonale (læger og sygeplejersker) på de to centre.

3. Grundlag

Første linje behandling

1. **Enkeltstof doxorubicin (styrke B)**

2. **Kombinationsbehandling med doxorubicin og ifosfamid kan anvendes i særlige tilfælde, specielt ved histologiske subtyper følsomme for ifosfamid, hvor tumorregression kan være en særlig fordel og hos patienter som er i god performance status. (styrke A)**

3. **Kombinationsbehandling med gemcitabin og docetaxel kan være alternativ første linje behandling specielt ved uterint leiomyosarkom. (styrke C)**

4. **Kombinationsbehandling med trabectidin og doxorubicin kan anvendes ved leiomyosarkom (styrke A)**

5. **Kombinationsbehandling med doxorubicin og dacarbazin kan anvendes ved leiomyosarkom (styrke B)**

6. **Kombinationsbehandling med pegyleret liposomalt doxorubicin (PLD) og ifosfamid kan anvendes som første linje (styrke C)**

Litteratur og evidensgennemgang

52 original-studier (se evidenstabel - doxorubicin) og 2 review-artikler (se evidenstabel – review) danner grundlaget for følgende anbefalinger.

Ved metastatisk sygdom er kemoterapeutiske regimer baseret på antracykliner som første linje behandling(6, 7) (evidens A).

Kombinationsbehandling med doxorubicin plus ifosfamid er ikke bedre end doxorubicin monoterapi, når det gælder overlevelse(5, 7-9). 3-stof kombination doxorubicin plus ifosfamid og dacarbazin er vist at give højere responsrater i forhold til 2-stof behandling med doxorubicin plus ifosfamid. 3-stof behandlingen er dog aldrig undersøgt i forhold til doxorubicin alene. Kombinationsbehandlingerne giver mere toksicitet end enkeltstof behandling med doxorubicin(10). Pegyleret liposomal doxorubicin, sammen med ifosfamid er forsøgt som første linje behandling og giver en ORR på 26% en DCR på 81%, en median PSF på 7.3 måneder og en OS på 20.6 måneder(11) (evidens C).

Median overlevelse ved enkeltstof doxorubicin øges fra ca. 8 til 19 måneder, med objektive responsrater (ORR) på mellem 9% og 24% og Progressions Fri Overlevelse (PFS) på mellem 2.7 og 6.4 måneder(5, 8, 9, 12-19). Doxorubicin enkeltstof kan give Disease Control Rate (DCR) på op til 68%(16).

Et randomiseret fase 3 studie har undersøgt doxorubicin vs ifosfamid som første linje behandling med bedste responsrater for doxorubicin(13) (evidens B). Doxorubicin vs epirubicin som første linje behandling er ligeledes undersøgt. Man fandt ingen forskel i PFS eller overlevelse, men der var et toksisk dødsfald (cardiotoksicitet) i epirubicin-gruppen(12).

Olaratumab er et humant monoklonalt platelet-derived growth factor (PDGF) antistof, hvis godkendelse bygger på et randomiseret fase 2 studie, som viste en overlevelsesfordel på 11.8 måneder for olaratumab plus doxorubicin i forhold til doxorubicin alene(17). Et senere fase 3 studie viste dog ingen effekt af doxorubicin i kombination med olaratumab i forhold til doxorubicin monoterapi, hvorfor denne kombination ikke anbefales(20) (evidens A). Et studie er ved at undersøge doxorubicin + dexrazoxane sammen med oloratumab hvor den kumulative dosis af doxorubicin er øget, interim undersøgelsen herfra har vist en median PFS på 8.4 måneder(21).

Kombinationsbehandling med gemcitabin og docetaxel versus enkeltstof doxorubicin som første linje behandling er undersøgt i et randomiseret fase 3 forsøg. Studiet fandt ingen signifikant forskel i PFS eller overlevelse, dog tendens til lidt bedre OS på 17.8 måneder for patienter behandlet med doxorubicin mod 15.7 måneder for patienter behandlet med gemcitabin plus docetaxel. Der var ingen signifikant forskel i graden af toksicitet eller livskvalitet(18). Gemcitabin plus docetaxel kan således være en alternativ første linjenbehandling (evidens A).

Et randomiseret forsøg med doxorubicin vs docetaxel som førstelinje-behandling blev lukket før tid, da ingen patienter responderede på docetaxel(22).

Et randomiseret forsøg har sammenlignet doxorubicin med trabectedin og ikke fundet forskel i PFS, studiet blev lukket og rapporterede ikke overlevelsesdata(23). I translokerede sarkomer har doxorubicin vist højere ORR i forhold til trabectedin som førstelinje-behandling(24). Kombinationsbehandling med doxorubicin og trabectedin medfører ikke en øget PFS ved dissemineret bløddelssarkom i forhold til doxorubicin monoterapi(25). Kombinationsbehandling med trabectidin og doxorubicin er undersøgt i leiomyosarkom med høje ORR på op til 59.6% og DCR på 87.3% for uterint leiomyosarkom mens ORR og DCR var henholdsvis 39.4% og 91.8% for ikke-uterint leiomyosarkom. PFS for uterint leiomyosarkom var 8.2 måneder og for ikke-uterint leiomyosarkom 12.9 måneder. 109 patienter indgik i dette single-arm studie(26). Et randomiseret studie fra 2022 viste at DCR for doxorubicin monoterapi var 78% mens den for doxrubicin + trabectedin og efterfølgende vedligeholdelsesbehandling med trabectedin var 91% og den mediane PSF for doxorubicin mono var 6.2 måneder mens den for kombinationsbehandlingen var 12.2 måneder. Patienter i kombinationsbehandlingen havde en median overlevelse på 33 måneder versus 24 måneder for patienter der kun modtog doxorubicin selvom omkring 56% af disse patienter på et senere tidspunk fik trabectedin(27, 28). Et nyere studie har vist at doxorubicin + lurbinectedin har en ORR på 60% og en median PFS på 16.5 måneder(29). samlet for doxorubicin + trabectedin vurderes det således at være en mulig behandling (evidens A).

Ifosfamid + epirubicin som første linje behandling har vist ORR på 48-52% , PFS mellem 6.3 og 8.5 måneder og på OS 9.3 til 24 måneder(30-35). Se evidenstabel (ifosfamid). Fælles for alle disse studier er, at der er få patienter og der er ingen randomisering, hvorfor evidensniveauet for denne behandling er lav (evidens C).

Et retrospektivt studie inkluderende 303 patienter med leiomyosarkom viste en signifikant øget PSF på 9.2 måneder ved kombinationsbehandling med doxorubicin og dacarbazin i forhold til doxorubicin monoterapi, som gav en PFS på 4.8 måneder. Der var ligeledes en signifikant øget overlevelse på 36.6 måneder ved kombinationsbehandling i forhold til doxorubicin monoterapi, som gav en overlevelse på 30.2 måneder (36)(evidens B).

Patientværdier og – præferencer

Valg af behandling afhænger i høj grad af patientens performance status og komorbiditet, da behandlingen kan medføre betydelig toksicitet herunder bl.a. myelosuppression og cardiotoksicitet.

Rationale

Rationalet bag udformningen af retningslinjen at supplere internationale guidelines med evidensbaserede retningslinjer der afspejler forhold på de danske sarkomcentre.

Bemærkninger og overvejelser

De anførte regimer er allerede veletableret standard i pallierende behandling af bløddelssarkom i Danmark. Der er således ingen logistiske udfordringer i at efterleve anbefalingerne.

Behandlinger efter første linje

7. **Ifosfamid højdosis såfremt dette ikke er anvendt i første linje - dog ikke ved uterint leiomyosarkom (styrke C)**

8. **Trabectedin - specielt ved myxoidt liposarkom og leiomyosarkom (styrke B)**

9. **Docetaxel+gemcitabin såfremt dette ikke er anvendt i førstelinje, og kun hvis der ikke er givet gemcitabin+dacarbazin (styrke B)**

10. **Pazopanib kan anvendes ved ikke-lipogent bløddelssarkom (styrke B). Pazopanib kan dog overvejes anvendt ved dedifferentieret liposarkom (styrke C)**

11. **Eribulin kan anvendes ved liposarkom (styrke B) og viser også effekt i leiomyosarkomer (styrke B)**

12. **Eribulin kan anvendes i kombination med lenvatinib (hvis denne behandling er tilgængelig) eller i kombination med gemcitabin ved liposarkom og leiomyosarkom (styrke C)**

13. **Regorafenib kan anvendes ved ikke-lipogent bløddelssarkom herunder angiosarkom og Ewing-lignende tumorer (styrke C)**

14. **Dacarbazin monoterapi kan anvendes til patienter med leiomyosarkom, hvis dette ikke er givet som førstelinje behandling (styrke B)**

15. **Check-point hæmmere kan anvendes til patienter med udifferentieret pleomorft sarkom, alveolar soft part sarkom og angiosarkom. Herudover kan check-point hæmmere evt. anvendes ved sjældne typer af sarkomer, hvor case-studier har vist en behandlingseffekt (styrke C).**

16. **Generelt skal patienter, der er progredieret på antracyklinbaseret kemoterapi indgå i kliniske forsøg, såfremt disse er tilgængelige for inklusion. Dette gælder også forsøg, som er baseret på genetiske forandringer (styrke C).**

17. **Trofosfamid kan anvendes (styrke B) evt i kombination med etoposid (styrke C)**

Litteratur og evidensgennemgang

Ifosfamid højdosis (evidens B)

Se evidenstabel – ifosfamid som inkluderer 25 studier samt 1 review (se evidenstabel – review), samt 1 studie fra evidenstabel omkring doxorubicin. Disse studier danner grundlaget for anbefalingen.
Flere single-arm, fase 2 studier har vist, at højdosis ifosfamid kan have en effekt ved forskellige histologiske undertyper af bløddelssarkom(37-42), Samme studier har vist, at leiomyosarkomer har lave objektive responsrater på <10% på denne behandling. Generelt varierer ORR ved ifosfamid monoterapi fra 16% til 39% og median PFS varierer mellem 3.5-8 måneder. I disse studier er ifosfamid anvendt efter anthracyklinbaseret kemoterapi. Effekten af trofosfamid er blevet undersøgt ved ældre patienter med en ORR på 6.6% og DCR på 40.8%, samt PFS på 2.8 måneder og en OS på 12.3 måneder(43). Der er ligeledes en retrospektiv opgørelse, der har set på effekten af trofosfamid i kombination med etoposid. Trofosfamid og etopisid kunne holde sygdommen i ro i 3.4 måneder(44).

Trabectedin (evidens B)

I forbindelse med udarbejdelsen af denne retningslinje er der identificeret 25 studier, der danner grundlag for anbefalingerne vedr. trabectedin (se evidenstabel – trabectedin).
Flere single-arm fase 2 undersøgelser har vist, at trabectedin har effekt på forskellige histologiske subtyper af bløddelssarkom. ORR svinger fra 5% til 26.6%, mens de samme studier har vist en median PFS mellem 1.6 og 5.9 måneder(45-54). For leiomyosarkom har man fundet en median PFS på op til 5.8 mdr. i et enkelt studie(55).
Et randomiseret fase 2 forsøg har undersøgt trabectedin mod best supportive care i translokerede sarkomer og fundet at trabectedin som 2. linjebehandling er bedre med en median PFS på 5.6 måneder versus 0.9 måneder for best supportive care(56). Et andet randomiseret fase 3 studie af Le Cesne bekræftede dette med en PFS på 3.1 måneder ved trabecticin behandling mod 1.5 måned ved best supportive care(57).To randomiserede studier har sammenholdt trabectedin vs dacarbazin som 2.-linjebehandling til liposarkom og/eller leiomyosarkom. Begge studier fandt bedre PFS ved trabectedin(58, 59). Et senere randomiseret fase

3 studie inkluderende 577 patienter viste, at der ikke var forskel i overlevelsen mellem de patienter, der havde modtaget trabectidin, versus de patienter, der havde modtaget dacarbazin(60). Høje responsrater er set ved specielt myxoidt liposarkom (61) og leiomyosarkomer. Bivirkninger til behandlingen er forbigående transaminasestigning og moderat myelosuppression (evidens B)

Trabectedin kan anvendes sammen med strålebehandling med god effekt også på de metastaser, som ikke bliver strålebehandlet(62-64).

Gemcitabin monoterapi eller kombinationsbehandling involverende docetaxel eller dacarbazin (evidens B)
Se evidenstabel - gemcitabin, som inkluderer 17 studier, der danner grundlag for anbefalingen.
I et af de første studier, der undersøgte effekten af gemcitabin enkeltstof, var der inkluderet 17 gastro-intestinale leiomyosarkomer, og ingen af disse responderede på gemcitabin. ORR for den resterende del af populationen var på 18%, mens median PFS var 3 måneder(65). Andre studier, som har undersøgt gemcitabin enkeltstof til bløddelssarkomer, har fundet lidt lavere såvel PFS som objektive responsrater(66-68). Af de studier der har undersøgt effekten af enkeltstof gemcitabin er respondere ofte fundet blandt subtypen angiosarkom(69).
Kombinationsbehandling med gemcitabin og docetaxel har vist sig mere effektiv end gemcitabin enkeltstof i flere histologiske undergrupper, kombinationsbehandlingen er dog mere toksisk. Et studie har vist at ORR for enkeltstof gemcitabin var 8% og for kombinationsbehandling 18 %, PFS for gemcitabin enkeltstof var 3 måneder og PFS for kombinationsbehandling var 6.2 måneder(70). I en retrospektiv opgørelse af kombinationsbehandling gemcitabin og docetaxel fandt man, at behandlingen var mere effektiv ved leiomyosarkomer i forhold til andre histologiske undertyper(71). Det nyeste prospektive studie hvor gemcitabin er kombineret med docetaxel viser en ORR på 5%, median PFS på 3 måneder og en OS på 14 måneder(72) Gemcitabin kombineret med dacarbazin har ligeledes vist sig mere effektiv end dacarbazin enkeltstof med en PFS på op til 9.25 måneder for kombinationsbehandlingen(73, 74). Gemcitabin plus vinorelbin i kombination er ligeledes undersøg med PFS på 3.4 måneder hos patienter med avanceret bløddelssarkom(75). Kombinationsbehandlingen gemcitabin og docetaxe/dacarbazin er mere effektiv end gemcitabin alene (evidens B) .

Dacarbazin (evidens B)
Se evidenstabel – (doxorubicin, trabectedin, gemcitabin og kemoterapi andet).
Flere studier har undersøgt dacarbazin enkelstof enten som single arm studie eller mod en kombinationsbehandling hvor dacarbazin indgår, eller mod eribulin. Generelt er ORR for dacarbazin monoterapi 3-18% afhængig af den histologiske subtype(76, 77). Den mediane PFS varierede mellem 1.5 og 4.2 mdr(58, 59, 77), OS mellem 8 og13.1 måneder afhængig af den histologiske subtype, og bedre hos patienter med leiomyosarkom end liposarkom(58, 59, 77). Dacarbazin er traditionelt anvendt i kombination med andre stoffer, specielt i kombination med doxorubicin i forskellige regimer hvor effekten er større end ved monoterapi. Se de enkelte afsnit (6, 78). (evidens B)

Pazopanib (evidens C)
Se evidenstabel - targeteret behandling, hvor 10 studier indgår i udarbejdelsen af anbefalingen.

Pazopanib er en multitargeteret tyrosinkinasehæmmer. Grundlaget for anvendelse af pazopanib er et fase 2 studie med 142 patienter og et randomiseret fase 3 studie med 372 patienter med metastatisk ikke lipogent bløddelssarkom. Der var en signifikant bedre median progressionsfri overlevelse på 4.6 måneder mod 1.6 måneder i placebo-armen. Total overlevelse var ikke signifikant bedre i pazopanib-armen(79) (evidens A). Bivirkninger inkluderede blandt andet forhøjet blodtryk og påvirkede leverparametre.
Et mindre studie inkluderende 42 patienter med liposarkom, påviste en DCR på 68%, en median PFS på 4.4 måneder og en median OS på 12.6 måneder. Den største effekt blev påvist for dedifferentieret liposarkom med PFS på 6.2 måneder mod 3.2 måneder for myxoidt liposarkom(80). En retrospektiv opgørelse har påvist at effekten af pazopanib hæmmes af samtidig behandling med syrepumpehæmmere.(81).
Selv hos patienter hvis almentilstand ikke tillod kemoterapi kunne der med pazopanib-behandling opnås en OS på 14 mdr. (Hirbe et la.)

Eribulin (evidens B)
Se evidenstabel – Kemoterapi andet, hvor 7 studier danner grundlag for anbefalingerne.
Et fase 3 forsøg har sammenlignet effekten af eribulin med dacarbazin hos patienter med bløddelssarkom, som tidligere har modtaget antracyklinbaseret kemoterapi. Eribulin og dacarbazin gav samme PFS på 2.6 måneder, herudover påviste forsøget en OS på 13.5 måneder for eribulin mod 11.5 måneder for dacarbazin(82). Subgruppeanalyse viste at patienter med liposarkom havde en DCR på 64% og en totaloverlevelse på 15.6 måneder for eribulin mod 8.4 måneder for dacarbazin(83). For patienter med leiomyosarkom er der formentlig bedre effekt af dacarbazin, men eribulin er også effektivt (Schöffski et al, Blay et al). I et tidligere fase 2 studie som inkluderede 128 patienter med STS fandt man en DCR på 47.6 % for dedifferentieret liposarkom(84). Eribulin er blevet undersøgt sammen med lenvatinib for leiomyosarkom og liposarkom patienter, hvilket viser en ORR på 20% og en PFS på 8.56 måneder, samt en OS på 27.1 måneder. Her havde liposarkom patienter i modsætning til data for enkeltstof eribulin, en lidt dårligere overlevelse på 23.6 måneder(85). Eribulin er også blevet forsøgt sammen med gemcitabin for liposarkom og leiomyosarkom patienter, dette gav en ORR på 16%, DCR på 78% en PFS på 5.6 måneder og en OS på 31.9 måneder(86).

Regorafenib (evidens C)
Se evidenstabel - targeteret behanding, hvor et randomiseret studie og 3 fase 2 studie ligger til grund for anbefalingen.
Regorafenib versus placebo har i et randomiseret forsøg med 182 patienter vist en effekt ved specielt synovialt sarkom med en DCR på 77% og en PFS på 5.6 måneder mod 1.0 måned for placebo. For liposarkom var der ingen effekt, hvorimod der for leiomyosarkom var en lille gevinst på PFS på 3.7 måneder for regorafenib mod 1.8 måneder i placebo gruppen(87). Regorafenib er blevet anvendt til behandling af Ewing-lignende tumorer med en PFS på 3.7 måneder(88).

Checkpoint-hæmmere (evidens C)
Se evidenstabel – check-point hæmmer, hvor 45 studier ligger til grund for denne anbefaling. Sarkom er en meget sjælden kræftform bestående af mange forskellige histologiske undertyper. De første studier hvor man undersøgte effekten af immunterapi inkluderede man flere forskellige histologiske undertyper(89). Der er efterhånden et stigende evidensgrundlag for at anvende check-point hæmmere ved særlige histologiske

undertyper. Studier har vist at 50 - 80% af patienter med udifferentieret pleomorft sarkom, angiosarkom, alveolar soft part sarkom, eller selektive meget sjældne undertyper har effekt af behandlingen. ORR for alle sarkomer uanset undertype ligger mellem 11 og 49%(90-96), for udvalgte grupper har man fundet DCR op til 70%(97). De forskellige studier påviste en median progressionsfri overlevelse mellem 2.7 og 8.1 måneder, hvilket er bedre end standard kemoterapi(90, 95, 96, 98). Et retrospektivt studie har fundet en median PFS på 24.4 måneder blandt patienter med effekt af behandlingen(95). Enkelte studier har ligeledes beskrevet patienter med komplet respons på behandlingen(99, 100). Forskellige kombinationer af kemoterapi/tyrosinkinase hæmmere og check point hæmmere er ved at blive undersøgt, og enkelte studier har vist lovende resultater(90, 92, 101-103).
Trabectedin er forsøgt med avelumab ved lipoksarkom og leiomyosarkom med ORR på 13% og DCR på 56% og PFS på 8.3 måneder, der er få patienter inkluderet men resultatet er interessant(104). Kombinationen af eribulin og pembrolizumab er undersøgt ved liposarkom med en PFS ved 12 måender på 69,6%(105).

Targeterbar behandling baseret på genetiske forandringer (evidens D)
Flere studier har undersøgt forekomsten af genetiske forandringer ved sarkomer, og selv om sarkomer generelt har en lav tumor mutations bryde (TMB), findes der ofte et højt copy number alterations (CNA).
I en undersøgelse fra Groisberg et al. fra 2017 fandt de, at ud af 102 sarkompatienter havde 94 (93%) mindst en genetisk fordring. De mest almindelige var *TP53, CDK4, MDM2, RB1, CDKN2A/B og FRS2*. Studiet viste, at 62 patienter (61%) havde et potentielt target, hvortil der findes en behandling(106).
I en artikel publiceret i 2018 af Lucchesi et al. fandt man tilsvarende tal for antallet af patienter med targeterbare genetiske forandringer. Her blev 584 patienter undersøgt og 494 (85%) havde mindst en mutation. Her fandt man ligeledes, at de mest almindelige mutationer var *TP53, MDM2, CDK4, RB, ATRX, CDKN2A, PTEN og NF1*. For 239 patienter (41%) fandt man en mutation, hvor der potentielt er behandling(107).
Den seneste opgørelse fra Gusho et al. 2021, hvor 136 sarkompatienter blev undersøgt, viste at 122 patienter havde mindst en mutation (89,4%), og at de mest almindelige mutationer var TP53, CDKN2A/B, RB1, CDKN2A, ATRX, FRS2 og MDM2/CDK4. 47.1% af patienterne havde en mutation, hvortil der var en behandling(108).

MDM2 hæmmere er undersøgt ved dedifferentieret liposarkom og giver en ORR på mellem 4-11% end DCR på mellem 58-74% og en median PFS på omkring 7.2 måneder. MDM2 hæmmer er undersøgt som førstelinje behandling mod doxorubicin(109, 110). Den kliniske anvendelse er ikke afklaret endnu.

Palbociclib er forsøgt ved patietner med CDK4 amplifikation. Der er tale om en tungt behandlet gruppe af patienter. ORR var 2%, DCR var 46%, median PFS var 16 uger og OS var 68 uger(111).

Kombination af en MDM2 og en CDK4/6 hæmmer er forsøgt med en ORR på 7% end DCR på 28% samt en PFS på 4.2 måneder, dette var for højt differentieret liposarkom og dedifferentieret liposarkom(112).

Et randomiseret forsøg med selinexor mod placebo for dedifferentieret liposarkom, viste ingen gevinst af denne behandling(113).

Andre behandlinger
Der er lavet et antal mindre studier med få patienter, hvor temozolomid har vist effekt med ORR 15.5% og PFS på 2.2 måneder(114). Ligeledes har bevacizumab vist effekt ved angiosarkom og epithloidt hæmangioendotheliom med ORR på 17% DCR på 50% og PFS på 12. måneder(115).

Den kliniske effekt af målrettet behandling hos sarkom patienter mangler at blive afklaret. Anvendelse af targeteret behandling baseret på genetiske forandringer må *bero* på individuel vurdering.. Genetiske undersøgelser kan, såfremt det er muligt, foretages *med henblik på at afklare om patienten kan indgå i studier med målrettet behandling" allerede efter 1. linje* eller såfremt det ud fra histologiske undertype findes hensigtsmæssigt. *Det kræver dog, at patienter har en almen tilstand, der tillader, at de kan indgå i off-label behandling, eller kliniske forsøg med targeterbare behandlinger.*

Patientværdier og – præferencer
Behandlingsvalg efter initial anthracyklinbaseret kemoterapi afhænger af histologisk subtype, komorbiditet, performance status samt patienthensyn.

Rationale
Rationalet bag udformningen af retningslinjen er at supplere internationale guidelines med evidensbaserede retningslinjer, der afspejler forhold på de danske sarkomcentre.

Bemærkninger og overvejelser
Sarkomer er en heterogen gruppe af tumorer og repræsenterer en meget heterogen gruppe af patienter. Det er derfor at det vigtig at tage hensyn til patientens alder, komorbiditet, almen tilstand, histologisk undertype, tidligere behandling og sygdomsudbredning samt individuelle patientønsker når behandlingsovervejelser diskuteres. Andre onkologiske behandlingsmodaliteter herunder blandt andet stråleterapi samt best supportive care bør naturligvis også indgå i behandlingsovervejelserne.
Ovenforstående anbefalinger bygger på en grundig litteraturgennemgang, klinisk erfaring og international konsensus. Studierne, der indgår i denne retningslinje, er ofte små eller inkluderer mange forskellige histologiske undertyper af sarkomer.

Pallierende behandling af specifikke histologiske subtyper

Angiosarkom

18. Ugentlig paclitaxel til patienter med angiosarkom er doxorubicin overlegen som føste linje behandling ved response rate og OS angår (styrke B)

19. Angiosarkom kan behandles med taxaner eksempelvis ugentlig paclitaxel (styrke B). Gemcitabin enkelstof (styrke C) evt. i kombination med docetaxel (styrke D). PLD samt pazopanib kan ligeledes anvendes på indikationen (styrke C)

20. Angiosarkom kan behandles med regorafenib (styrke C)

21. Angiosarkom kan behandles med pembrolizumab (styrke C)

Litteratur og evidensgennemgang

Angiosarkom

PLD versus doxorubicin (evidenstabel – doxorubicin) er blevet undersøgt i et randomiseret studie med 94 patienter. ORR for både doxorubicin og PLD var lave i dette studie formentlig pga. et stort antal patienter med gastrointestinal stromal tumor (GIST), som udgjorde 33% af alle patienterne. Man fandt, at PLD og doxorubicin havde samme ORR og PFS, men at PLD var langt mindre marv- og cardiotoksisk men mere hudtoksisk(116). PLD ophobes i tumor og hud og har en halveringstid på op til 50 timer. Et lille case-baseret studie med 6 patienter med angiosarkom har vist effekt af PLD(117). PLD har vist sig effektiv ved den vaskulære tumor Kaposis sarkom, hvorfor PLD ligeledes tænkes anvendt ved angiosarkom (118)(evidens D). En retrospektiv undersøgelse omfattende 125 patienter med angiosarkom fandt PFS på 4.2 måneder ved behandling med PLD (11 patienter havde modtaget denne behandling), 4.0 måneder ved paclitaxel (41 patienter), 2.2 måneder ved enkelstof gemcitabin (11 patienter) og 1.6 måneder ved ifosfamid (12 patienter)(119). En retrospektiv opgørelse har vist at enkeltstof gemcitabin har effekt ved angiosarkom med ORR på 68% og median OS på 17 måneder. 3 af disse patienter blev behandlet med kombination gemcitabin plus taxan, 2 havde partielt respons og en havde stabil sygdom(120).

Angiosarkomer er følsomme for taxaner, som derfor kan anvendes som førstelinje behandling. (evidens B). Paclitaxel (evidenstabel - kemoterapi) som enkeltstof har i single-arm studier vist en ORR på 7 til 53% med størst ORR for angiosarkom(121). Generelt er disse studier dog små. Behandling af angiosarkom med paclitaxel er vist at give en PFS på 6.6 måneder og en OS 19.5 måneder(122).
Et større randomiseret studie har undersøgt doxorubicin versus paclitaxel til behandling af angiosarkom. ORR for doxorubicin var 29% og for paclitaxel 53%, PFS for doxorubicin var 3 måneder mod 5.8 måneder for paclitaxel. OS var 10.3 måneder for paclitaxel mod 5.5 måneder for doxorubicin(123) (evidens A).
Paclitaxel er forsøgt kombineret med bevacizumab ved angiosarkom i et randomiseret fase 2 studie. Kombinationsbehandlingen havde samme PFS som paclitaxel alene 6.6 måneder(122).

Pazopanib anvendt ved vaskulære sarkomer har vist ORR på 23%, DCR på 54%, PFS på 3 måneder og OS på ca. 10 måneder(124).Regorafenib er blevet anvendt til behandling af angiosarkom med en ORR på 17%, DCR på 60% og en median PFS på 5.5 måneder(125), For angiosarkom har man vist, at pembrolizumab monoterapi kan give en median PFS på 6.2 måneder og en median OS på 72.6 måneder med bedst effekt på de viscerale angiosarkomer(126).

Patientværdier og – præferencer

Valget af behandling bygger primært på klinisk erfaring, patientperformance samt komorbiditet.

Rationale

Rationalet bag udformningen af retningslinjen at supplere internationale guidelines med evidensbaserede retningslinjer der afspejler forhold på de danske sarkomcentre.

Bemærkninger og overvejelser

Angiosarkom er en sjælden subtype af bløddelssarkom. Anbefalingerne i denne retningslinje bygger på små prospektive studier og retrospektive opgørelser.

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5. Metode

Litteratursøgning

Foreliggende litteratur er tilvejebragt på basis af grundig litteraturgennemgang (se søgeprotokol – bilag 1, søgeprotokol bilag 1 version 2, søgeprotokol bilag 1b). Der er primært taget udgangspunkt i originallitteratur, hvorudfra der er fortaget en grov selektion med frasortering af ikke relevante publikationer (se bilag 2). Evidenstabeller (bilag 3 – 10, og 12) er efterfølgende udfærdiget, evidensniveauet er anført. Retningslinjerne er herefter udarbejdet og efterfølgende justeret/suppleret med informationer fra internationale guidelines (se søgeprotokol – bilag 1, søgeprotekol bilag 1 version 2). Reviewartikler er anvendt i begrænset omfang for at sikre, at relevant litteratur er inkluderet (se flowchart - bilag 2, flowchart bilag 2 version 2). Metaanalyser er anvendt i det omfang de har været tilgængelige og relevante. Hvor der ikke har været evidens bygger anbefalingerne på ekspertkonsensus.

Litteraturgennemgang

Litteraturgennemgang er foretaget af Bodil Elisabeth Engelmann og Ninna Aggerholm Pedersen. Det er primært originallitteratur med specifikt fokus på kliniske forsøg, der danner grundlaget for denne retningslinje.

Formulering af anbefalinger

Anbefalingerne er formuleret a fBodil Elisabeth Engelmann, Ninna Aggerholm Pedersen og Philip Blach Rossen. Anbefalingerne forelægges og diskuteres ved årsmøde i DSG primo januar 2019. Denne er efterfølgende revideret. Den revideret er fremlagt og diskuteret på DSG årsmøde januar 2022. Version 3 er diskuteret DSG årsmøde januar 2025.

Interessentinvolvering

Der har ikke været patienter eller andre ikke-DSG medlemmer involveret i udarbejdelsen af denne retningslinje. De to centre deltager i national og internationale studier, både investigator initieret og firmastudier og det vurderes ikke at forfatternes habilitet er kompromitteret.

Høring

Retningslinjen er sendt til høring blandt DSG's medlemmer forud for DSG's årsmøde primo januar 2019. Version 3 er sendt til høring december 2024. Retningslinjen for pallierende medicinsk behandling af patienter med bløddelssarkom vil blive forelagt og diskuteret ved DSG's årsmøde og forventes efterfølgende godkendt af DSG's medlemmer og bestyrelse.

Godkendelse

Faglig godkendelse:
Retningslinjen er fagligt godkendt af DSG.

Administrativ godkendelse:
Retningslinjen er administrativt godkendt af Sekretariatet for Kliniske Retningslinjer på Kræftområdet.

Anbefalinger, der udløser betydelig merudgift

De i retningslinjen direkte anførte behandlingsanbefalinger vil ikke medføre betydelige merudgifter, da de i væsentligt omfang allerede er implementerede på de 2 nationale sarkomcentre. Behandling med immunterapi anvendes i dag off-label på AUH og som standard behandling på Herlev. Der er søgt om tilladelse til at anvende immunterapi som standard behandling på AUH. Da behandlingen gives off-label vil det således ikke betyde en merudgift.

Nationalt samt internationalt samarbejde med fokus på at forbedre behandlingsmuligheder for sarkompatienter aktuelt samt fremadrettet er væsentligt. Fokus på og styrkelse af internationalt klinisk samt forskningsmæssigt samarbejde er essentielt og bør prioriteres højt. Løbende udvikling og forbedring af eksisterende behandlingstilbud til sarkompatienter er væsentlig. Anbefalingen omkring deltagelse i kliniske forsøg kan medføre merudgifter. Deltagelse i kliniske forsøg, nationalt og internationalt, medfører merudgifter til GCP-monitorering, KFE støtte, juridisk bistand, medarbejderfrikøb mhp. varetagelse af protokolansvar mm.

Behov for yderligere forskning

Der er i høj grad behov for yderlige forskning inden for behandling herunder pallierende behandling af sarkompatienter. Prognosen for disse patienter er dårlig, og evidensen for mange at de behandlinger der tilbydes, bygger på små ikke-randomiserede studier. Sarkomer er, som tidligere anført, en sjælden og heterogen sygdom, med de forsknings- og behandlingsmæssige implikationer det medfører. Der er derfor behov for yderligere forskning indenfor området samt udvikling af nye behandlingsstrategier og optimere brugen af allerede eksisterende behandling. Dette kræver en høj grad af nationalt og internationalt samarbejde også vedrørende kliniske forsøg – et samarbejde der bør fremmes såvel internationalt som ved de 2 nationale sarkomcentre.

Forfattere og habilitet

- Bodil Elisabeth Engelmann, Klinisk onkolog, speciallæge, Afdelingen for kræftbehandling, Herlev og Gentofte Hospital.
- Philip Blach Rossen, klinisk onkolog, overlæge, Kræftafdelingen, Aarhus Universitetshospital
- Ninna Aggerholm Pedersen, klinisk onkolog, overlæge, Kræftafdelingen, Aarhus Universitetshospital

Jf. Habilitetspolitikken henvises til deklaration via Lægemiddelstyrelsens hjemmeside for detaljerede samarbejdsrelationer: https://laegemiddelstyrelsen.dk/da/godkendelse/sundhedspersoners-tilknytning-til-virksomheder/lister-over-tilknytning-til-virksomheder/apotekere,-laeger,-sygeplejersker-og-tandlaeger

Plan for opdatering

Retningslinjen opdateres i regi af DSG.

Version af retningslinjeskabelon

Retningslinjen er udarbejdet i version 10 af skabelonen.

6. Monitorering

Standarder og indikatorer

Da sarkomer er en sjælden og meget heterogen sygdomsgruppe omfattende mange forskellige histologiske subgrupper, vil behandlingen ofte bygge på en individualiseret behandlingsstrategi. Det er således ikke meningsfyldt at udvælge og monitorere på specifikke standarder og indikatorer i forbindelse med den palliative behandling af sarkom patienter.

Plan for audit og feedback

Retningslinjen skal med passende intervaller opdateres ud fra nationale og internationale peer review publicerede data.

7. Bilag

Bilag 1 – Ændringslog fra tidligere versioner

Nyt siden version 1.0

Retningslinjeafsnit	**Beskrivelse af ændring** *Beskriv kort de udførte ændringer ud for det relevante afsnit, så det er tydeligt, hvilke ændringer der er foretaget og hvorfor)*
Anbefalinger	Bløddelssarkomer er anbefalinger uændret men tilføjet tekst som forklarer overvejelser ud fra nyere studier. Rhabdomyosarkom: • tilføjet anbefaling 4 som er en præcisering af eksisterende retningslinjer. • tilføjet anbefaling 5 som er ny
Referencer	Ændret til nyeste ESMO og NCCN guidelines inkl henvisning til FaR RMS protokol samt tilføjet 7 nye artikler jvf referenceliste og evidenstabel.
Litteratursøgning	Ny søgning foretaget indeholdende litteratur i perioden januar 2019 – november 2021.

Bilag 2 – Søgestrategi bilag 1 (oprindelige søgestrategi), bilag 1 version 2 søgestrategi for revision, bilag 1b søgestrategi for immunterapi, version 3 er seneste revideret, dette gælder både for kemoterapi og immunterapi

Arbejdsdokument – Søgeprotokol

Emne

Titel (på retningslinje)	*Pallierende kemoterapi til patienter med bløddelsarskom*
DMCG	*DSG*
Kontakt med metodespecialist	*Nej*
Senest udfyldt	*22/12/2018*

Afgrænsning af emne	
Baggrund	*Pallierende kemoterapi til patienter med bløddelssarkom*
Inklusions- og eksklusionskriterier	Publikationsdato (periode): 1990 – 2008 *Sprog: Engelsk, dansk, svensk* *Publikationstyper: Guidelines, reviews, originale artikler*

Emneord	Populationen	Intervention	Sammenlignings intervention	Outcomes
Dansk *Alle tænkelige søgeord bør indsættes.*	*Sarkom, bløddelssarkom, kræft i bløddele, kræft i bindevæv*	*Kemoterapi, targeteret behandling*	*Fase 1, 2 og 3 forsøg, kliniske forsøg*	*Effekt af behandlingen, overlevelsen, tid til progression.*
Engelsk *Alle tænkelige søgeord bør indsættes.*	*Sarcoma, soft tissue sarcoma,*	*Chemotherapy, targeted treatment,*	*Clinical trials, phase I, II or III studies*	*Effect, overall survival, time to progression*

Søgning efter guidelines

Databaser (Guidelines)	Dato for søgning	Ansvarlig for søgningen
G-I-N International http://www.g-i-n.net/library/international-guidelines-library	**(19/11/2018)**	NAP (16 hits 4 udvalgt – 2 findes ved andre links)
NICE (UK) https://www.nice.org.uk/guidance/published?type=apg,csg,cg,mpg,ph,sg,sc	**(19/11/2018)**	NAP (1 guideline)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/our-guidelines.html	**(19/11/2018)**	NAP (ingen)
Helsedirektoratet (Norge) https://helsedirektoratet.no/retningslinjer	**(19/11/2018)**	NAP (1 guideline)
Socialstyrelsen (Sverige) http://socialstyrelsen.se/	**(19/11/2018)**	NAP (1 guideline)
Australian Clinical Practice Guidelines https://clinicalguidelines.gov.au/	**(19/11/2018)**	NAP (1 guideline)
European Society for Medical Oncology http://www.esmo.org/Guidelines	**(19/11/2018)**	NAP (1 guideline)
National Comprehensive Cancer Network https://www.nccn.org/professionals/physician_gls/default.aspx	**(19/11/2018)**	NAP (1 guideline)

Søgning efter systematiske reviews

Databaser (systematiske reviews)	*Dato for søgning*	*Ansvarlig for søgningen*
Medline	**(13/11/2018)**	NAP
The Cochrane Library	**(19/11/2018)**	NAP

Søgning efter primærlitteratur (fx randomiserede kontrollerede forsøg)

Databaser (primær litteratur)	Dato for søgning (dd/mm/åååå)	Ansvarlig for søgningen (navn(e))
Medline	**(28/10/2018)**	NAP

Søgestrategier

Guidelines søgning. Søgningen på de forskellige guidelines blev fortaget den 19.11.2018.
Følgende søgeord anvendt: Sarkom; Sarcoma; kemoterapi, cytoterapi, Chemotherapy.

Medline: søgestreng anvendt til at finde review artikler. Søgning foretaget 13.11.2018.

"Sarcoma"[Mesh] AND (advanced[All Fields] AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields])) AND "humans"[MeSH Terms] AND English[lang] AND Review[ptyp] AND (Review[ptyp] AND ("1990/01/01"[PDAT] : "2018/12/31"[PDAT]) AND "adult"[MeSH Terms]) NOT Kaposi's[All Fields]

Medline: søgestreng anvendt til at finde original litteratur. Søgningen foretaget 28.10.2018.

"Sarcoma"[Mesh] AND (advanced[All Fields] AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields])) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang])

Cochrane Library Reviews. Søgningen foretaget den 19.11.2018. Søgeord “Sarcoma and chemotherapy”

Arbejdsdokument – Søgeprotokol

Emne

Titel (på retningslinje)	*Pallierende kemoterapi og targeteret behandling til patienter med bløddelsarskom*
DMCG	*DSG*
Kontakt med metodespecialist	*Nej*
Senest udfyldt	*15/10/2021*

Afgrænsning af emne	
Baggrund	*Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom*
Inklusions- og eksklusionskriterier	Publikationsdato (periode): 1990 – 2018 til version 1, 2018 til 2021 til version 2 *Sprog: Engelsk, dansk, svensk* *Publikationstyper: Guidelines, reviews,, originale artikler*

Emneord	Populationen	Intervention	Sammenlignings intervention	Outcomes
Dansk *Alle tænkelige søgeord bør indsættes.*	*Sarkom, bløddelssarkom, kræft i bløddele, kræft i bindevæv*	*Kemoterapi, targeteret behandling*	*Fase 1, 2 og 3 forsøg, kliniske forsøg*	*Effekt af behandlingen, overlevelsen, tid til progression.*
Engelsk *Alle tænkelige søgeord bør indsættes.*	*Sarcoma, soft tissue sarcoma,*	*Chemotherapy, targeted treatment,*	*Clinical trials, phase I, II or III studies*	*Effect, overall survival, time to progression*

Søgning efter guidelines

Databaser (Guidelines)	Dato for søgning	Ansvarlig for søgningen
G-I-N International http://www.g-i-n.net/library/international-guidelines-library	**(19/11/2018)**	NAP (16 hits 4 udvalgt – 2 findes ved andre links)
NICE (UK) https://www.nice.org.uk/guidance/published?type=apg,csg,cg,mpg,ph,sg,sc	**(19/11/2018)**	NAP (1 guideline)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/our-guidelines.html	**(19/11/2018)**	NAP (ingen)
Helsedirektoratet (Norge) https://helsedirektoratet.no/retningslinjer	**(19/11/2018)**	NAP (1 guideline)
Socialstyrelsen (Sverige) http://socialstyrelsen.se/	**(19/11/2018)**	NAP (1 guideline)
Australian Clinical Practice Guidelines https://clinicalguidelines.gov.au/	**(19/11/2018)**	NAP (1 guideline)
European Society for Medical Oncology http://www.esmo.org/Guidelines	**(19/11/2018)**	NAP (1 guideline)
National Comprehensive Cancer Network https://www.nccn.org/professionals/physician_gls/default.aspx	**(19/11/2018)**	NAP (1 guideline)

Søgning efter systematiske reviews

Databaser (systematiske reviews)	*Dato for søgning*	*Ansvarlig for søgningen*
Medline	**(13/11/2018)** **Ver. 1.0** **(xx/10/2021)** **Ver. 2.0**	NAP

The Cochrane Library	**(19/11/2018)** **Ver 1.0** **(xx/10/2021)** **Ver 2.0**	NAP

Søgning efter primærlitteratur (fx randomiserede kontrollerede forsøg)

Databaser (primær litteratur)	**Dato for søgning (dd/mm/åååå)**	**Ansvarlig for søgningen (navn(e))**
Medline	**(28/10/2018)** **Ver. 1.0** **(25/10/2021)** **Ver. 2.0**	NAP

Søgestrategier

Søgning i forbindelse med version 1.0 af retningslinjen.
Guidelines søgning. Søgningen på de forskellige guidelines blev fortaget den 19.11.2018.
Følgende søgeord anvendt: Sarkom; Sarcoma; kemoterapi, cytoterapi, Chemotherapy.

Medline: søgestreng anvendt til at finde review artikler. Søgning foretaget 13.11.2018.

"Sarcoma"[Mesh] AND (advanced[All Fields] AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields])) AND "humans"[MeSH Terms] AND English[lang] AND Review[ptyp] AND (Review[ptyp] AND ("1990/01/01"[PDAT] : "2018/12/31"[PDAT]) AND "adult"[MeSH Terms]) NOT Kaposi's[All Fields]

Medline: søgestreng anvendt til at finde original litteratur. Søgningen foretaget 28.10.2018.

"Sarcoma"[Mesh] AND (advanced[All Fields] AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields])) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang])

Cochrane Library Reviews. Søgningen foretaget den 19.11.2018. Søgeord "Sarcoma and chemotherapy"

Søgning i forbindelse med version 2.0 af retningslinjen.
Samme søgestreng anvendt til at gennemgå litteraturen: søgningen blev fortaget den 25.10.2021 af NAP

Arbejdsdokument – Søgeprotokol

Emne

Titel (på retningslinje)	*Pallierende kemoterapi og targeteret behandling til patienter med bløddelsarskom*
DMCG	*DSG*
Kontakt med metodespecialist	*Nej*
Senest udfyldt	*03/10/2024*

Afgrænsning af emne	
Baggrund	*Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom*
Inklusions- og eksklusionskriterier	Publikationsdato (periode): 1990 – 2018 til version 1, 2018 til 2021 til version 2, version 3 2021 til 2024 *Sprog: Engelsk, dansk, svensk* *Publikationstyper: Guidelines, reviews,, originale artikler*

Emneord	Populationen	Intervention	Sammenlignings intervention	Outcomes
Dansk *Alle tænkelige søgeord bør indsættes.*	*Sarkom, bløddelssarkom, kræft i bløddele, kræft i bindevæv*	*Kemoterapi, targeteret behandling*	*Fase 1, 2 og 3 forsøg, kliniske forsøg*	*Effekt af behandlingen, overlevelsen, tid til progression.*
Engelsk *Alle tænkelige søgeord bør indsættes.*	*Sarcoma, soft tissue sarcoma,*	*Chemotherapy, targeted treatment,*	*Clinical trials, phase I, II or III studies*	*Effect, overall survival, time to progression*

Søgning efter guidelines

Databaser (Guidelines)	Dato for søgning	Ansvarlig for søgningen
G-I-N International http://www.g-i-n.net/library/international-guidelines-library	**(19/11/2018)**	NAP (16 hits 4 udvalgt – 2 findes ved andre links)
NICE (UK) https://www.nice.org.uk/guidance/published?type=apg,csg,cg,mpg,ph,sg,sc	**(19/11/2018)**	NAP (1 guideline)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/our-guidelines.html	**(19/11/2018)**	NAP (ingen)
Helsedirektoratet (Norge) https://helsedirektoratet.no/retningslinjer	**(19/11/2018)**	NAP (1 guideline)
Socialstyrelsen (Sverige) http://socialstyrelsen.se/	**(19/11/2018)**	NAP (1 guideline)
Australian Clinical Practice Guidelines https://clinicalguidelines.gov.au/	**(19/11/2018)**	NAP (1 guideline)
European Society for Medical Oncology http://www.esmo.org/Guidelines	**(19/11/2018)**	NAP (1 guideline)
National Comprehensive Cancer Network https://www.nccn.org/professionals/physician_gls/default.aspx	**(19/11/2018)**	NAP (1 guideline)

Søgning efter systematiske reviews

Databaser (systematiske reviews)	*Dato for søgning*	*Ansvarlig for søgningen*
Medline	**(13/11/2018)** **Ver. 1.0** **(xx/10/2021)** **Ver. 2.0**	NAP

The Cochrane Library	**(19/11/2018)** **Ver 1.0** **(xx/10/2021)** **Ver 2.0**	NAP

Søgning efter primærlitteratur (fx randomiserede kontrollerede forsøg)

Databaser (primær litteratur)	**Dato for søgning (dd/mm/åååå)**	**Ansvarlig for søgningen (navn(e))**
Medline	**(28/10/2018)** **Ver. 1.0** **(25/10/2021)** **Ver. 2.0** **(25/9/2024)** **Ver.3.0**	NAP

Søgestrategier

Søgning i forbindelse med version 1.0 af retningslinjen.
Guidelines søgning. Søgningen på de forskellige guidelines blev fortaget den 19.11.2018.
Følgende søgeord anvendt: Sarkom; Sarcoma; kemoterapi, cytoterapi, Chemotherapy.

Medline: søgestreng anvendt til at finde review artikler. Søgning foretaget 13.11.2018.

"Sarcoma"[Mesh] AND (advanced[All Fields] AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields])) AND "humans"[MeSH Terms] AND English[lang] AND Review[ptyp] AND (Review[ptyp] AND ("1990/01/01"[PDAT] : "2018/12/31"[PDAT]) AND "adult"[MeSH Terms]) NOT Kaposi's[All Fields]

Medline: søgestreng anvendt til at finde original litteratur. Søgningen foretaget 28.10.2018.

"Sarcoma"[Mesh] AND (advanced[All Fields] AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields])) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms] AND English[lang])

Cochrane Library Reviews. Søgningen foretaget den 19.11.2018. Søgeord "Sarcoma and chemotherapy"

Søgning i forbindelse med version 2.0 af retningslinjen.
Samme søgestreng anvendt til at gennemgå litteraturen: søgningen blev fortaget den 25.10.2021 af NAP

Arbejdsdokument – Søgeprotokol

Emne

Udfyld ét arbejdspapir for hvert emne.

Titel (på retningslinje)	*Pallierende kemoterapi og targeteret behandling til patienter med bløddelsarskom*
DMCG	*DSG*
Kontakt med metodespecialist	*Nej*
Senest udfyldt	*01/11/2021*

Afgrænsning af emne	
Baggrund	*Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom*
Inklusions- og eksklusionskriterier	Publikationsdato (periode): 1990 – dd *Sprog: Engelsk, dansk, svensk* *Publikationstyper: Guidelines, Reviews, originale artikler*

Emneord	Populationen	Intervention	Sammenlignings intervention	Outcomes
Dansk *Alle tænkelige søgeord bør indsættes.*	*Sarkom, bløddelssarkom, kræft i bløddele, kræft i bindevæv*	*Pembrolizumab* *immunterapi*	*Fase 1, 2 og 3 forsøg, kliniske forsøg* *Cohorte undersøgelser,* *Cases*	*Effekt af behandlingen, overlevelsen, tid til progression.*
Engelsk *Alle tænkelige søgeord bør indsættes.*	*Sarcoma, soft tissue sarcoma,*	*Pembrolizumab* *immuntherapy*	*Clinical trials, phase I, II or III studies* *Cohort studies* *Case rapport*	*Effect, overall survival, time to progression*

Søgning efter guidelines

Databaser (Guidelines)	Dato for søgning	Ansvarlig for søgningen
SSG (scandinavian sarcoma group) https://www.ssg-org.net/treatment-protocols-and-recommendations/ongoing	**(01/11/2021)**	NAP

Søgning efter systematiske reviews

Databaser (systematiske reviews)	*Dato for søgning*	*Ansvarlig for søgningen*
Medline	**20/09/2021**	NAP
Embase	**20/9/2021**	NAP

Søgning efter primærlitteratur (fx randomiserede kontrollerede forsøg)

Databaser (primær litteratur)	Dato for søgning (dd/mm/åååå)	Ansvarlig for søgningen (navn(e))
Medline	**20/9/2021**	NAP
Embase	**20/9/2021**	NAP

Søgestrategier

Søgning i forbindelse med version 2.0 af retningslinjen, som også giver en anbefaling for anvendelse af immunterapi.
Guidelines søgning. Søgningen på de forskellige guidelines blev fortaget den 01.11.2021

Medline: søgestreng anvendt til at finde primær publiationer og review artikler. Søgning foretaget 20.09.2021.

((“pembrolizumab”[supplementary Concept] OR “pembrolizumab”[All fields]) AND (“sarcoma”[MeSH Terms] OR “sarcoma”[All Fields] OR “sarcomas”[All Fields] OR sarcoma s”[All Fields])) AND((fft[Filter]) AND (English[Filter]))

Antal publikationer 141

immunotherapy and sarcoma Filters: Full text, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review, English Sort by: Publication Date

(("immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields] OR "immunotherapies"[All Fields] OR "immunotherapy s"[All Fields]) AND ("sarcoma"[MeSH Terms] OR "sarcoma"[All Fields] OR "sarcomas"[All Fields] OR "sarcoma s"[All Fields])) AND ((clinicaltrial[Filter] OR meta-

analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) Translations immunotherapy: "immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields] OR "immunotherapies"[All Fields] OR "immunotherapy's"[All Fields] sarcoma: “sarcoma”[MeSH Terms] OR "sarcoma"[All Fields] OR "sarcomas"[All Fields] OR "sarcoma's"[All Fields]

Antal publikationer 718

Embase: søgestreng anvendt til at finde original litteratur ore review artikler. Søgningen foretaget 13.10.2021

Der fremkom 698 efter fjernelse af duplikater var der 556 tilbage som blev systematiske gennemgået.

Søgestreng: (´sarcoma´/exp OR sarcoma) AND pembrolizumab AND treatment.

Yderlige 17 kliniske forsøg eller retrospektiv opgørelser bliv identificeret. De fleste af disse var studie protokoller. Dette gav anledning til inklusion af yderlige 2 studier.

Det total antal studier inkluderet er således 30, hvoraf den ene er en pooled analyse.

Arbejdsdokument – Søgeprotokol

Emne

Titel (på retningslinje)	*Pallierende kemoterapi og targeteret behandling til patienter med bløddelsarskom*
DMCG	*DSG*
Kontakt med metodespecialist	*Nej*
Senest udfyldt	*01/11/2021*

Afgrænsning af emne	
Baggrund	*Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom*
Inklusions- og eksklusionskriterier	Publikationsdato (periode): Version 11990 – 2021, Der findes ingen version 2, Version 3 2021 til 2024 *Sprog: Engelsk, dansk, svensk* *Publikationstyper: Guidelines, Reviews, originale artikler*

Emneord	Populationen	Intervention	Sammenlignings intervention	Outcomes
Dansk *Alle tænkelige søgeord bør indsættes.*	*Sarkom, bløddelssarkom, kræft i bløddele, kræft i bindevæv*	*Pembrolizumab* *immunterapi*	*Fase 1, 2 og 3 forsøg, kliniske forsøg* *Cohorte undersøgelser,* *Cases*	*Effekt af behandlingen, overlevelsen, tid til progression.*
Engelsk *Alle tænkelige søgeord bør indsættes.*	*Sarcoma, soft tissue sarcoma,*	*Pembrolizumab* *immuntherapy*	*Clinical trials, phase I, II or III studies* *Cohort studies* *Case rapport*	*Effect, overall survival, time to progression*

Søgning efter guidelines

Databaser (Guidelines)	**Dato for søgning**	Ansvarlig for søgningen
SSG (scandinavian sarcoma group)	**(01/11/2021)**	NAP

https://www.ssg-org.net/treatment-protocols-and-recommendations/ongoing		

Søgning efter systematiske reviews

Databaser (systematiske reviews)	*Dato for søgning*	*Ansvarlig for søgningen*
Medline	**20/09/2021**	NAP
Embase	**20/9/2021**	NAP

Søgning efter primærlitteratur (fx randomiserede kontrollerede forsøg)

Databaser (primær litteratur)	**Dato for søgning (dd/mm/åååå)**	**Ansvarlig for søgningen (navn(e))**
Medline	**20/9/2021** **Version 1** **25/9 2024** **Version 2**	NAP
Embase	**20/9/2021**	NAP

Søgestrategier

Søgning i forbindelse med version 2.0 af retningslinjen, som også giver en anbefaling for anvendelse af immunterapi.
Guidelines søgning. Søgningen på de forskellige guidelines blev fortaget den 01.11.2021

Medline: søgestreng anvendt til at finde primær publiationer og review artikler. Søgning foretaget 20.09.2021.

((“pembrolizumab”[supplementary Concept] OR “pembrolizumab”[All fields]) AND (“sarcoma”[MeSH Terms] OR “sarcoma”[All Fields] OR “sarcomas”[All Fields] OR sarcoma s”[All Fields])) AND((fft[Filter]) AND (English[Filter]))

Antal publikationer 141

immunotherapy and sarcoma Filters: Full text, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review, Systematic Review, English Sort by: Publication Date

(("immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields] OR "immunotherapies"[All Fields] OR "immunotherapy s"[All Fields]) AND ("sarcoma"[MeSH Terms] OR "sarcoma"[All Fields] OR "sarcomas"[All Fields] OR "sarcoma s"[All Fields])) AND ((clinicaltrial[Filter] OR meta-

analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) Translations immunotherapy: "immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields] OR "immunotherapies"[All Fields] OR "immunotherapy's"[All Fields] sarcoma: “sarcoma”[MeSH Terms] OR "sarcoma"[All Fields] OR "sarcomas"[All Fields] OR "sarcoma's"[All Fields]

Antal publikationer 718

Embase: søgestreng anvendt til at finde original litteratur ore review artikler. Søgningen foretaget 13.10.2021

Der fremkom 698 efter fjernelse af duplikater var der 556 tilbage som blev systematiske gennemgået.

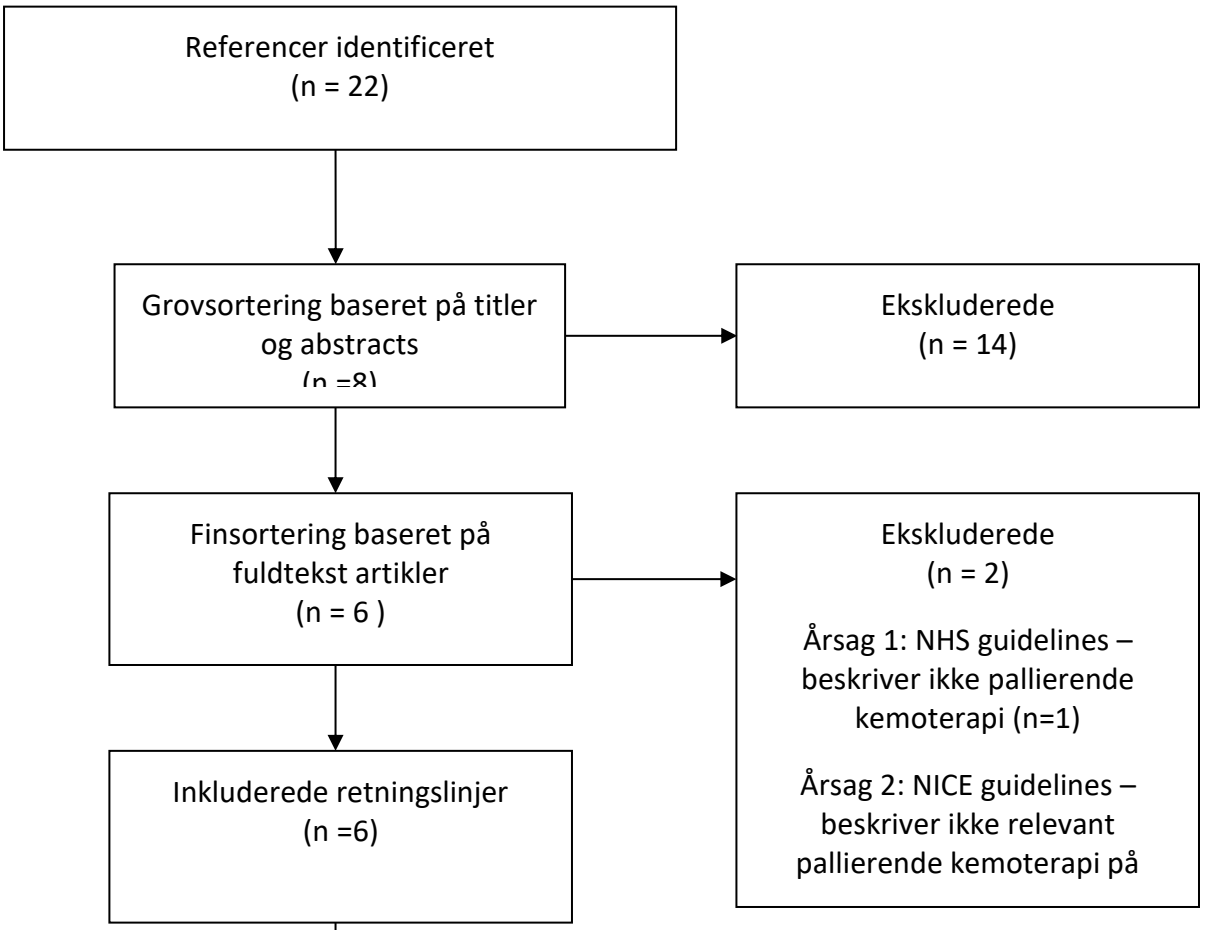
Søgestreng: (´sarcoma´/exp OR sarcoma) AND pembrolizumab AND treatment.

Yderlige 17 kliniske forsøg eller retrospektiv opgørelser bliv identificeret. De fleste af disse var studie protokoller. Dette gav anledning til inklusion af yderlige 2 studier.

Det total antal studier inkluderet er således 30, hvoraf den ene er en pooled analyse.

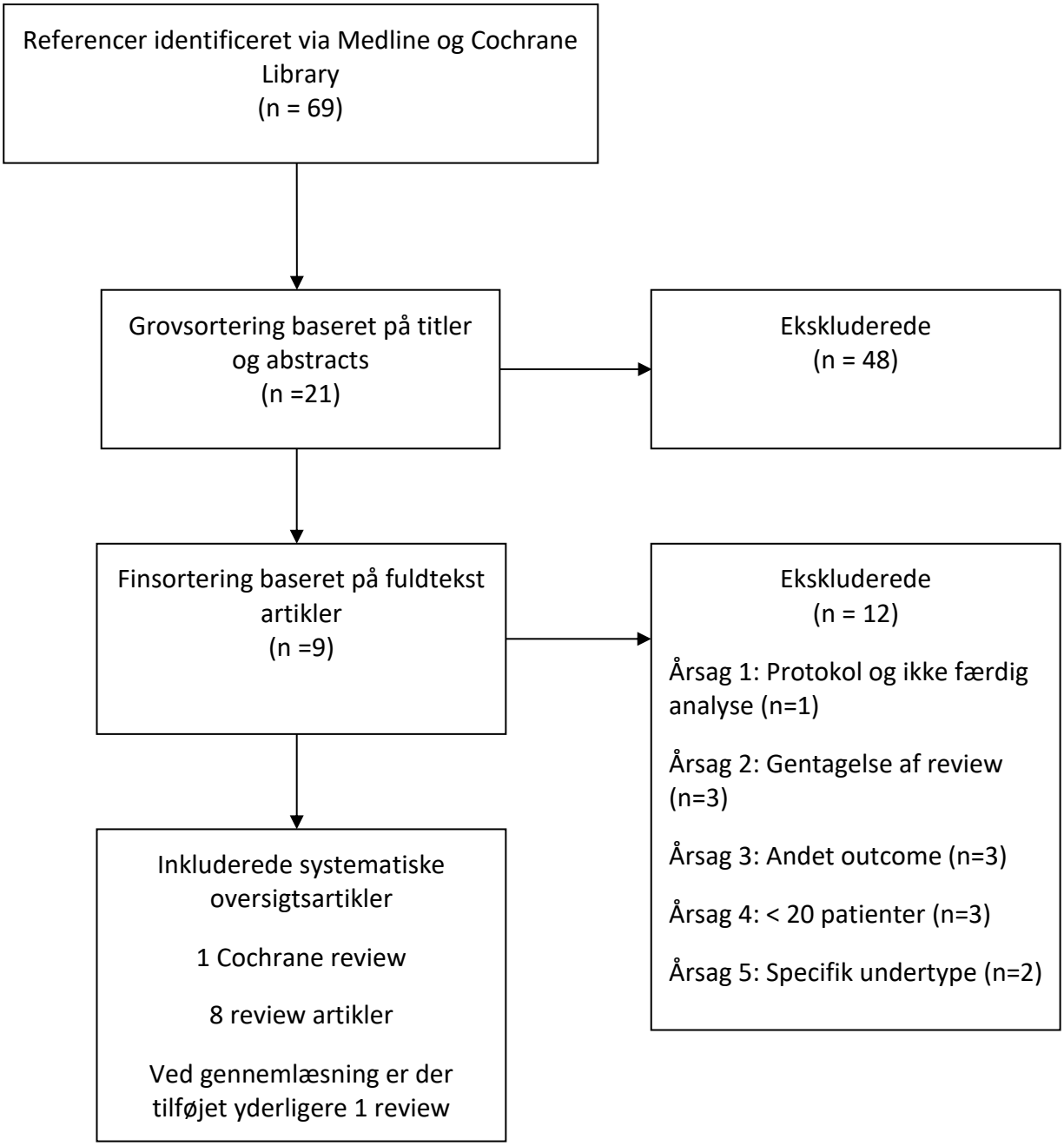
Bilag 3 – Flowchart over selekteret litteratur bilag 3 (oprindelige flow), bilag 3 version 2 flowchart over selekteret litteratur til revision, bilag 3b er flowchart over selekteret litteratur i forbindelse med immunterapi. Version 3 er for nyeste opdatering gæler både for kemoterapi og immunterapi

Flowchart – Guidelines

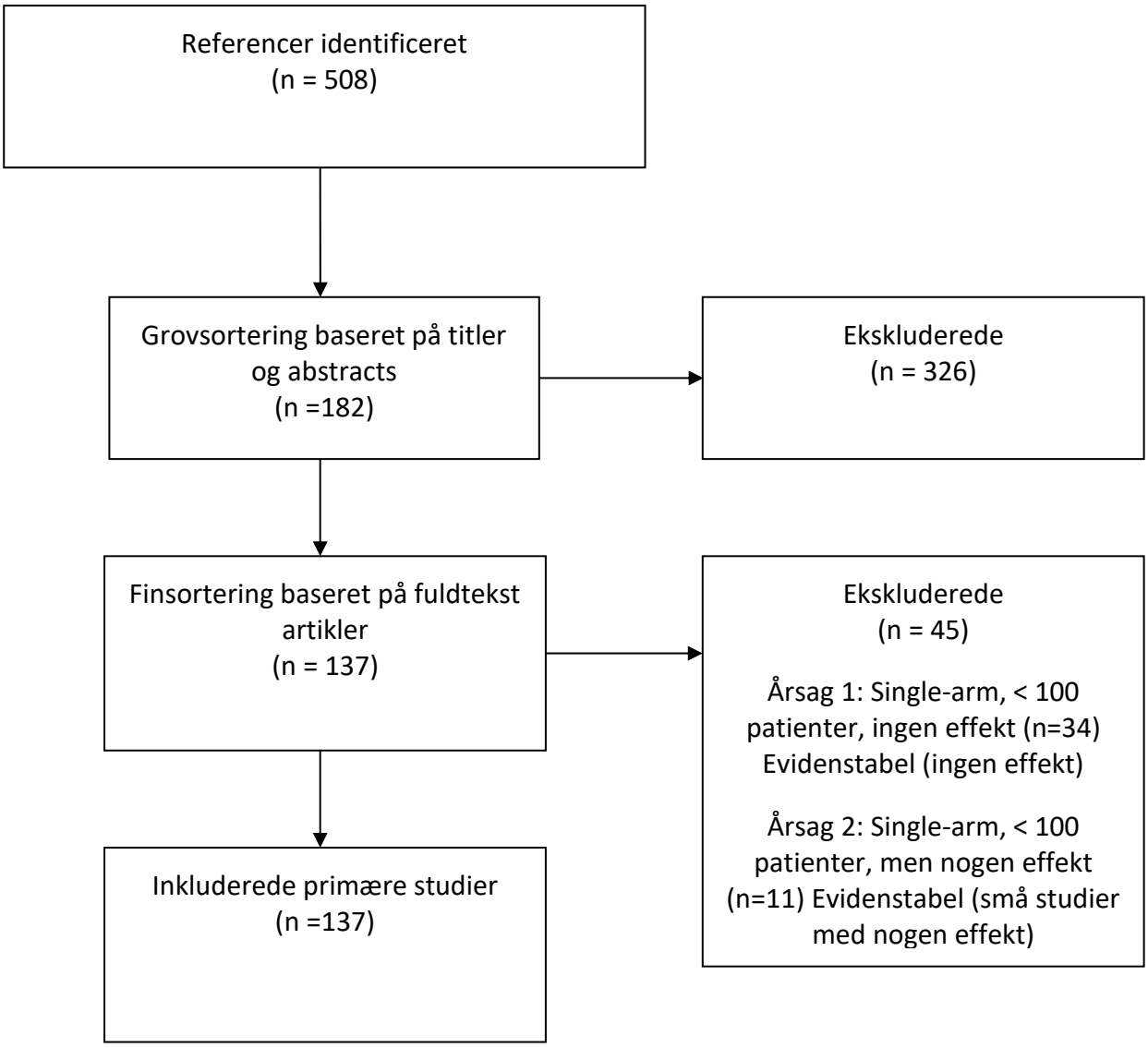


Emne 1	Helsedirektoratet Norge: Handlingsprogram – sarkom- Norge
Emne 2	Australasian Sarcoma Study Group: What is the role for systemic therapy in advanced soft-tissue sarcoma?
Emne 3	NCCN: Soft Tissue Sarcoma, Version 2.2016
Emne 4	ESMO-EURACAN: Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up
Emne 5	Sverige: Skelett- och mjukdelssarkom i extremiteter och bålvagg – nationellt vårdprogram
Emne 6	Dansk Sarkom Gruppe (DSG): Referance-program

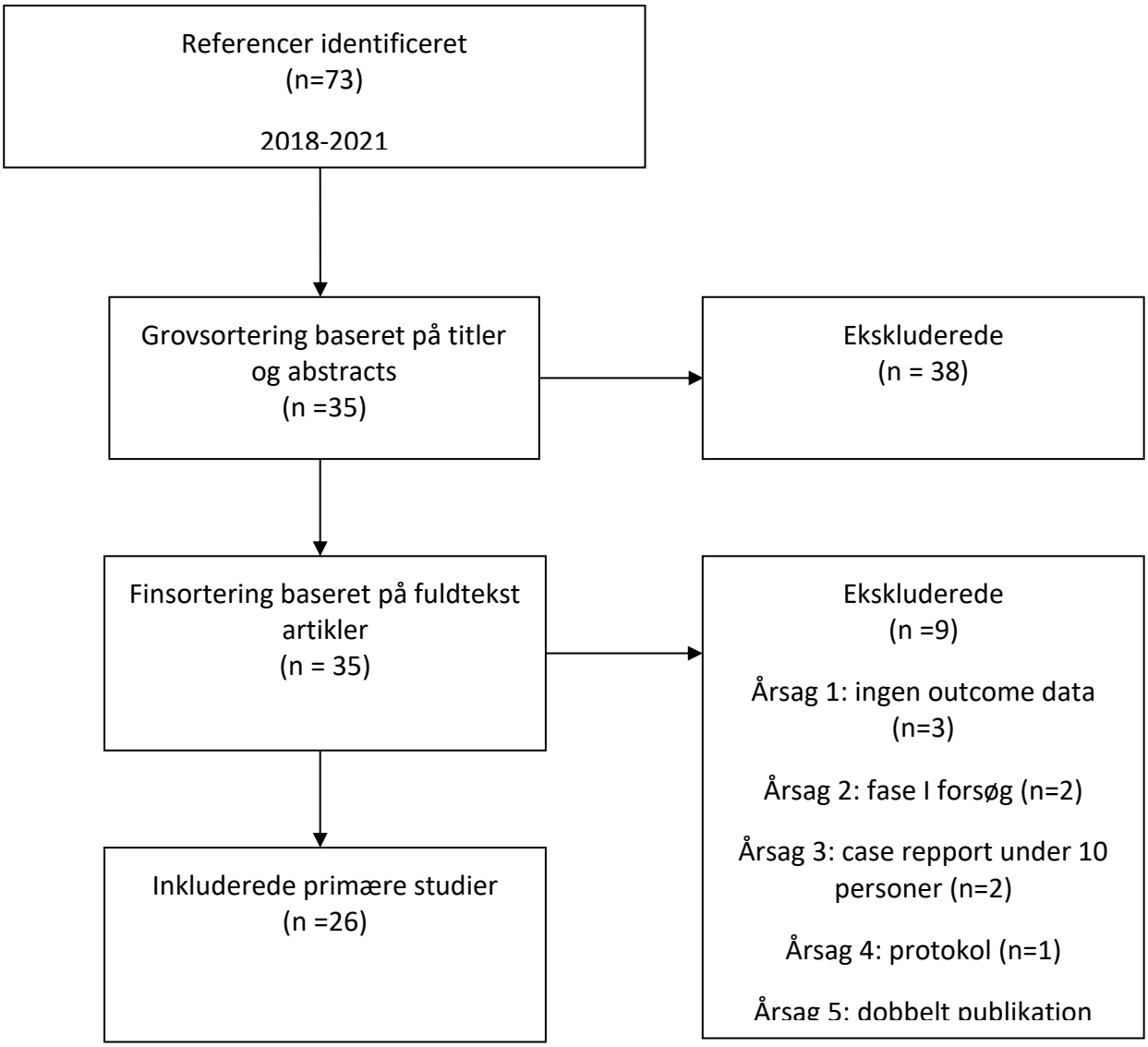
Flowchart – Systematiske oversigtsartikler



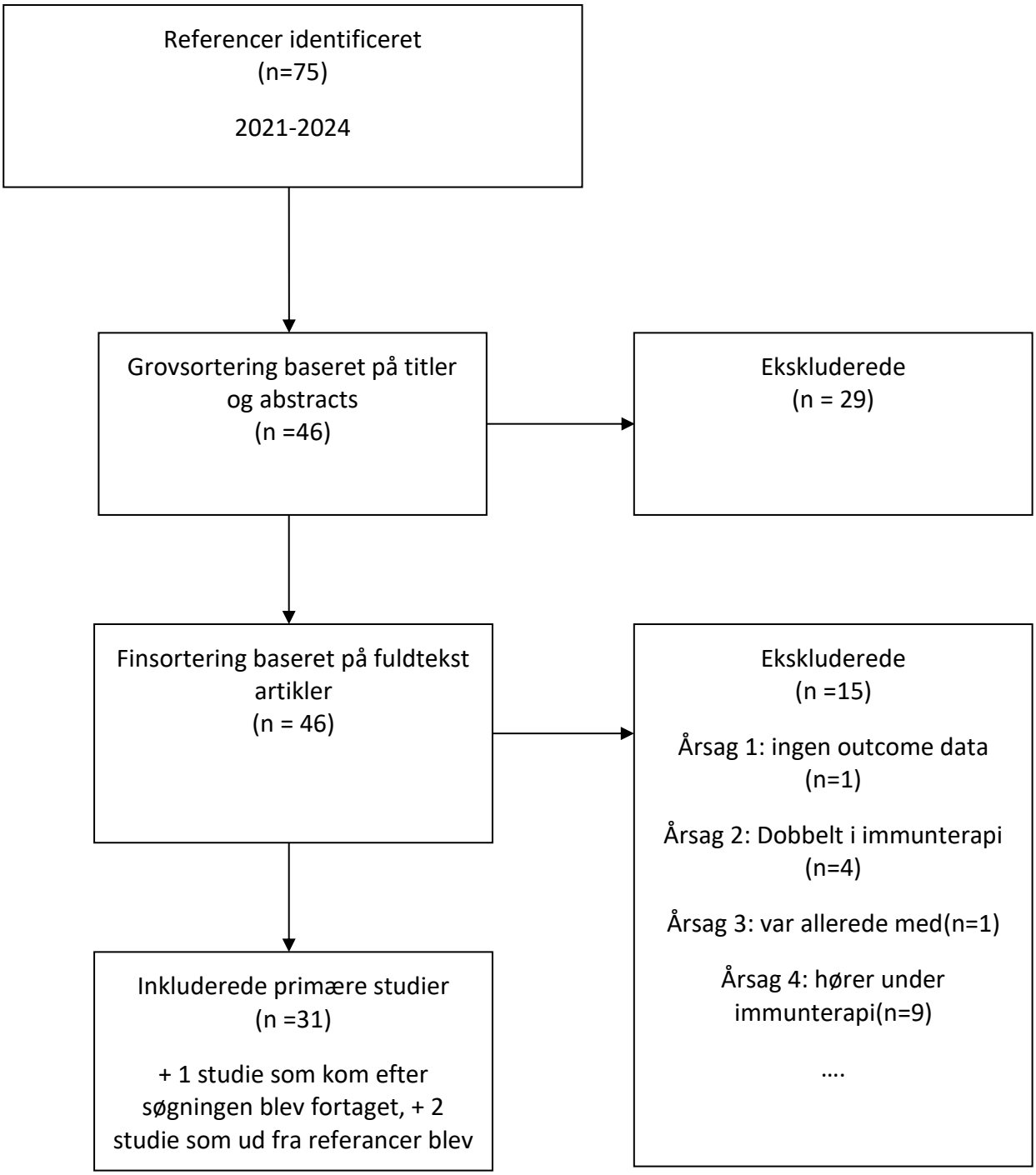
Flowchart – Primære studier



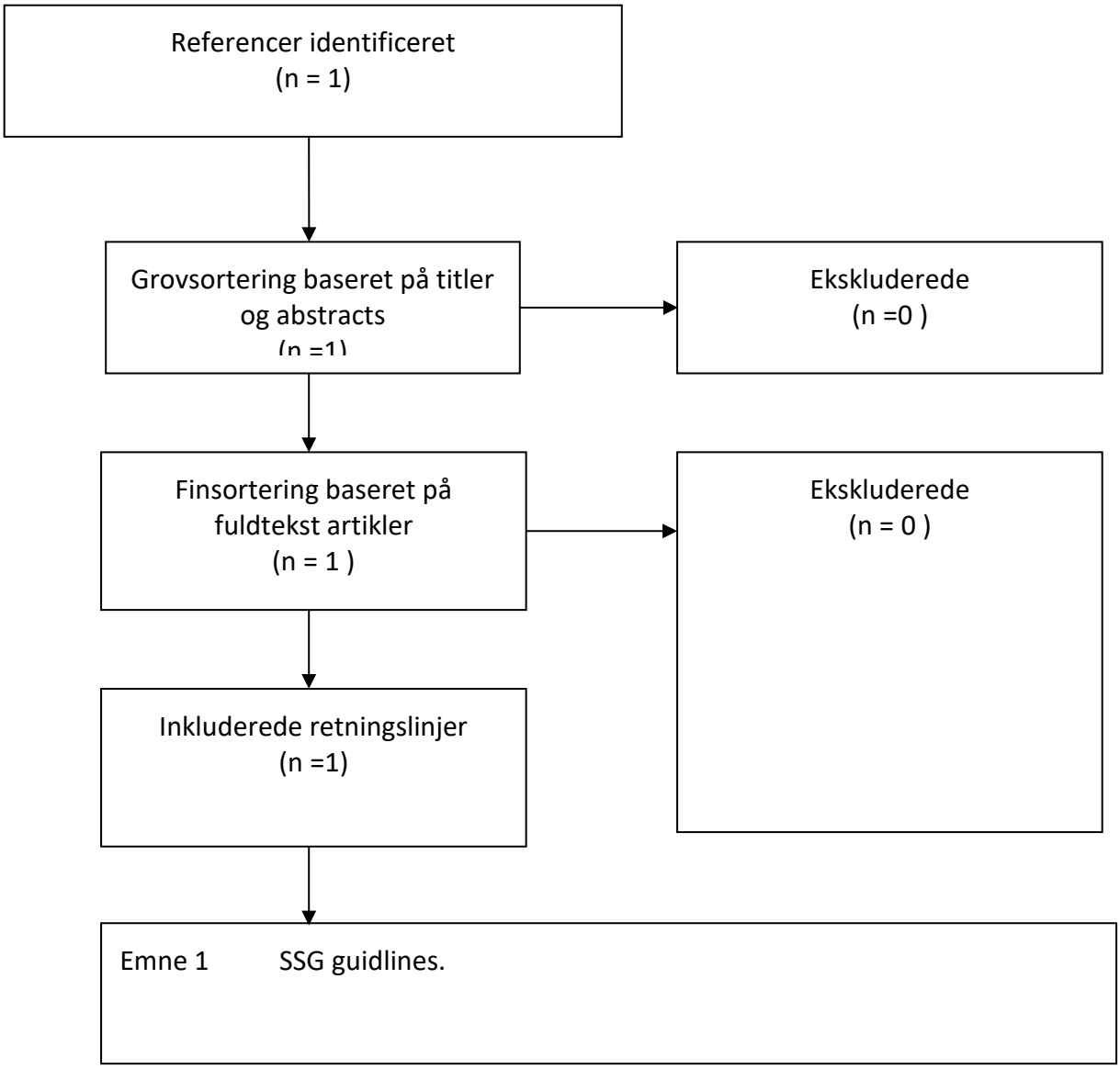
Flowchart – Primære studier fra 2018



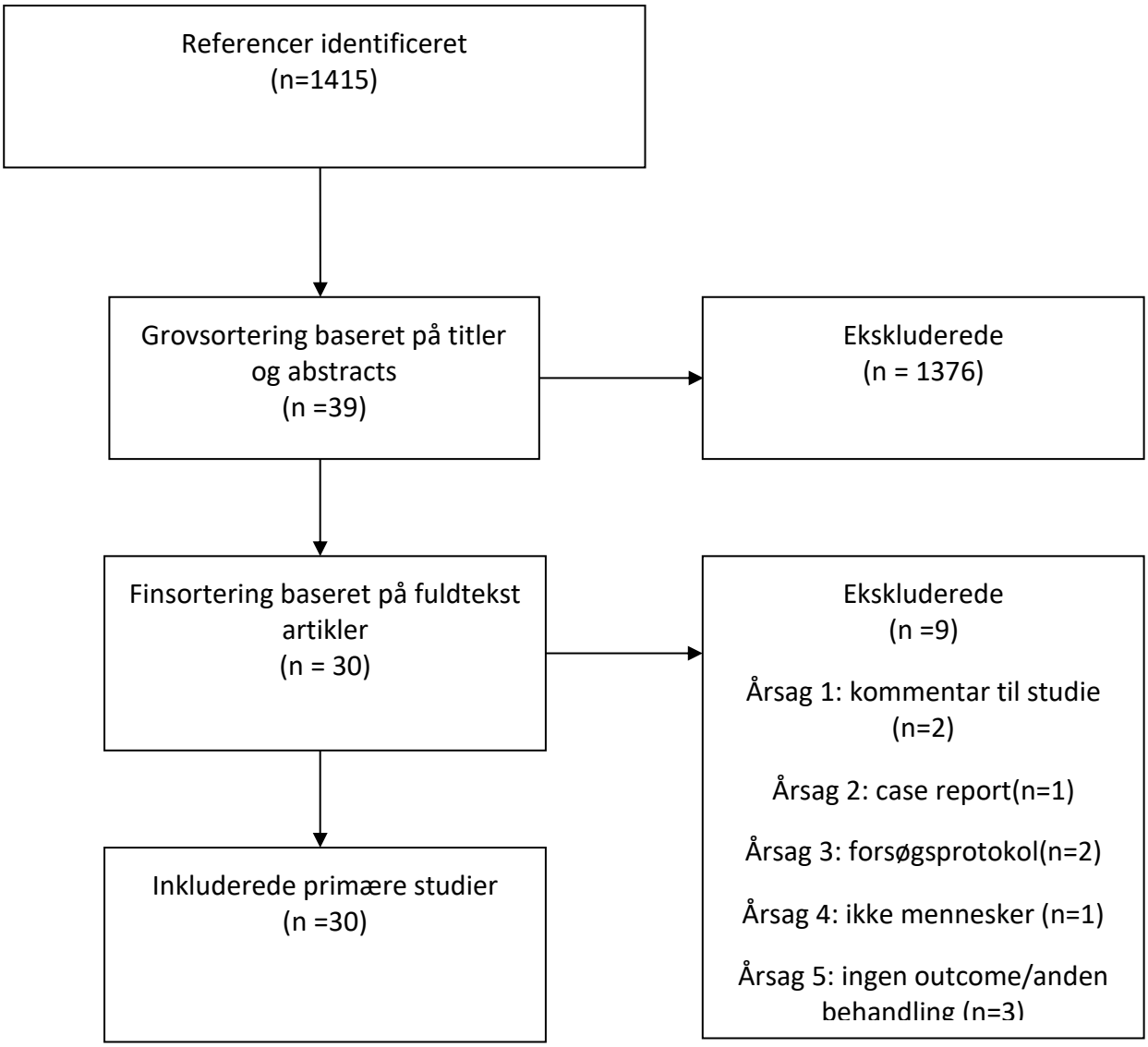
Flowchart – Primære studier fra 2021



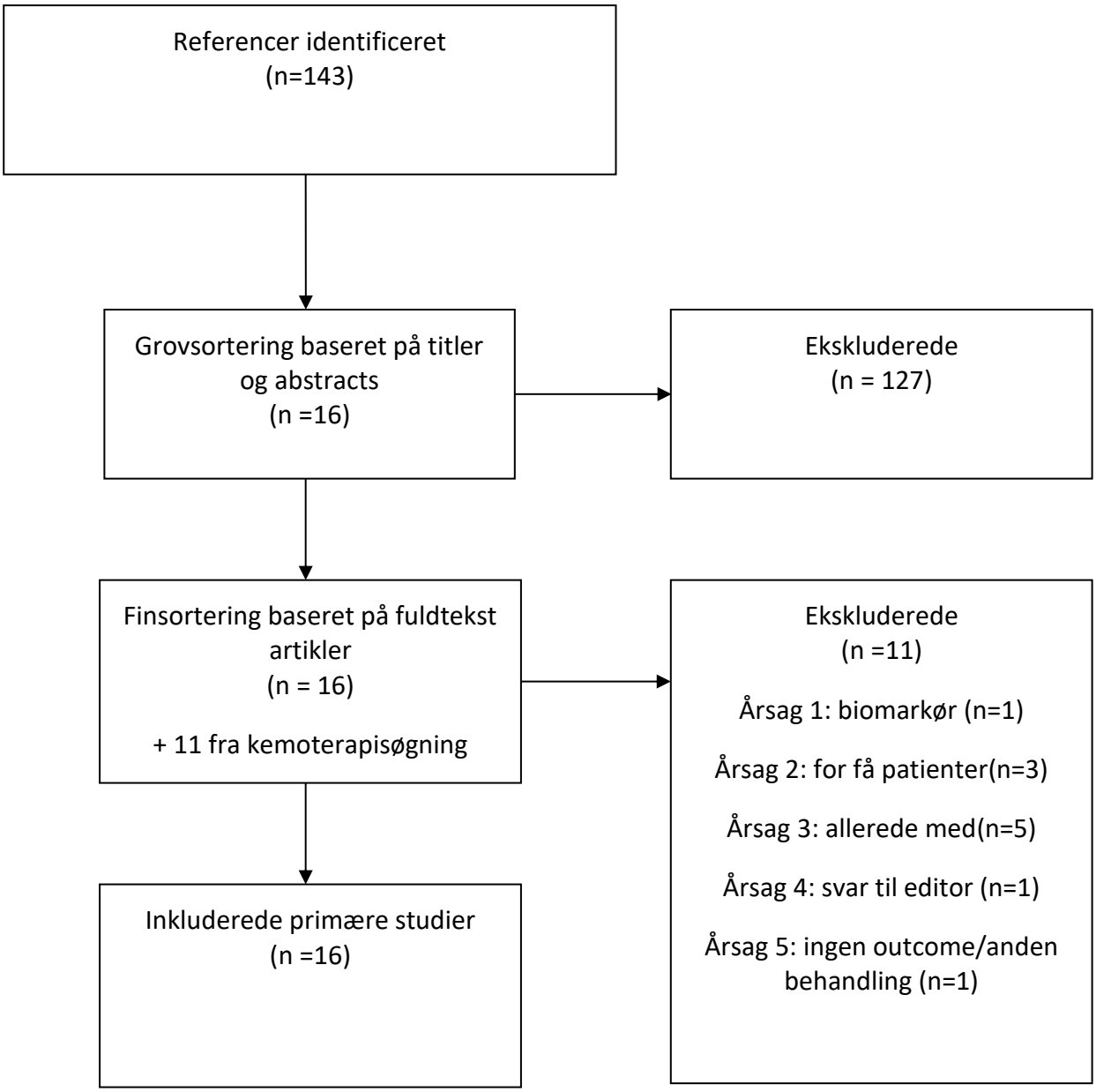
Flowchart – Guidelines immunterapi



Flowchart – Primære studier immunterapi



Flowchart – Primære studier immunterapi fra 2021



Bilag 4 – Evidenstabel (Doxorubicin)

Arbejdsdokument – Evidenstabel (doxorubicin)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom - doxorubicin*							
Forfatter/ kilde	**År**	**Undersøgelses-type/design**	**Under-søgel-sens kvalitet jf. Oxford**	**Intervention**	**Sammenlignings intervention**	**Patient-population**	**Resultater (outcome)**	**Kommentarer**
Steward WP et al.(127)	*1991*	*Single-arm, fase 2*	*2B*	*Doxorubicin + ifosfamid*		*STS (52)*	*ORR 43%*	
Wiklund TA et al.(128)	*1992*	*Single-arm, fase 2*	*2B*	*Doxorubicin + ifosfamid, + vincristin + dacarbazine*		*STS (37)*	*ORR 46% PFS 5 m OS 9.6 m*	
Edmonson JH et al.(129)	*1993*	*Randomiseret, fase 3*	*1B*	*Doxorubicin*	*Doxorubicin+ ifosfamid eller doxorubicin + cispaltin*	*STS (279)*	*ORR dox 20%, ORR ifos+dox 34%*	*Ingen overlevelses gevinst, men mere myelosuppression ved kombinationsbehandlinger*

					mitocycin			
Antman K et al(10)	*1993*	*Randomiseret, fase 3*	*1B*	*Doxorubicin + dacarbazine (ad)*	*Doxorubicin + ifosfamid + dacarbazine (adi)*	*STS (340)*	*ORRad 17% ORRadi 32% PFSad 4 m PFSadi 6 m OSad 13 m OSadi 12 m*	
Schütte J et al.(130)	*1993*	*Single-arm, fase 2*	*2B*	*Doxorubicin + ifosfamid*		*STS (203)*	*ORR 35% PFS 6.7 m OS 13.5 m*	
Santoro A et al.(9)	*1995*	*Randomiseret, fase 3*	*1B*	*Doxorubicin (a)*	*CYADIC (cy) eller doxorubicin + ifosfamid (ai)*	*STS (663)*	*ORR 24% ORRa 21.3 ORRcy 26.8% ORRai 25.2%*	*Ingen forskel i OS mellem behandlinger OSa 52 uger OScy 51 uger OSai 55 uger*
Sutton G et al.(131)	*1996*	*Single-arm, fase 2*	*2B*	*Doxorubicin + ifosfamid*		*Uterint leiomyosarkom (25)*	*ORR 30.3% OS 9.6 m*	
Jäger E et al.(132)	*1996*	*Single-arm, fase 2*	*2B*	*Doxorubicin + ifosfamid +*		*STS (56)*	*ORR 30.3% PFS 4.5 m*	

				Cisplatin + *5FU*			*OS 11.8 m*	
Antman K et al.(133)	*1998*	*Single-arm, fase 2*	*2B*	*Doxorubicin +* *ifosfamid +* *dacarbazine* *mesna(MAID)*		*Rhabdomyosarkom (25)*	*ORR 62%* *PFS 10 m* *OS 15 m*	
Sandler A et al.(134)	*1998*	*Single-arm, fase 2*		*Doxorubicin +* *paclitaxel*		*STS (29)*	*ORR 22.2%* *PFS 4.5 m* *OS 10.2 m*	*Konklusionen som doxorubicin enkeltstof*
De Pas T et al.(135)	*1998*	*Single-arm, fase 2*	*3*	*Doxorubicin +* *ifosfamid*		*STS (23)*	*ORR 50%* *PFS 9 m*	*Meget toksisk*
Buesa JM et al.(136)	*1998*	*Single-arm, fase 2*		*Ifosfamide efterfulgt af doxorubicin*		*STS (27)*	*ORR 31%* *PFS 4.9 m* *OS14.7 m*	*2 linjebehandling*
Palumbo R et al.(137)	*1998*	*Single-arm, fase 2*		*Vincristine +* *doxorubicin +* *cyclophosphamide* *alternerende med*		*STS (20)*	*ORR 45%* *OS10 m*	*2 CR, 7 PR*

				ifosfamid + etoposid				
Nielsen OS et al.(12)	*1999*	*Randomiseret, fase 3*	*1B*	*Doxorubicin*	*Epirubicin*	*STS (334)*	*PFSdox 3.7 m* *PFSepi 3.3 m* *OSdox 10.5 m* *OSepi 10.9 m*	*1. linjebehandling* *2 dødsfald i epi gruppen (cardiotox)* *Ingen forskel i PFS og OS*
Le Cesne A et al.(138)	*2000*	*Randomiseret, fase 3*	*1B*	*Doxorubicin +* *ifosfamid*	*Doxorubicin (højdosis) +* *ifosfamid*	*STS (314)*	*PFSlav 4.7 m* *PFShøj 7.2 m* *OSlav 13.1 m* *OShøj 12.8 m*	*Ingen forskel i OS* *Mere toksisk ved højdosis dox*
Verweij J et al.(22)	*2000*	*Randomiseriet, fase 2*	*2B*	*Doxorubicin*	*Docetaxel*	*STS (86)*	*ORR dox 30%* *ORR docetaxel 0%*	*Lukket før tid pga. ingen respondere til docetaxel – 1. linjebehandling*
Comandone A et al.(139)	*2000*	*Single-arm, fase 2*	*2B*	*Doxorubicin +* *ifosfamid*		*STS (42)*	*ORR 28%* *OS 7.6 m*	

Edmonson JH et al.(140)	*2002*	*Single-arm, fase 2*	*2B*	*Doxorubicin +* *mitocycin +* *cisplatin*		*Uterint leiomyosarkom (41)*	*ORR 23 %* *OS 6.3 m*	
van Rijswijk RE et al.(141)	*2003*	*Single-arm, fase 2*	*2B*	*Doxorubicin +* *ifosfamid +* *cisplatin*		*Uterint carcinosarkom (48)*	*ORR 56%* *OS 26 m*	*Meget toksisk*
Kalofonos HP et al.(142)	*2004*	*Single-arm, fase 2*	*3*	*Doxorubicin +* *cisplatin*		*STS (30)*	*ORR 16.7 %* *PFS 6 m* *OS 11.5 m*	
Maurel J et al.(143)	*2004*	*Single-arm, fase 2*	*2B*	*Sekventiel* *ifosfamid efterfulgt af doxorubicin*		*STS (60)*	*ORR 38%* *PFS 6 m*	
Kawai A et al.(144)	*2005*	*Single-arm, fase 2*	*2B*	*Alternerende ifosfamide og doxorubicin eller cyclohosphamid*		*Non-small round cell STS (42)*	*ORR 47.2%*	*Ingen PFS eller OS data*
Leyvraz S et al.(145)	*2006*	*Single-arm, fase 2*	*2B*	*Doxorubicin +* *ifosfamid (højdosis)*		*Uterint sarkom (37)*	*ORR 49%* *PFS 27.7 m* *OS 30.5 m*	
Leyvraz S et al.(146)	*2006*	*Single-arm, fase 2*	*2B*	*Doxorubicin (højdosis) +*		*STS (46)*	*ORR 48%*	*Mange bivirkninger*

				ifosfamid(højdosis)			*PFS 16.2 m* *OS 19 m*	
Lorigan P et al.(13)	*2007*	*Randomiseret, fase 3*	*1B*	*Doxorubicin*	*Ifosfamid*	*STS (326)*	*ORRdox 11.8%* *ORRifos 8.4%*	*Lukket præmaturt. Ingen gevinst af ifosfamid I forhold til doxorubicin ifosfamid mere toksisk*
Fayette J et al.(147)	*2009*	*Randomiseret, fase 3*	*2B*	*MAID*	*MAID højdosis*	*STS (162)*	*ORRmaid 35%* *ORRmaidhøj 38%*	
Maurel J et al.(148)	*2009*	*Randomiseret, fase 2*	*2B*	*Doxorubicin*	*Sekventiel doxorubicin + ifosfamid*	*STS (132)*		*Lukket præmaturt. Ingen forskel*
De Pas T et al.(149)	*2011*	*Single-arm, fase 2*	*2B*	*Doxorubicin +* *ifosfamid (kontinuert)*		*STS (34)*	*PFS 7.1*	*Meget toksisk*
Italiano A et al.(123)	*2012*	*Randomiseret, fase 2*	*2B*	*Doxorubicin*	*Paclitaxel (ugentlig)*	*Angiosarkom (117)*	*ORRdox 29%* *ORRpac 53%* *PFSdox 3 m* *PFSpac 5.8 m*	

							OSdox 5.5 m *OSpac 10.3*	
Demetri GD et al.(14)	*2012*	*Randomiseret, fase 1 og 2*	*2B*	*Doxorubicin*	*Doxorubicin +* *conatumumab*	*STS (128)*	*PFSdox 6.4m* *PFStest 5.6 m*	*Ingen forskel*
Gelderblom H et al.(15)	*2013*	*Randomiseret, fase 2*	*2B*	*Doxorubicin*	*Brostallicin*	*STS(118)*	*PFSdox 6.1 m* *PFSbro 1.6* *OSdox 13.2 m* *OSbro12.7 m*	*1. linjebehandling, ingen forskel i OS*
Judson I et al.(5)	*2014*	*Randomiseret, fase 3*	*1B*	*Doxorubicin*	*Doxorubicin +* *ifosfamid*	*STS (555)*	*PFSdox 4.6 m* *PFStest 7.4 m* *OSdos 12.8 m* *OStest 14.3*	*Ingen signifikant forskel I OS. Kombinationsbehandlingen gav mere toksicitet*
Chawla SP et al.(16)	*2015*	*Randomiseret, fase 2*	*2B*	*Doxorubicin*	*Aldoxorubicin*	*STS (126)*	*DCRdos 68%* *DCRaldox 77%* *PFSdox 2.7m*	*ORRdox 5%, ORRaldox 26%*

							PFSaldox 5.6m *OSdox 14.3 m* *OSaldox 15.8 m*	
Tap WD et al.(17)	*2016*	*Randomiseret, fase 2*	*2B*	*Doxorubicin*	*Doxorubicin +* *olaratumab*	*STS (133)*	*PFSdox 4.1 m* *PFStest 6.6 m* *OSdox 14.7 m* *OStest 26.5 m*	*ORRdox 11.9%, ORRtest 18.2%*
Seddon B et al.(18)	*2017*	*Randomiseret, fase 3*	*1B*	*Doxorubicin*	*Gemcitabin +* *docetaxcel*	*STS (257)*	*ORRdox 20%* *ORRgem 20%* *PFSdox 5.4 m* *PFSgem 5.5 m* *OSdox 17.8 m*	*1.linjebehandling*

							OSgem 15.7m	
Tap WD et al.(19)	*2018*	*Randomiseret, fase 3*	*1B*	*Doxorubicin*	*Doxorubicin +* *evofosfamid*	*STS (640)*	*OSdox 19 m* *OSdoxevo 18.4 m*	*Ingen effekt*
Grunwald V et al. (150)	*2020*	*Randomiseret, fase 2*	*1B*	*Doxorubicin*	*Pazopanib*	*STS > 60 år ikke tidligere behandlet* *Dox (n=39) pazopanib (n=81)*	*ORRdox 15.4%* *ORRpazo 12.3%* *Ingen forskel i PFS eller OS.*	*Flere med neutopen feber ved dox behandlingen.*
Tap W et al.(20)	*2020*	*Randomiseret, fase 3*	*1B*	*Doxorubicin*	*Doxorubicin + olaratumab*	*STS 509*	*ORRdox 18.3%* *ORRdoxol 14%* *PFSdox 5.4 m* *PFSdoxol 6.8 m* *OSdox 19.7 m*	

							OSdosol 20.4m	
D'Ambrosio et al.(36)	2020	Retrospektiv kohorte studie	2B	Doxorubidin (dox) (n=115)	Doxorubicin + Ifosfamid (doxi) (n=71) Doxorubicin + dacarbazine(doxd) (n=117)	Leiomyosarkom. (303)	ORRdox 25.6% ORRdoxi 19.5% ORRdoxd 30.9% PFSdox 4.8 m PFSdoxi 8.2 m PFSdoxd 9.2 m OSdox 30.3 m OSdoxi 21.9 m OSdoxd 36.8 m	Første linje behandling
Hartmann JT et al.(151)	2020	Randomiseret fase 2	2A	Dosorubicin (n=40)	Trofosfamid (n=80)	STS ikke tidligere	ORRdox 7.7%	

						behandlet (120)	*ORRtro 6.6%* *PFSdox 4.3 m* *PFStro 2.8 m* *OSdox 9.8 m* *OStro 12.3 m*	
Pautier p et al. (152)	*2021*	*Single-arm, fase 2,* *Long term follow-up*	*2B*	*Doxorubicin + trabectedin*		*Leiomyosarkom (108)*	*PFS 10.1 m* *OS 34.4 m*	*Kirurgi af metastaser var tilladt.*
Schlemann et al.(153)	*2021*	*Single-arm, fase 1*	*2C*	*Doxorubicin +L19TNF*		*SFS(15)*	*ORR % (1 CR, 1PR, 7 SD)* *PFS 3.08 m* *OS 14.9 m*	*Antistof mod tumor nekrosis faktor.* *Tung behandlet gruppe af patienter.*
Lewin J et al. (154)	*2021*	*Single-arm, fase 1b*	*2C*	*Doxorubicin + selinexor*		*STS (25)*	*ORR 21% (5/24 PR) (15 SD)* *PFS 5.5 m*	*Bivirkninger neutropeni og anæmi*

							OS 10.5 m	
Van Tine BA et al.(21)	*2021*	*Single-arm, fase II,* *Interim undersøgelse*	*2B*	*Doxorubicin + upfront dexrazoxane + olaratumab*		*STS(33 out of 65 patients has been enroled)*	*PFS 8.4 m*	*Historisk kontrol 4.6 m PFS,* *3 patienter har haft hjerte toks (fik over 600 mg/m2 doxorubicin).*
Pautier P et al.(27)	*2022*	*Randomiseret, multicenter, open-label, fase 3*	*2A*	*Doxorubicin (n=76)*	*Doxorubicin + trabectidin (doxT) efterfulgt af trabectidin vedligeholdsbehandling (n=74)*	*Leiomyosarkom (150)*	*DCRdox 78.9%* *DCRRdoxT 91.1%* *PFSdox 6.2 m* *PFSdoxT 12.2 m*	*27 patienter I doxorubicin gruppe fik trabectedin som 2 linje behandling. Data forelægger ikke på dette.*
Cote GM et al. (29)	*2024*	*Single-arm, fase 1b*	*2B*	*Doxorubicin + lurbinectedin*		*STS (10)*	*ORR 60% (6/10 PR)* *PFS 16.5 m*	*Bivirkninger fatigue og kvalme*
Pautier P et al(28)	*2024*	*Randomiseret, multicenter, open-label, fase 3*	*2A*	*Doxorubicin (n=76)*	*Doxorubicin + trabectidin (doxT) efterfulgt af trabectidin vedligeholdsbehandling (n=74)*	*leiomyosarkom*	*PFS doxT 12 m* *PFS dox 6 m*	*Omkring 56% af patienter fik trabectedin på et tidspunkt efter doxorubicin i den arm hvor der kun blev givet doxorubicin.*

							OS doxT 33 m OS dod 24 m	
Toma S et al.(155)	2000	Single-arm, fase 2	2B	Caelyx		STS (25)	ORR 12% DCR 88%	2. linjebehandling
Judson I et al.(116)	2001	Randomiseret, fase 2	2B	Doxorubicin	Caelyx	STS (94)	ORRdox 9% ORRcalyx 10% PFSdox 2.73 m PFScal 2.16 m OSdox 8.2 m OScal 10.6	Mindre toksisk behandling med caelyx.
Bafaloukos D et al.(156)	2004	Single-arm, fase 2	2B	Caelyx + paclitaxel		STS (42)	ORR 16% PFS 5.7 OS 13.2 m	
Sutton G et al.(157)	2005	Single-arm, fase 2	2B	Liposomalt doxorubicin		Uterint leiomyosarkom (35)	ORR 16.1%	Ingen PFS eller OS data
Liu X et al. (11)	2022	Single-arm, fase 2	2B	Pegylated liposomal		STS (69)	ORR 26.1%	Første linje behandling

				doxorubicin + ifosfamid			*DCR 81.2%* *PFS 7.3 m* *OS 20.6 m*	

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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Bilag 5 – Evidenstabel (Ifosfamid)

Arbejdsdokument – Evidenstabel (ifosfamid)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom - ifosfamid*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Blackledge G et al.(158)	*1992*	*Review*		*Ifosfamid*		*STS*		*Artiklen kunne ikke findes*
Bramwell VH et al.(159)	*1993*	*Randomiseret, fase 2*	*1B*	*Ifosfamid*	*Cyclophosphamid*	*STS (171)*	*ORRcy 7.5%* *ORRifos 18%*	*1. linjebehandling*
Frustaci S et al.(30)	*1993*	*Single-arm, fase 2*	*2B*	*Ifosfamid +* *epirubicin*		*STS (64)*	*ORR 28%* *OS 13 m*	*Bedre i non-viscerale sarkomer*
Chevallier B et al.(31)	*1993*	*Single-arm, fase 2*	*2C*	*Ifosfamid +* *epirubicin*		*STS (30)*	*ORR 48%* *PFS 6.3 m* *OS 9.3 m*	*1. linjebehandling*
Sutton GP et al.(160)	*1994*	*Single-arm, fase 2*	*2C*	*Ifosfamid +* *mesna*		*Mixed mesodermale ovarie tumorer (31)*	*ORR 17.9%*	*2. linjebehandling*

Le Cesne A et al.(37)	*1995*	*Single-arm, fase 2*	*2C*	*Ifosfamid (højdosis) +* *tidligere behandlet med ifosfamid (lavdosis)*		*STS (40)*	*ORR 22%* *PFS 8 m* *OS 12 m*	*2. linjebehandling,* *Leiomyosarkom virker resistent.*
Tursz T et al.(38)	*1996*	*Single-arm, fase 2*	*2C*	*Ifosfamid (højdosis)*		*STS (36)*	*ORR 33%*	*2. linjebehandling.* *Ingen leiomyosarkomer havde respons*
Saeter G et al.(32)	*1997*	*Single-arm, fase 2*	*2B*	*Ifosfamid +* *epirubicin*		*STS (92)*	*ORR 42%*	
Palumbo R et al.(39)	*1997*	*Single-arm, fase 2*	*2C*	*Ifosfamid (højdosis)*		*STS (38)*	*ORR 39%* *OS 19 m*	*2. linjebehandling.* *Ingen leiomyosarkomer responderede (4 patienter med SD)*
Reichardt P et al.(33)	*1998*	*Single-arm fase 2*	*2B*	*Ifosfamid +* *epirubicin + filgrastim*		*STS (46)*	*ORR 52%* *OS 24 m*	*1. linjebehandling, toksicitet relativ høj*
Yalçin S et al.(161)	*1998*	*Single-arm, fase 2*	*2C*	*Ifosfamid + etoposide+* *mesna*		*STS (26)*	*ORR 41.6%* *PFS 13.3 m*	*2. linjebehandling*
Buesa JM et al.(162)	*1998*	*Single-arm, fase 2*	*2B*	*Ifosfamid*		*STS (48)*	*ORR 37.7%*	*1. linjebehandling, høj toksicitet*

Palumbo R et al.(34)	*1999*	*Single-arm, fase 2*	*2B*	*Ifosfamid + epirubicin*		*STS (39)*	*ORR 59%*	*1. linjebehandling*
Papai Z et al.(163)	*2000*	*Single-arm, fase 2*	*2B*	*Etoposid+ ifosfamid+ cisplatin*	*Ingen*	*STS (104)*	*ORR 46% DCR 87%*	
Nielsen OS et al.(40)	*2000*	*Single-arm, fase 2*	*2B*	*Ifosfamid (højdosis)*		*STS (124)*	*ORR 16% DCR 48% PFS 3.5 m OS 12.8 m*	*Leiomyosarkomer responderede ikke. 2. linjebehandling ORR 16% DCR 37% Meget toksicitet*
Sutton G et al.(164)	*2000*	*Randomiseret, fase 3*	*1B*	*Ifosfamid*	*Ifosfamid + cisplatin*	*Uterint carcinosarkom (224)*	*ORRifos 47% ORRifoscis 61% PFSifos 4 m PFSifoscis 5 m OSifos 7.6 m OSifoscis 9.4 m*	*Høj toksicitet, lille gevinst på PFS, men ingen på OS*
Serrone L et al.(165)	*2001*	*Single-arm, fase 2*	*2C*	*Ifosfamid + epirubicin*		*STS (22)*	*ORR 37% OS 15 m*	

Serrone L et al.(35)	*2001*	*Single-arm, fase 2*	*2B*	*Ifosfamid + epirubicin*		*STS (44)*	*ORR 35% PFS 8.5 m OS 13.5 m*	*1. linjebehandling*
van Oosterom AT et al.(166)	*2002*	*Randomiseret, fase 2*	*1A*	*Ifosfamid 1. linjebehandling*	*Ifosfamid 2. linjebehandling*	*STS (182)*	*ORR1lday 10 % ORR1L3day 24% ORR2l1day 6% ORR2l3day 8%*	*1. linjebehandling DCR1day 45%, DCR3day 53% 2. linjebehandling DCR1day 34% DCR3day 58%*
Yalcin B et al.(167)	*2004*	*Single-arm, fase 2*	*2B*	*Ifosfamid (højdosis) + GM-CSF*		*STS (39)*	*PFS 7 m OS 10 m*	
Siehl JM et al.(168)	*2005*	*Single-arm, fase 2*	*2B*	*Ifosfamid + liposomal daunorubicin*		*STS (40)*	*PFS 6 m OS 14 m*	
Homesley HD et al.(169)	*2007*	*Randomiseret, fase 2*	*1A*	*fosfamid*	*Ifosfamid + paclitaxel*	*Uterintcarcinosarkom (214)*	*PFSifos 3.6 m PFSkomb 5.8 m OSfos 8.4 m OSkombi 14.5 m*	
Lee SH et al. (42)	*2011*	*Single-arm, fase 2*	*2C*	*Ifosfamid (højdos)*		*STS (30)*	*ORR26%*	*2. og 3. linjebehandling*

							PFS 2.9 m OS 8.7 m	
Martin-Liberal J et al.(170)	2013	Retrospektivt studie	2C	Ifosfamid		STS (34)	ORR 20 % DCR 48% PFS 4.2 OS 11.2	
Ahlstrom M et al. (44)	2017	Retrospektiv studie	2C	Trofosfamid + etoposis		STS(69)	PFS 3.4 m	Dette er patienter som er behandlet tungt inden denne behandling er givet
Schoffski P et al. (171)	2021	Randomiseret, fase 2	2B	Ifosfamid	nintedanib	STS		Efter første linje behandling Studiet lukkede da der ikke var patienter i nintadanib armen der ikke havde PD efter 12 uger.

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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Bilag 6 – Evidenstabel (Trabectidin)

Arbejdsdokument – Evidenstabel (trabectedin)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom - trabectedin*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Le Cesne A et al.(52)	*2004*	*Single-arm, fase 2*	*2B*	*ET-743*	*Ingen*	*STS (104)*	*ORR 8%* *PFS 3.5 m* *OS 9.2 m*	
Yovine A et al.(54)	*2004*	*Single-arm, fase 2*	*2B*	*Ecteinascidin-743*	*Ingen*	*ST (54)*	*ORR 4%* *PFS 1.9 m* *OS 12.8 m*	
Garcia-Carbonero et al.(45)	*2005*	*Single-arm, fase 2*	*2B måske C*	*Ecteinascidin-743*	*Ingen*	*STS (36)*	*ORR 17%* *PFS 1.6 m* *OS 15.8 m*	
Roylance R et al.(46)	*2007*	*Singelarm, fase 2*	*2B måske C*	*Trabectedin*	*Ingen*	*STS (21)*	*ORR 14%* *PFS 3.9 m*	

							OS 9.9 m	
Demetri GC et al.(47)	*2009*	*Randomiseret, fase 2*	*A*	*Trabectedin*	*Ingen*	*Liposarkom og leiomyosarkom (270)*	*ORR 5.6%* *PFS 3.3 m* *OS 13.9 m*	*Randomisering ved infusion 24 h vs 3 h. 24 h er bedst*
Monk BJ et al.(55)	*2011*	*Single-arm, fase 2*	*2B*	*Trabectedin*	*Ingen*	*Uterint leiomyosarkom (20)*	*ORR 10%* *PFS 5.8 m* *OS 26.1 m*	
Paz-Ares L et al.(48)	*2012*	*Randomiseret, fase 2*	*2B*	*Trabectedin*	*Trabectidin + dexametason*	*STS (40)*	*ORR 3%* *PFS 2.1* *OS 10.2 m*	*Samme overlevelse og PFS*
Samuels BL et al.(49)	*2013*	*Single-arm, fase 2*	*2B*	*Trabectedin*	*Ingen*	*STS (807)*	*ORR 5.9%* *OS 11.9 m*	
Blay JY et al.(51)	*2013*	*Single-arm, fase 2*	*2B*	*Trabectedin*	*Ingen*	*Liposarkom/leiomyosarkom (129)*	*ORR 6.4%* *PFS 4.4 m* *OS 17.4 m*	*Som 2. linje eller efterfølgende linjer. Bedst når givet som 2 linje.*
Blay JY et al.(24)	*2014*	*Randomiseret, fase 3*	*A*	*Trabectedin*	*Doxorubicin*	*Translokeret sarkom (121)*	*ORR 27% dox* *ORR 5,9% TRA*	*Som 1. linjebehandling. Doxorubicin bedst respons*

Pautier P et a.(26)	*2015*	*Single-arm, fase 2*	*2B*	*Trabectedin + doxorubicin*	*Ingen*	*Leiomyosarkom (109)*	*ORR 59.6%* *PFS 8.2 m* *OS 20.2 m*	*Som 1. linjebehandling*
Kawai A et al.(56)	*2015*	*Randomiseret, fase 2*	*2B*	*Trabectedin*	*Best supportive care*	*Translokeret sarkom (76)*	*PFS 5.6 m*	*2. linjebehandling*
Bui-Nguyen B et al.(23)	*2015*	*Randomiseret, fase 2*	*2B*	*Trabectedin*	*Doxorubicin*	*STS (133)*	*PFSdox 3.1 m* *PFStra 5.5 m*	*1. linjebehandling* *Lukket pga manglende superioreffekt af trabectedin*
Demetri GD et al.(58)	*2015*	*Randomiseret, fase 3*	*A*	*Trabectedin*	*Dacarbazin*	*Liposarkom/leiomyosarkom (518)*	*PFS 4.2 m* *OS 12.4 m*	
Martin-Broto J et al.(25)	*2016*	*Randomiseret, fase 2*	*2B*	*Doxorubicin*	*Doxorubicin + trabectedin*	*STS (115)*	*PFSdox 5.5 m* *PFStest 5.7 m*	
Hensley ML et al.(59)	*2017*	*Randomiseret fase 3*	*2A*	*Trabectedin*	*Dacarbazin*	*Leiomyosarkom uterint (232)*	*PFSdac 1.5 m* *PFStra 4 m* *OSdac 12.9 m* *OStra 13.4 m*	*Subgruppe analyse.* *2. linjebehandling*
Buonadonna A et al.(50)	*2017*	*Single-arm, fase 4*	*2B*	*Trabectedin*	*Ingen*	*STS (219)*	*ORR 26.6%*	

							PFS 5.9 m	
Takahashi M et al.(53)	*2017*	*Single-arm, fase 2*	*2B*	*Trabectedin*	*Ingen*	*Translokeret sarkom (66)*	*PFS 5.9 m* *OS 17.5 m*	*Specielt effektiv i myxoid/roundcell liposarkomer PFS 7.4*
Gadducci A et al.(172)	*2018*	*Single arm/randomiseret, fase 2*	*1B*	*Trabectedin*	*Ingen eller randomisering mod gemcitabien/docetaxel hvis de ikke havde fået denne behandling før.*	*Relaps af uterin leiomyosarkom* *Total 168* *126 (45 pt randomiseret og 81 havde tidligerege fået gem/doc)* *42 pt til gem/doc*	*PFStra 4.1 m* *PFSg/d 6.9 m* *OStra 20.6 m* *OSg/d 36.7 m*	
Jones R et al. (77)	*2018*	*Randomiseret, fase 3* *Subgruppe analyse*	*1B*	*Trabectedin*	*Dacarbazine*	*577 patienter* *131 over 65 år*	*ORRtra 9%* *PFStra 4.9 m* *OStra 15 m* *ORRdec 3%* *PFSdec 2.5 m* *OSdec 8 m*	

Grignani E et al.(173)	*2018*	*Single arm, fase (1/2 studie*	*2B*	*Trabectedin + olaparib*		*50 STS*	*7/50 PR*	*Fase 2 er i gang.*
Patel S et al. (60)	*2019*	*Randomiseret, fase 3*	*1B*	*Trabectedin*	*Dacarbazine*	*Liposarkom eller leiomyosarkom patienter* *577* *Alle patietnerne havde modtaget behandling før*	*OStra 13.7 m* *OSdac 13.1 m*	
Grosso F et al. (174)	*2020*	*Single arm, fase 2*	*2B*	*Trabectedin som førstelinje*		*24 patienter,* *> 70 år*	*PFS 4 m* *OS 12 m*	
Hentschel L et al.(175)	*2020*	*Randomiseret*	*1B*	*Trabectedin*	*Trabectedin + intervention på Patient reported outcome.*		*OScontrol 389 dage* *OSinterven 648 dage*	
Le Cesne et al.(57)	*2021*	*Randomiseret, fase III*	*1B*	*Trabecteding* *Efter 1-3 tidligere behandlinger*	*Best supportive care*	*103 patienter*	*PFStra 3.1 m* *PFSbes 1.5 m*	*Livskvaliteten blev ikke forringet under behandlingen.*

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons

SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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Bilag 7 – Evidenstabel (Gemcitabin)

Arbejdsdokument – Evidenstabel (gemcitabin)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom - gemcitabin*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Patel SR et al.(65)	*2001*	*Single-arm, fase 2*	*2B*	*Gemcitabin*		*STS (56)*	*ORR 18%* *PFS 3 m* *OS 13.9 m*	
Hensley ML et al.(176)	*2002*	*Single-arm, fase 2*	*2B*	*Gemcitabin +* *docetaxel*		*Leiomyosarkom (44)*	*ORR 53%* *PFS 5.6 m*	
Okuno S et al. (66)	*2002*	*Single-arm, fase 2*	*2B*	*Gemcitabin*		*STS (30)*	*ORR 3%* *PFS 2.1 m*	
Svancarova L et al.(67)	*2002*	*Single-arm, fase 2*	*2B*	*Gemcitabin*		*STS (32)*	*ORR 3.23%* *PFS 1.5* *OS 8.9 m*	
Okuno S et al. (177)	*2003*	*Single-arm, fase 2*	*2B*	*Gemcitabin*		*STS (25)*	*PFS 13 m*	

							OS 15 m	
Von Buton G et al. (68)	*2006*	*Single-arm, fase 2*	*2B*	*Gemcitabin*		*STS (48)*	*ORR 7%* *OS 6 m*	
Maki RG et al. (70)	*2007*	*Randomiseret, fase 2*	*1B*	*Gemcitabin*	*Gemcitabin + docetaxel*	*STS (122)*	*ORRgem 8%* *ORRkombi 16%* *PFSgem3 m* *PFSkombi 6.2 m* *OSgem11.5 m* *OSkombi17.9 m*	*Mere toksicitet i kombinationsbehandlingen*
Losa R et al.(73)	*2007*	*Single-arm, fase 2*	*2B*	*Gemcitabin + dacarbazine*		*STS (26)*	*PFS 9.25 m*	
Bay JO et al. (71)	*2007*	*Single-arm, fase 2*	*2B*	*Gemcitabin + docetaxel*		*STS (133)*	*OS 12.1 m*	
Dileo P et al. (75)	*2007*	*Single-arm, fase 2*	*2B*	*Gemcitabin + vinorelbin*		*STS (49)*	*PFS 3.4 m*	
Hensley ML et al. (178)	*2008*	*Single-arm, fase 2*	*2B*	*Gemcitabin + docetaxel*		*Uterin leiomyosarkom (42)*	*PFS 4.4 m* *OS 16 m*	

Garcia-Del-Muro X et al. (74)	*2011*	*Randomiseret, fase 2*	*1B*	*Dacarbazin*	*Gemcitabine + dacarbazine*	*STS (113)*	*PFS 2 dac* *PFS 4.2 kombi* *OS 8.2 dac* *PFS 16.8 kombi*	
Lee EM et al. (179)	*2011*	*Single-arm, fase 2*	*2B*	*Gemcitabin +* *docetaxel*		*STS (30)*	*PFS 2.5 m*	
Stacchiotti et al.(120)	*2012*	*retrospektivt*	*2C*	*Gemcitabin +/- taxaner*		*Angiosarkom (25)*	*ORR 68%* *PFS 7 m* *OS 17 m*	
Schmitt T et al. (180)	*2013*	*Single-arm, fase 2*	*2B*	*Gemctitabin +* *docetaxel*		*STS (34)*	*PFS 8.6 m* *OS 22.4 m*	
Luo Z et al. (181)	*2015*	*Single-arm, fase 2*	*2B*	*Gemcitabin + vincristin +* *cisplatin.*		*STS (26)*	*ORR 23.1%* *PFS 4.8 m* *OS 15 m*	
Martin-Liberal J et al. (182)	*2018*	*Single-arm, fase 2*	*2B*	*Gemcitabine +* *sirolimus*		*STS (28)*	*ORR 0%* *PFS 1.85 m* *OS 9.2 m*	*Tidligere behandlet med dox*

Pautier et al.(183)	*2020*	*Single-arm, fase 2*	*2B*	*Gemcitabine + pazopanib*		*STS (106)*	*PFS 6.5 m* *OS 22.4 m*	
Tansir G et al (72)	*2023*	*Single-arm, fase 2*	*2B*	*Gemcitabine + docetaxel*		*STS (22)*	*ORR 4.5%* *PFS 3 m* *OS 14 m*	*Førte prospektive studie*

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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Bilag 8 – Evidenstabel (Kemoterapi andet)

Arbejdsdokument – Evidenstabel (kemoterapi andet)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom – kemoterapi andet*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Jelić S et al.(184)	*1990*	*Single-arm*	*2C*	*Epirubicin + cisplatin*		*STS (35)*	*ORR 57.1% OS 4 m*	*1. linjebehandling*
Lopez M et al.(185)	*1991*	*Single-arm*	*2B*	*Epirubicin + dacarbazine*		*STS (56)*	*ORR 48% OS 14 m*	*Cardiotoksisk*
Jelić S et al.(186)	*1997*	*Randomiseret*	*1B*	*Epirubicin (høj)*	*Epirubicin (høj) + cisplatin*	*STS (106)*	*ORRepi 29% ORRepicis 54%*	*Kombinationsbehandlingen mere toksisk*
Jelić Set al.(187)	*2000*	*Randomiseret*	*1A*	*Epirubicin (høj) + cisplatin*	*Epirubicin (lav) + cisplatin*	*STS (159)*	*ORRepihøj 53% ORRepilav 30%*	*Samme toksicitet*

							OShøj 14 m OSlav 11 m	
Wang ZM et al. (188)	2022	Single-arm, fase 2	2C	Epirubicin + Anlotinib + anlotinib vedligeholdsbehandling		STS (30)	ORR 13.33% DCR 80% PFS 11.5 m	
Van Hoesel OG et al. (189)	1994	Single-arm, fase 2	2C	Docetaxel	Ingen	STS (29)	ORR 17%	
Kostler WJ et al.(190)	2001	Single-arm, fase 2	2C	Docetaxel	Ingen	STS (27)	ORR 15% PFS 2.4 m OS 7.7	
Balcerzak SP et al.(191)	1995	Single-arm, fase 2	2B	Paclitaxel	Ingen	STS (48)	ORR 12.5%	
Casper ES et al.(192)	1998	Single-arm, fase 2	2C	Paclitaxel	Ingen	STS (28)	ORR 7% PFS 3.5 m	
Sutton G et al.(193)	1999	Single-arm, fase 2	3	Paclitaxel	Ingen	Uterint leiomyosarkom (24)	ORR 9.1 % DCR 33.1 %	

Curtin JP et al.(194)	*2001*	*Single-arm, fase 2*	*2B*	*Paclitaxel*	*Ingen*	*Uterint carcinosarkom (53)*	*ORR 18.2%*	
Gallup DG et al.(195)	*2003*	*Single-arm, fase 2*	*2B*	*Paclitaxel*	*Ingen*	*Uterintleiomyo sarkom (53)*	*ORR 8.4%* *DCR 31.3 %* *PFS 1.5 m* *OS 12.1 m*	
Penel N et al.(121)	*2008*	*Single-arm, fase 2*	*2C*	*Ugentlig paclitaxel*	*Ingen*	*Angiosarkom (30)*	*ORR 18%* *PFS 4 m* *OS 8 m*	
Powell MA et al.(196)	*2010*	*Single-arm, fase 2*	*2B*	*Paclitaxel + carboplatin*	*Ingen*	*Uterint carcinosarkom (45)*	*ORR 54%* *PFS 7.6 m* *OS 14.7 m*	
Ray-Coquard IL et al.(122)	*2015*	*Randomiseret, fase 2*	*2B*	*Paclitaxel*	*Paclitaxel + bevacizumab*	*Angiosarkom (52)*	*ORRpax 45.8% ORRpaxb 28%* *PFSpax 6.6 m* *PFSpaxb 6.6 m* *OSpax 19.5m*	

							OSpaxb 15.9 m	
Schöffski P et al. (84)	*2011*	*Single-arm, fase 2*	*2B*	*Eribulin*	*Ingen*	*STS (128)*	*ORRadi 6%,* *ORRleio 0%, ORRsyn 5% ORRother 4%*	*DCR dedifferentieret liposarkom 47.6 %,* *PFS adipocystisk 2.6 m* *PFS leiomyosarkom 2.9 m* *PFS synovial sarkom 2.6 m* *PFS andre 2.1 m*
Schöffski P et al. (82)	*2016*	*Randomiseret, fase 3*	*1B*	*Eribulin*	*Dacarbazin*	*Leiomyosarkom/liposarkom (452)*	*ORReri 4% ORRdac 5%* *PFSeri 2.6 m* *PFSda 2.6 m* *OSeri 13.5 m* *OSeri 11.5 m*	*DCReri 56%, DCRdac 53%* *Effekt ved liposarkom, ved leiomyosarkom var dacarbazin lige så godt*
Demetri GD et al. (83)	*2017*	*Randomiseret, fase 3*	*1B*	*Eribulin*	*Dacarbazin*	*Liposarkom (143)*	*DCReri 64%* *DCRdac 44.4%* *PFSeri 2.9 m* *PFSdac 1.7 m*	

							OSeri 15.6 m OSdac 8.4 m	
Kawai A et al. (197)	2017	Single-arm, fase 2	2B	Eribulin	Ingen	STS (52)	PFSlipo/leio 5.5 m	
Blay JY et al.(198)	2019	Randomiseret, fase 3 Subgruppe analyse	1B	Eribulin	Dacarbazin	Leiomyosarkom 309 patienter 42% uterin leiomyosarkom	ORReri 5% ORRdac 7% PFSeri 2.2m PFSdac2.6 m OSeri 12.7 m OSdac 13.0 m	
Chen TW et al.(85)	2022	Single-arm, fase Ib/II	2B	Eribulin + lenvatinib		Leiomyosarkom og liposarkom (30)	ORR 20% PFS 8.56 m OS 27.1 m	Liposarkom havde en dårligere OS på 23.6 måneder.
Kim CT et al.(86)	2022	Single-arm, fase II	2B	Eribulin + gemcitabine		Liposarkom og leiomyosarkom (37)	ORR 16.2% DCR 78.4% PFS 5.6 m OS 31.9 m	

Bramwell VH et al. (199)	*1995*	*Single-arm, fase 2*	*2C*	*Topotecan* *(topoisomerase I hæmmer)*	*Ingen*	*STS (22)*	*ORR 10.3%*	*Ingen effekt*
Miller DS et al. (200)	*2000*	*Single-arm, fase 2*	*2B*	*Topotecan*	*Ingen*	*Uterint leiomyosarkom (26)*	*ORR 11%* *DCR 19%*	*Ingen effekt*
Budd GT et al. (201)	*2002*	*Single-arm, fase 2*	*3*	*Topotecan*	*Ingen*	*STS (22)*	*ORR 0%* *OS 12 m*	
Miller DS et al. (202)	*2005*	*Single-arm, fase 2*	*2B*	*Topotecan*	*Ingen*	*Uterint sarkom carcinosarkom a (27)*		*Ingen effekt*
Toulmonde M et al.(203)	*2022*	*Randomized, fase 2*	*3*	*Iv oncolytic virus + low dose cyclophosphamide*				*Stopped før tid, ingen effekt*
Van Tine et al(204).	*2024*	*Single-arm, fase 1b*	*3*	*Dacarbazin + unesbulin*		*Leiomyosarkom (27)*	*ORR 21.6%* *DCR 54.1%*	*PFS og OS blev ikke rapporteret*

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter

ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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Bilag 9 – Evidenstabel (Targeteret)

Arbejdsdokument – Evidenstabel (targeteret behandling)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom – targeteret behandling*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Sleijfer S et al.(205)	*2009*	*Single-arm, fase 2*	*2B*	*Pazopanib*	*Ingen*	*STS (142)*	*ORRleio 44%, ORRsyn 49% ORRother 39%*	*Adipocystisk STS lukket.* *PFSleio 3.0 m, PFSsyn 5.4 m, PFSoth 3.0m, OSleio 11.8 m, OSsyn 10.3 m, OSoth 10 m*
van der Graaf WT et al. (79)	*2012*	*Randomiseret, fase 3*	*1B*	*Pazopanib*	*Placebo*	*STS (372)*	*ORRpazo 6% ORRpla 0%* *PFSpazo 4.6 m* *PFSpla 1.6 m* *OSpazo 12.5 m* *OSpla 10.7 m*	*DCRpazo 63%* *DCRpla 38%*

Benson C et al. (206)	*2016*	*Subgruppe analyse*	*2B*	*Pazopanib*	*Ingen*	*Uterint sarkom (44)*	*ORR 11.4%* *DCR 68.2%* *PFS 3 m* *OS 17.5 m*	
Kollár A et al. (124)	*2016*	*Retrospektivt*	*3*	*Pazopanib*	*Ingen*	*Vaskulært sarkom (angiosarkom, epithelioidt hemangioendotheliom og intimal sarkom) (52)*	*ORR 23.1 %* *DCR 54.3%* *PFS 3 m* *OS 9.9 m*	
Samuels BL et al. (80)	*2017*	*Single-arm, fase 2*	*2B*	*Pazopanib*	*Ingen*	*Liposarkom (41)*	*ORR 2.4%* *DCR 44%* *PFS 4.4 m* *OS 12.6 m*	
Subbiah V et al. (207)	*2018*	*Single-arm, fase 2*	*2C*	*Pazopanib +* *trametinib (MEK hæmmer)*	*Ingen*	*STS (25)*	*ORR 8%* *PFS 2.3 m*	
Sharma A et al.(208)	*2019*	*Retrospektiv opgørelse*	*4*	*pazopanib*		*STS (33)*	*ORR 6%* *PFS: 5 m* *OS: 18 m*	

Mir O et al.(81)	*2019*	*Retrospektiv opgørelse*	*4*	*Pazopanib (pazo)*	*Pazopanib + syrepumpehæmmer (pazo+)*	*STS(333) 59 fik pazopanib og syrepumpehæmmer*	*PFSpazo 4.6 m* *PFSpazo+ 2.8 m* *OSpazo 12.6 m* *OSpazox 8 m*	
Vos M et al.(209)	*2019*	*Retrospektiv analyse*	*2B*	*pazopanib*		*STS (259)*	*Ingen association mellem bivirkninger og outcome.*	
Hirbe A C et al.(210)	*2020*	*Single-arm, fase 2*	*2B*	*Pazopanib* *Første linje behandling*		*STS patienter som ikke er kandidater til kemoterapi (56)*	*DCR: 39%* *PFS: 3.7 m* *OS 14.2 m*	
Nishida Y et al. (211)	*2021*	*Single-arm-fase 2*	*2B*	*Pazopanib*		*Malign perifer nerve skede tumor (MPNST) 12 patienter*	*PFS 5.4 m* *OS 10.6 m*	
Jones RL et al. (212)	*2022*	*Randomized, fase*	*1B*	*Pazopanib (n=53)*	*Pazopanib + TRC105 (n=61)*	*Angiosarkom*	*PFSpa 4.3m* *PFSpat 4.2 m*	*Ingen effekt*
Maki et al. (213)	*2009*	*Single-arm, fase 2*	*2B*	*Sorafenib*	*Ingen*	*STS (145)*	*ORR angio 14%* *PFS 3.2 m* *OS 14.3 m*	*Aktiv ved angiosarkom, men begrænset aktivitet ved andre.*

								PFS angio 3.8 m OS, angio 14.9 m *Måske lidt effekt i leiomyosarkom*
von Mehren M et al. (214)	*2011*	*Single-arm, fase 2*	*2B*	*Sorafenib*	*Ingen*	*Vaskulært sarkom, liposarkom, leiomyosarkom (51)*		
Ray-Coquard I et al. (215)	*2012*	*Single-arm, fase 2*	*2B*	*Sorafenib*	*Ingen*	*Angiosarkom (41)*		
Santoro A et al. (216)	*2013*	*Single-arm, fase 2*	*2B*	*Sorafenib*	*Ingen*	*STS (101)*	*ORR 14.5%* *DCR 47.4%* *PFS 4.2 m* *OS 11.9 m*	*Særlig effektiv ved leiomyosarkom*
D'adamo et al. (217)	*2018*	*Single-arm, fase 2*	*2B*	*Sorafenib +* *dacarbazine*	*Ingen*	*STS (37)*	*DCR 46%* *PFS 3.1 m* *OS 13.2 m*	
Garcia Del Muro X et al.(218)	*2018*	*Single-arm, fase 2*	*2B*	*Sorafenib + ifosfamide.*		*STS (34)*	*ORR: 17%* *DCR:49%* *PFS:4.8 m* *OS 16.2 m*	

Chawla SP et al. (219)	*2012*	*Single-arm, fase 2*	*2B*	*Ridaforolimus (mTOR inhibitor)*	*Ingen*	*STS (212)*	*DCR 28.8 %* *PFS 3.8 m* *OS 10 m*	
Demetri GD et al. (220)	*2013*	*Randomiseret, fase 3*	*1B*	*Placebo*	*Ridaforolimus* *(mTOR inhibitor)*	*STS (711)*	*DCRrida 40.6%* *DCRplac 28.6%* *PFSrida 4.13 m* *PFSplac 3.4 m*	*Beskeden effekt med stort studie*
Mir O et al. (87) *Regosarc*	*2016*	*Randomiseret*	*1B*	*Placebo*	*Regorafenib*	*STS (182)*	*ORR 11%* *DCR 67%* *PFSrego2.9 m* *PFSplac 1.0 m*	*Liposarkom DCR 45 % ORR 0%* *Liposarkom PFSrego 1.1 m* *Liposarkom PFSplac 1.7 m* *Leiomyosarkom DCR 86%, ORR 0%* *Leiomyosarkom PFSrego 3.7 m* *Leiomyosarkom PFSplac 1.8 m* *Synovial DCR 77%, ORR 8%* *Synovial PFSrego 5.6 m*

								Synovial PFSplac 1.0 m
Brodowicz T et al.(221) ***Regosarc***	*2018*	*Randomiseret.* *Cross over* *.*	*1B*	*placebo*	*regorafenib*	*STS (139)* *Non-adipocytisk sarkomer*	*81% af patienterne crossed-over til ragorafenib.* *Ingen forskel i OS.*	
Marrari A et al.(222)	*2020*	*Single arm, fase 2*	*2B*	*regorafenib*		*STS (21)*	*ORR: 4.7%* *DCR: 62%* *PFS 3.8 m* *OS 14.8 m*	
Panel N et al.(223)	*2020*	*Randomiseret, fase 2*	*1B*	*placebo*	*regorafenib*	*STS pt som tidligere er blevet behandlet med kemoterapi og pazopanib (non adipocytisk STS) (37)*	*PFSplac 1.1 m* *PFSpazo 2.1 m* *OSplac 8.2 m* *OSpazo 17.8 m*	
Riedel RF et al.(224)	*2020*	*Randomiseret, fase 2*	*1B*	*placebo*	*regorafenib*	*Liposarkom, vel differentieret var ekskluderet. (48)*	*PFSpla 2.07 m* *PFSrago 1.87 m* *OSpla 4.89 m* *OSrago 6.46 m*	

Agulnik M et al.(125)	*2021*	*Single-arm, fase 2*	*2B*	*Regorafenib*		*Angiosarkom (31) 23 patienter kunne evalueres*	*ORR 17.4% (2 CR, 2 PR)* *DCR 60.8%* *PFS 5.5 m*	
Attia S et al.(88)	*2023*	*Single arm, fase 2*	*2B*	*Regorafenib*		*Ewing og Ewing ligende tumorer (30) 60% udenfor knogler*	*PFS 3.7 m* *OS 53 uger*	*Herunder CIC_DUX tranlokationer*
Schoffski P et al.(225)	*2018*	*Single arm, fase 2*	*2B*	*Crizotinib*		*Alveolar soft part sarkom ASPS (48) opdelt i to subcohorter afhængig af om det havde et TFE3 re-arrangement*	*+rearrangement (40 pt)* *ORR:2.5%* *DCR:90%* *PFS (1 år): 37.5%* *OS (1 år):97.4%* *-rearrangement* *(4 patienter)* *ORR: 25%* *DCR: 100%*	

							PFS (1 år): 50% OS(1 år): 75%	
Veitch Z et al.(226)	2019	Single arm, fase 2	2B	ENMD-2076 aurora A kinase hæmmer		STS (25)	ORR 9% PFS 2.5 m Os 14.1 m	
Liao Z et al. (227)	2019	Single-arm, fase 2	2B	Apatinib (VEGFR2 hæmmer)		STS (59)	ORR 15% DCR 58% PFS 7.9 m OS 17 m	
Gounder M et al.(228)	2020	Single-arm, fase 2	2B	Tazemetostat	ingen	Epithelioid sarkom (62)	ORR. 15% PFS5.5 m OS 19 m	
Demetri GD et al. (229)	2021	Single-arm, fase 1	3	Leucine-rich repeat containing 15 (LRRC15)-inhibitor		Osteosarcoma/UPS (10 osteosarcoma, 10 UPS)	ORR. 20% (4 PR)	
Abdul R et al.(112)	2022	Single arm, fase Ib	2B	Siremadlin + ribociclip		Liposarkom højt differentieret og dedifferentieret (74)	ORR 7%. 3pt PR, 38 pt SD: DCR 28% PFS 4.2 m	MDM2 and CDK4/6 inhibitor. Behandlingen blev givet i forskellige doser, dette er de bedste responsrater

Gounder MM et al.(113)	*2022*	*Randomiseret, dobbel blindet, placebo kontroleret studie*	*1B*	*Selinexor (n=188)*	*Placebo (n=97)*	*Dedifferentieret liposarkom (285)*	*ORRse 2.7%* *ORRp 0%* *PFSse 2.8m* *PFSp 2.1 m* *OSse 10 m* *OSp 12.9 m*	
Woll PJ et al.(230)	*2023*	*Single-arm, fase 2*	*2B*	*Axitinib (vaskulær endothelia growth factor receptor hæmmer)*		*STS (145)*	*PFS 2.9 m*	
Ingham M et al.(231)	*2023*	*Single-arm, fase 2*	*2B*	*Sitravatinib*		*Liposarkom højt og dediff (29)*	*DCR 41%* *PFS 11.7 uger* *OS 31.7 uger*	
Gounder MM et al.(109)	*2023*	*Single-arm, fase 1*	*2B*	*Milademetan (MDM2 inhibitor)*		*Dedifferentieret liposarkom (53)*	*ORR. 4%* *DCR 58.5%* *PFS 7.2 m*	

LoRusso P et al.(110)	*2023*	*Single-arm, fase 1*	*2B*	*Brigimadlin (MDM2 inhibitor)*		*Dedifferentieret liposarkom (19)*	*ORR. 11.1%* *DCR 74.1%* *PFS 7.2 m*	*Kvalme og opkast.* *Dette er for alle patietne rogså andre histologiske undertype, dog bedst for dediff liposarkom*
Schuetze S et al.(111)	*2024*	*Single arm, fase I*	*2B*	*Palbociclib*		*STS med CDK4 amplifikation (42)*	*ORR. 2%* *DCR 46%* *PFS 16 uger* *OS 69 uger*	*ALAT stigning, anæmi, fatigue, hypophosphaemia.*
Movva S et al. (232)	*2024*	*Single arm, fase II*	*2B*	*Ribociclib + everolimus*		*Dediff liposarcoma og leiomyosarkom (48)*	*ORRlms. 0%* *DCRlms 44.8%* *PFSlms 15.7 uger* *OSlms 15.2 m* *ORRlipo. 8.3%* *DCRlipo 58.3%* *PFSlipo 15.4 uger* *OSlipo 20.2 m*	

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.

DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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Bilag 10 – Evidenstabel (Check-point hæmmer)

Arbejdsdokument – Evidenstabel

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi go targeteret bahandling til patienter med bløddelssarkom – check point hæmmer*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlign ings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Maki et al.(89)	*2013*	*Single arm, fase 1*	*4*	*Ipilimumab (anti-CTLA4 hæmmer)*	*ingen*	*7 synovial sarkom patienter*	*Ingen effekt*	
Merchant et al.(233)	*2016*	*Single arm, fase 1*	*2b*	*ipilimumab*	*ingen*	*33 patienter, 17 havde sarkom*	*3 sarkom patietner havde stabilisering af sygdommen, 1 osteosarkom, en med clear celle sarkom og en med synovial sarkom*	
Weiss G et al.(234)	*2017*	*Single arm, fase 1b 6 behandlingsarme*	*4*	*Undersøge kombinationen af pembrolizumab og forskellige former for kemoterapi*		*Solide tumorer 49 patienter.* *7 sarkom patienter med avanceret sygdom*	*Patienter som havde gavn* *1 Liposarkom* *1Uterin leiomyosarkom* *Følgende havde ikke gavn* *1 Clear celle sarkom* *2 synovial sarkom* *1 fibromyxoid sarkom* *1 malign fibrøs histiocytom*	*Alle sarkom patienterne havde modtaget op mod 4 linjer kemoterapi forud for behandlingen.*

Schur S et al.(235)	*2017*	*Retrospektiv opgørelse*		*Pembrolizumab behandling*		*18 patienter*	*Outcome data forekommer ikke*	
Tawbi HA et al.(97)	*2017*	*Single arm, fase 2*	*1c*	*Effekten af pembrolizumab ved sarkom patienter*		*Metastatisk sarkom sygdom.* *86 patienter og 80 kunne evalueres for respons* *40 patienter med bløddelssarkom* *40 patienter med knoglesarkom*	*Leiomyosarkom 6/10 pt havde SD: DCR=60%* *UPS 1/10 havde CR, 3/10 havde PR, 3/10 havde SD, DCR=70%. Ved 12 uger var PFR 70%* *Liposarkom 2/10 PR, 4/10 SD* *DCR=60%. ved 12 uger var PFR=60%* *Synovial sarkom 1/10 PR, 2/10 SD. DCR=30%*	*Der var ingen korrelation mellem PD-L1 udtrykket og respons* *Burgess, 2017.*
Ben-Ami et al.(236)	*2017*	*Single arm, fase 2*	*4*	*Checkpoint hæmmer (nivolumab) til leiomoysarkom*		*12 patienter med uterin leiomyosarkom*	*Ingen responderede på behandlingen.*	
Toulmonde M et al.(237)	*2018*	*Single arm, fase 2*	*1c*	*Effect af PD-1 hæmning sammen med lavdosis kemoterapi cyclophosphamide*		*57 sarkom patienter* *Leiomyosarkom (15 pt)* *UPS (16 pt)* *Andre (16 pt)* *GIST (10 pt)*	*Stabil sygdom for 3 leiymoysarkomer, 7 UPS, 8 indenfor gruppen andre og 3 gist.*	

D-Angelo et al.(238)	*2018*	*Single arm, fase 2*	*1c*	*Behandling med nivolumab (PD-1 hæmmer) og ipilimumab (CTLA-4 hæmmer)*		*85 patienter* *76 patietner blev evalueret*	*Nivolumab: ORR 5%* *Nivolumab+ipilimumab: ORR 16%*	*Repondere var blandt UPS, mangiosarkom og myxofibrosarkom.*
Wilky et al.(239)	*2019*	*Single arm, fase 2*	*2b*	*Axitinib (VEGFR receptor tyrosin kinase hæmmer) sammen med pembrolizumab*		*33 sarkom patienter.* *12 med alveolar soft-part sarkom.* *2 pt ikke uterin leiomyosarkom* *3 uterin leiomyosarkom* *5 UPS* *2 liposarkomer* *3 kan ikke evalueres* *6 andre*	*ASPS: DCR 73%* *Partiel repons:* *1 pt med epitheloidt sarkom* *1 pt med leiomyosarkom (ikke uterin)* *Stabil sygdom (mindre end 30% reducktion)* *1 leiomyosarkom (ikke uterin)* *3 UPS* *1 synovial sarkom*	*Meget blandet gruppe af histologiske undertyper* *Total 2 leiomyosarkomer (ikke uterine),*
Le Cesne et al.(240)	*2019*	*Single arm, fase 2*	*2b*	*Pembrolizumab sammen med lavdosis kemoterpi cyclophosphamide*		*17 osteosarkom patienter 15 kunne evalueres*	*PR 1 patient.* *6 måneders PFS =13.3% (1.7-40% 95% CI)*	*Begrænset aktivitet ved osteosarkom.*
Florou et al.(241)	*2019*	*Retrospektiv analyse*	*2C*	*Pooled data fra* *1 pemborlizumab + axitinib studiet (1 pt)* *2 patienter behandlet med CTLA-4 hæmmer*		*7 patienter med spredt angiosarkom*	*PR: 71%* *CR 1/7 patienter.*	

				4 patienter med pembrolizumab				
Kelly et al.(98)	*2019*	*Single arm, fase 2*	*2b*	*Pembrolizumab sammen med epacadostat (IDO1 hæmmer)*		*29 patienter* *Leiomyosarkom (17%), UPS (17%) myxofibrosarkom (7%) liposarkom (11%), angiosarkom(3%)*	*PR: 1 leiomyosarkom patient* *SD: 13 patienter.* *Median PFS: 8 måneder (95%CI: 6.9-26.7)*	
Tian et al.(90)	*2020*	*Retrospektiv analyse*	*2c*	*Pembrolizumab sammen med kemoterapi (doxorubicin) i behandling af sarkomer*		*21 patienter med spredt bløddelssarkom*	*ORR: 47.6 %* *DCR: 71.4%* *Median PFS: 6 måneder (95% CI 2-8 måneder)*	*Ikke de store bivirkninger til behandlingen.*
Quiroga et al.(91)	*2020*	*Retrospektiv analyse*	*2c*	*Behandling med nivolumab eller pembrolizumab*		*56 patieneter:* *Liposarkom 11* *Leiomyosarkom 7* *Synovial sarkom 4* *Chordom 4* *Tencelle sarkom 4* *Osteosarkom 3* *UPS 3* *Andre 20*	*ORR: 11.5%*	*Kun 26 patienter kunne evalueres.*
Pollack S et al.(92)	*2020*	*Single arm, fase 1/2*	*1c*	*Behandling med doxorubicin I kombination med pembrolizumab*		*37 patienter*	*ORR:19%* *PFS median: 8.1 måneder (95% CI 7.6-10.8)*	*Patienterne tålte behandlingen godt.*

							2/3 UPS og 2/4 dedifferentieret liposarkomer havde PR	*Mange forskellige histologiske typer var inkluderes*
Naing et al.(242)	*2020*	*Single arm, fase 2*	*1c*	*Behandlingen med pembrolizumab*		*127 patienter* *Antallet af sarkom patienter kan ikke bestemmes ud fra artiklen.*		
Monga V et al.(100)	*2020*	*Retrospektiv*	*2c*	*Behandling med immunterapi*		*88 sarkom patienter med forskellige histologi* *Totale antalt UPS=25 patienter*	*CR: 1 UPS patient* *PR: 20 patienter (7 UPS, 9 leiomyosarkomer, 1 ASPS, 3 andre)* *SD: 28 patienter*	
Kelly CM et al.(93)	*2020*	*Single arm, fase 2*	*2b*	*T-VEC (vaccine) I kombination med pembrolizumab*		*20 sarkom patiener med metastatiske sygdom*	*ORR: 30%.* *DCR:70%*	*Ingen alvorlig bivirkninger* *Mange forskellige histologiske diagnoser*
Italiano A et al.(94)	*2020*	*Meta-analyse*	*2a*	*Fase II forsøg som har undersøgt effekten af PD1 eller PDL1 hæmmere i bløddelsarkomer*		*384 patienter med sarkom, 153 af disse blev kun behandlet med PD1 eller PDL1 hæmmere*	*ORR (monoterapi): 18,7%* *DCR (monoterapi): 63.6%* *UPS: ORR 15,7%, DCR: 50.5%* *LMS: ORR 6.9%, DCR: 54.1%* *DDLPS: ORR 7.3% DCR: 54,5%*	*Indenfor de forskellige undertyper er der forskellige ORR og DCR*

							ASPS: ORR 48.8%, DCR: 80,5%	
Callaghan CM et al.(243)	*2020*	*Retrospektiv analyse*	*4*	*Undersøgelse af strålebehandling sammen med PD1 hæmmer*		*5 patienter* *10 metastaser behandlet*	*50% metastaser med komplet respons* *10% med PR* *30% med SD*	*Ingen alvorlige bivirkninger*
Martin-Broto et al.(101)	*2020*	*Single arm, fase 1b/2*	*2b*	*Undersøgelse af checkpoint hæmmer med tyrosin kinase hæmmer sunitinib*		*68 patienter med bløddelsarkom*	*6 måneder PFS: 48% (95%CI 41-55%)*	
Zhou et al.(95)	*2020*	*Retrospektiv analyse*	*2c*	*Undersøgelse af checkpoint hæmmere nivolumab og ipilimumab i kombination.*		*38 patienter med bløddelssarkom.* *Leiomyosarkom 9* *Liposarkom 6*	*ORR: 15%* *DCR: 34%* *PFS 2.7 måneder (95%CI:2.3-4.5)* *For patienter med CR og PR* *PFS: 23.4 måneder (95% CI: 7-?)*	*Behandlingen blev tålt god.*
Geoerger et al.(244)	*2020*	*Single arm, fase ½*	*2b*	*Undersøgelse af atezolizumab en PD-L1 hæmmer*		*87 patienter inkluderet(alle under 18 år).* *42 patienter havde sarkom* *Primært Ewing sarkom (n=11), non-rhabdomyosarkom (n=9), osteosarkom (n=10), Rhabdomyosarkom (n=10)* *Malign rhabdoid tumour (n=3)*	*2 Ewing sarkom patienter havde stabil sygdom og en malignt rhabdoid tumor havde complet respons.*	

Geoerger et al. (245)	*2020*	*Single arm fase ½*	*2b*	*Pembrolizumab behandling til PD-L1 postivie sarkomer + mange andre diagnoser*		*155 patienter inkluderet.* *Sarkomer udgjorde 21% (n=33).*	*PR: 2 sarkom patienter* *SD: 1 sarkom patienter.*	
Scheinberg T et al.(246)	*2021*	*Retrospektiv analyse*	*2c*	*Anslyse af PD-1 hæmmer ved unge og unge voksne med sarkom*		*18 patienter* *Antal patienter som kunne evalueres*	*CR: 7%* *PR: 7%* *SD: 7%* *DCR: 21%*	
Livingston MB et al.(102)	*2021*	*Single arm, fase 2*	*2b*	*Doxorubicin og pembrolizumab som kombinations behandling*		*30 patienter, bløddelssarkomer*	*ORR 36,7 % (95% CI 19-9-56-1).* *DCR: 80%.* *PFS: 5.7 måneder*	
Liu et al.(96)	*2021*	*Single arm, fase 2*	*2b*	*Pembrolizumab behandling*		*36 patienter, bladet histologiske grupper*	*ORR: 19.4% 7/36 patienter* *PFS: 2.9 måneder (95%CI: 2.4 – 3.4)*	*Mange forskellige histologiske undergrupper og nogle havde fået pembrolizumab i kombination med anden behandling.*
Wagner et al.(247)	*2021*	*Single arm, fase 2*	*2b*	*Ipilimumab behandling sammen med nivolumab*		*16 angiosarkom patienter*	*ORR: 25%* *6 måneders PFS var 38%*	*Der var i i særdeleshed effekt hos patienter med kutant angiosarkom*
Smrke et al.(103)	*2021*	*Single arm, fase 1*	*2b*	*Gemcitabine I combination med pembrolizumab.*		*13 patienter.* *2 med UPS*	*Bedste respons 9 uger efter start af behandling*	

						11 LMS	*LMS stabil sygdom for 8/11 patienter* *UPS partiel respons 2/2.* *Mediane PFS var 5.1 måned (95%CI: 2-7 måneder)*	
Italiano et al (248)	*2022*	*Single arm, fase 2*	*2b*	*Pembrolizumab i kombination med oral lavdosis cyclofosfamid*	*ingen*	*30 patienter med STS positiv for tertiary lymphoid structures*	*6-måneders NPR = 40%* *ORR = 4,9%*	
Klemen et al(249)	*2022*	*Pooled analyse af 4 single arm fase 2 studier (4; 12;18; 34)*	*2b*	*PD-1 antistof alene eller i kombination med ipilimumab eler T-VEC, eller bempgaldesleukin , eller epacadostat*	*ingen*	*134 patienter* *20 (15%) nivolumab ± ipilimumab,* *18 (13%) pembrolizumab plus T-VEC,* *68 (51%) nivolumab plus bempegaldesleukin,* *28 (21%) pembrolizumab plus epacadostat.*	*Twenty-one (16%) of 134 patients had a CR/PR, 48 (36%) had SD, 45 (34%) had PD, and 15 (11%) had HPD* *5 histologies ORR > 30%.:angiosarcoma (2 CR, 3 PR in 12 ptt), myxofibrosarcoma (1 CR, 1 PR in 5 ptt), epithelioid sarcoma (2 PR in 5 ptt), UPS (5 PR in 16 ptt)*	*Median PFS for ptt m* *CR/PR: 15 mdr* *SD: 5,5 mdr* *PD: 1,6 mdr* *HPD (an increase in TGR of 50% or more in target lesions): 1,6 mdr*
Ravi et al(126)	*2022*	*Retrospektiv kohorte*	*2c*	*pembrolizumab*	*ingen*	*25 ptt med angiosarcoma, deraf 72% med metastatisk sygdom*	*ORR: 18%* *DCR: 59%* *Median PFS 6,2 mdr* *Median OS 72,6 mdr*	*PFS ikke signifikant forskelligt for kutan vs viszeral angiosarkom (4.7 vs 6.2 mdr)*
Wagner et al(104)	*2022*	*Single arm, fase 1/2*	*2b*	*Trabectedin + avelumab*	*ingen*	*Liposarkom 11ptt* *Leiomyosarkom 24 ptt*	*23 evalueret patienter* *ORR 13% (3 ptt PR)* *DCR 56% (+ 10 ptt SD)*	

							PFS 8.3 m	
Spalato-Ceruso et al.(250)	*2022*	*Single arm, fase 2*	*2b*	*pembrolizumab, lavdosis oral cyclofosfamid og intratumoral injektion af toll-like receptor 4 agonist G-100*	*ingen*	*18 ptt med avanceret STS*	*Median PFS 1.8 mdr.; 6-mdr PFS rate 11.8%. Median OS 10.6 mdr*	*"increase in lymphocytic infiltration did not translate into substance clinical benefit"*
Somaiah et al.(251)	*2022*	*Single arm, fase 2*	*2b*	*Durvalumab + tremelimumab*	*ingen*	*62 ptt, 47 SST, 15 ptt knoglesarkomer*	*ORR(all)=12%* *PFS (all)=2.8 m* *OS (all)=21.6 m*	*1/5 ptt med kutan angiosarkom havde PR 1/5 patienter med UPS*
Lui et al.(252)	*2022*	*Single arm, fase 2*	*2b*	*TQB2450 (PD-L1 antistof) + anlotinib*	*ingen*	*30, ASPS udgør 12 patienter.*	*ORR 36.7%* *DCR 76.7%* *PFS 7.85 m* *OS not reached*	
Chawla et al(253)	*2022*	*Randomiserede fase 2*	*1b*	*Atezolizumab + CMB305 (vaccine primer NY-EKO-1 specifikke CD8 celler)*	*Atezolizumab + (kontrol)*	*89 patienter*	*PFSint=2.6 m* *PFScon=1.6 m* *OSint=18 m* *OScon=18 m*	
Blay et al.(254)	*2023*	*Subgruppe analyse fra single arm, fase 2 basket studie*	*2c*	*pembrolizumab*	*ingen*	*97 ptt med "rare sarcomas" (incidens < 1 ud af 1mio)*	*12 ugers ORR 6·2%; ingen CR, 6 ptt med PR*	*34 (35%) ptt m. kordomer; 14 (14%) ASPS, 12 (12%) SMARCA4-deficient sarkomer/ malignant rhabdoid tumorer, 8 (8%) desmoplastic small round cell, 6 (6%) epitelioide*

								sarkomer, 4 (4%) dendritic cell sarkomer, 3 (3%) clear cell sarkomer, SFT, myxoid liposarcomas, 10 (10%) ultra-rare subtyper
Kelly et al(255)	*2023*	*Single arm, fase 2*	*2b*	*Epacadostat og pembrolizumab*	*ingen*	*30 ptt med STS (UPS/myxofibro; LMS, liposarcoma; vascular sarcoma; other STS)*	*24 uger ORR 3,3%* *Median PFS 7,6 uger*	*Veltolereret, "limited activity"; IDO1-hæmning ikke adekvat*
Miao et al.(256)	*2023*	*Retrospektiv kohorte*	*2c*	*Anti-PD1*	*ingen*	*84 ptt med STS, deraf 19 med kutan primærtumor*	*Kutan vs ikke kutan primærtumor: clinical benefit rate 58% vs. 11%, p < 0.001; median PFS 8.6 vs. 2.5 mdr, p = 0.003; median OS 19.0 vs. 9.2 mdr, p = 0.011*	
Schöffski et al(257)	*2023*	*Prospektiv fase 1a/b*	*2b*	*Pembrolizumab + olaratumab*	*ingen*	*41 ptt., deraf 28 ptt i dose expansion cohort*	*For expansion cohort:* *PR 6 ud af 28 ptt.* *Median PFS 2,7 mdr* *Median OS 14,8 mdr*	
Zhou et al(258)	*2023*	*Single arm,* *Prospektiv fase 1*	*2b*	*MASCT-1 (multiple-antigen stimulated celle therapi) + camrelizumab og apatinib*	*ingen*	*13 STS ptt*	*ORR 30.8%* *DCR 76.9%* *PFS 12.9 m*	
Chen et al(259)	*2023*	*Single arm, fase 2*	*2b*	*Atezolizumab*	*ingen*	*Alveolar soft part sarkom (ASPS) 52 ptt*	*ORR 37% 1 CR og 18 PR* *PFS 20.8 m*	*Ikke mange alvorlige bivirkninger*
D'Angelo et al(260)	*2024*	*Single arm, fase 2*	*2b*	*Afamitregene autoleucel (afami-cel)*	*ingen*	*44 synovial sarkom patienter*	*ORR37%* *PFS: 3.7 mdr.*	*Patienter havde modtaget mange typer behandlinger før denne*

						8 myoxid rund celle liposarkomer		
Haddox et al (105)	*2024*	*Single arm phase 2*	*2b*	*Eribulin + pembrolizumab*	*ingen*	*57 ptt.: LPS (n = 20), LMS (n = 19), UPS/Other (n = 18)*	*PFS-12: LMS 36.8%, LPS 69.6%, UPS/other 52.6%*	*Promising for LMS*

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

NP non-progression rate; HPD hyperprogressive disease

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Bilag 11 – Evidenstabel (Små studier med nogen effekt)

Arbejdsdokument – Evidenstabel (små studier med nogen effekt)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targetere behandling til patienter med bløddelssarkom – små studier med nogen effekt*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Garcia del Muro X et al.(114)	*2005*	*Single-arm, fase 2*	*2B*	*Temozolomid* *(alkylerende)*	*Ingen*	*STS (49)*	*ORR 15.5%* *PFS 2.2 m* *OS 8.1 m*	*5 ud af 11 havde uterintleiomyosarkom*
Leahy M et al.(261)	*2006*	*Single-arm, fase 2*	*2B*	*Brostallicin* *(alkylerende)*	*Ingen*	*STS (43)*	*ORR 5 %* *DCR 50%* *PFS 2.9 m* *OS 7.7 m*	*2. linjebehandling*
Hartmann JT et al.(262)	*2007*	*Single-arm fase 2*	*2B*	*Bendamustin hydrochlorid* *(aklylerende)*	*Ingen*	*STS (36)*	*ORR 3%* *DCR 34%*	*6 ud af 15 patienter med leiomyosarkom havde stabil sygdom*
Wagner AJ et al.(263)	*2012*	*Single-arm, fase 2*	*2B*	*Tivantinib* *(MET inhibitor)*	*Ingen*	*ASPS (27)*	*PFS 5.5 m*	

Agulnik M et al.(264)	*2012*	*Singelarm, fase 2*	*2B*	*Bevacizumab*	*Ingen*	*Angiosarkom, epitheloidt hemangioendotheliom (32)*	*ORR 17%* *DCR 50%* *PFS 12.4 m*	*Studier fra kombinationer og fase 3 forsøg kommer senere*
Dickson MA et al.(265)	*2012*	*Single-arm, fase 2*	*2B*	*CDK4 hæmmer*	*Ingen*	*Differentieret og dedifferentieret liposarkom(30)*	*ORR 3%* *DCR: 15%* *PFS 4.5 m*	
George S et al.(266)	*2014*	*Singelarm, fase 2*	*2B*	*Letrozol*	*Ingen*	*Uterint leiomyosarkom ER og PR pos (27)*	*PFS 4 m*	
Gupta S et al.(267)	*2016*	*Singelarm, fase 2*	*2C*	*Amrubicin*	*Ingen*	*STS (24)*	*PFS 5.8 m* *OS 26 m*	
Dickson MA et al.(268)	*2016*	*Singelarm, fase 2*	*2B*	*Palbociclib* *(CDK4 inhibitor)*	*Ingen*	*Differentieret og dedifferentieret liposarkom (30)*	*PFS 4.4 m*	*Anden tidsperiode*
Schöffski P et al.(269)	*2017*	*Singelarm, fase 2*	*2C*	*Crizotinib* *(tyrsin kinase hæmmer)*	*Ingen*	*Clear celle sarkom med MET alterationer (27)*	*ORR 3.8%* *DCR69.2 %* *PFS 4.4 m* *OS 9.2 m*	
Tawbi HA et al.(97)	*2017*	*Singelarm, fase 1*	*2B*	*Pembrolizumab*	*Ingen*	*STS (40)*	*ORR 18%*	*Dvs. 4 ud af 10 UPS patienter responderede*

				(immunterapi)			*UPS (4/10) og dedifferentier et liposakom (2/10)*	

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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Bilag 12 – Evidenstabel (Ingen effekt)

Arbejdsdokument – Evidenstabel (ingen effekt)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom – ingen effekt*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Taylor SA et al.(270)	*1990*	*Single-arm, fase 2*	*2B*	*Echinomycin* *(interkalerende peptid)*	*Ingen*	*STS (34)*	*ORR 0%*	*Ingen effekt*
Earhart RH et al.(271)	*1990*	*Randomiseret, fase 2*	*2B*	*6-diazo5oxoL norleucine (DON)* *(glutamin antagonist)*	*Aclacinomycin A (ACM)*	*STS (98)*	*ORRdon 0%* *OSdon 4.8 m* *OSacm 6.8 m*	*Ingen effekt*
Muss HB et al.(272)	*1990*	*Single-arm, fase 2*	*2C*	*Mitoxantrone* *(type II topoisomerase hæmmer)*	*Ingen*	*Uterint leiomyosarkom a (29)*	*PFS 1.4 m* *OS 4.1 m*	
Casper ES et al.(273)	*1991*	*Single-arm, fase 2*	*3*	*PALA + dipyridamole*	*Ingen*	*STS (21)*		*Ingen effekt*

				(phosphodiesterase hæmmer)				
Kerbrat P et al.(274)	*1992*	*Single-arm, fase 2*	*2C*	*Fotemustine (alkylerende)*	*Ingen*	*STS (31)*		*Ingen effekt*
Somers R et al.(275)	*1992*	*Single-arm, fase 2*	*2C*	*Mitozolomide (alkylerende)*	*Ingen*	*STS (29)*		*Ingen effekt*
Schiesel JD et al.(276)	*1992*	*Single-arm, fase 2*	*2C*	*Piritrexin*	*Ingen*	*STS (26)*		*Ingen effekt*
Kraut EH et al.(277)	*1992*	*Single-arm, fase 2*	*2B*	*Merbarone (topoisomerase II hæmmer)*	*Ingen*	*STS (37)*		*Ingen effekt*
Casper ES et al.(278)	*1993*	*Single-arm, fase 2*	*2B*	*Edatrexate*	*Ingen*	*STS (35)*	*ORR 14%*	*Sparsom effekt fraset ved MFH*
Zalupski MM et al.(279)	*1993*	*Single-arm, fase 2*	*2C*	*Piroxantrone*	*Ingen*	*STS (25)*	*ORR 9%*	*Ingen effekt*
Borden EC et al.(280)	*1993*	*Single-arm, fase 2*	*2B*	*Interferon alfa*	*Ingen*	*STS (87)*	*ORR 5%*	*Ingen effekt*
Verweij J et al.(281)	*1994*	*Single-arm, fase 1*	*3*	*MTP/PE*	*Ingen*	*STS (20)*		*Ingen effekt*
Knowling M et al.(282)	*1994*	*Single-arm, fase 2*	*2C*	*10-EDAM*	*Ingen*	*STS (31)*		*Ingen effekt*
Asbury R et al.(283)	*1995*	*Single-arm fase 2*	*3*	*Aminothiadiazole*	*Ingen*	*Uterintleiomyosarkom (21)*	*ORR 0%*	*Ingen effekt*

							DCR 25%	
Curé H et al.(284)	1998	Single-arm, fase 2	2B	Cystemustine	Ingen	STS (32)	ORR 3.6%	Ingen effekt
Woll PJ et al.(285)	1999	Single-arm, fase 2	2B	Temozolomide (alkylerende)	Ingen	STS (31)	ORR 3.3% PFS 1.8 m OS 6.3 m	Ingen effekt
Blay JY et al.(286)	1999	Single-arm, fase 2	3	Raltitrexed (antimetabolit)	Ingen	STS (23)		Ingen effekt
Smith HO et al.(287)	2002	Single-arm, fase 2		Trimetrexate	Ingen	Uterint leiomyosarkom (28)		Ingen effekt
Kuenen BC et al.(288)	2003	Single-arm, fase 2	2C	SU5416 (tyrosin kinase hæmmer)	Ingen	STS (31)	PFS 2 m	Ingen effekt
Patel SR et al.(289)	2003	Single-arm, fase 2	2B	9-nitrocamptothecin (topoisomerase hæmmer)	Ingen	STS (56)	ORR 8%	Ingen effekt
Okuno S et al.(290)	2005	Single-arm, fase 2	3	Epothilone B (hæmmer microtubili funktion)	Ingen	STS (21)	PFS 4.5 m OS 16.4 m	Ingen effekt

Bailey HH et al.(291)	*2006*	*Single-arm, fase 2*	*3*	*Perifosine* *(Akt inhibitor og PI3K inhibitor)*	*Ingen*	*STS (23)*	*DCR 9%*	*Ingen effekt*
Patel S et al.(292)	*2006*	*Single-arm, fase 2*	*2C*	*TZT-1027*	*Ingen*	*STS (29)*	*PFS 1.5 m* *OS 5.9 m*	*Ingen effekt*
Reichardt P et al.(293)	*2007*	*Single-arm, fase 2*	*2B*	*Exatecan* *(strukturel analog)*	*Ingen*	*STS (39)*	*DCR 60%*	*Ingen effekt*
Ray-Coquard I et al.(294)	*2008*	*Single-arm, fase 2*	*2B*	*Gefitinib* *(EGFR hæmmer)*	*Ingen*	*HER1 synovialt sarkom (48)*		*Ingen effekt*
Baker LH et al.(295)	*2009*	*Single-arm, fase 2*	*2B*	*Thrombospindin-1 minetic angiogenesis inhibitor*	*Ingen*	*STS (42)*	*PFS 3.1 m*	*Ingen effekt*
Okuno S et al.(296)	*2011*	*Single-arm fase 2*	*2B*	*Temsirolimus* *(mTOR hæmmer)*	*Ingen*	*STS (41)*	*PFS 2.1*	*Ingen effekt*
Schuetze SM et al.(297)	*2012*	*Randomiseret, fase 2*	*1B*	*Sirolimus (makrolid) + cyclophosphamid)*	*Ingen*	*STS (49)*	*PFS 3.4* *OS 9.9*	*Ingen effekt*
Ha HT et al.(298)	*2013*	*Single-arm, fase 2*	*2C*	*Cetuximab*	*Ingen*	*STS (21)*	*PFS 1.7 m*	*Ingen effekt*

				(EGFR hæmmer)			*OS 7.7 m*	
Cassier PA et al.(299)	*2013*	*Single-arm, fase 2*	*2B*	*Panobinostat* *(histrone deacetylase hæmmer)*	*Ingen*	*STS (47)*		*Ingen effekt*
Eroglu Z et al.(300)	*2015*	*Randomiseret, fase 2*	*2B*	*Selumetinib* *(hæmmer af MAPK/ERK pathway) BRAF mut*	*Selumetinib +* *temsirolimus*	*STS (71)*		*Ingen effekt*
Toulmonde M et al.(301)	*2015*	*Single-arm, fase 2*	*2B*	*Aplidin*	*Ingen*	*Dedifferentieret liposarkom (24)*	*PFS 1.6 m* *OS 9.2 m*	*Ingen effekt*
Schmitt T et al.(302)	*2016*	*Single-arm, fase 2*	*2B*	*Vorinostat* *(historne deacetylase hæmmer)*	*Ingen*	*STS (40)*	*ORR 0%* *DCR 9%* *PFS 3.2 m* *OS 12.3 m*	*Ingen effekt* *2. linjebehandling eller senere*
Dickson MA et al.(303)	*2016*	*Single-arm, fase 2*	*2B*	*Alisertib* *(aurora A kinase hæmmer)*	*Ingen*	*STS (72)*		
Større studier uden effekt, ikke sammenlignet med tidligere anvendte stoffer.								

Chugh R et al.(304)	*2009*	*Single-arm, fase 2*	*2A*	*Imatinib*		*STS (185)*		*Ingen effekt*
Schuetze SM et al. (305)	*2016*	*Single-arm, fase 2*	*2A*	*Dasatinib*		*STS (200)*		*Evt. lidt effekt i UPS*

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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Bilag 13 – Evidenstabel (Review)

Arbejdsdokument – Evidenstabel (review)

Dette arbejdspapir kan anvendes til kritisk gennemgang af den litteratur, der skal danne grundlag for retningslinjens anbefalinger.

DMCG: DSG	Retningslinjens emne/titel: *Pallierende kemoterapi og targeteret behandling til patienter med bløddelssarkom - review*							
Forfatter/ kilde	***År***	***Undersøgelses-type/design***	***Under-søgel-sens kvalitet jf. Oxford***	***Intervention***	***Sammenlignings intervention***	***Patient-population***	***Resultater (outcome)***	***Kommentarer***
Pang A et al.(306)	*2016*	*Review*		*Pallierende kemoterapi til STS*				*Generelt anvendt til at sikre at relevant original litteratur er inkluderet i denne retningslinje*
Le Cesne A et al.(307)	*2015*	*Review*		*Trabectedin*				*Trabectedin kan anvendes ved ældre og flere behandlinger giver ikke mere toksicitet*

Radaelli S et al.(308)	*2014*	*Review*		*Pallierende kemoterapi til STS*				*Generelt, anvendt til at sikre at relevant original litteratur er inkluderet i denne retningslinje*
Jain A et al.(309)	*2009*	*Review*		*Pallierende kemoterapi til STS*				*Generelt, anvendt til at sikre at relevant original litteratur er inkluderet i denne retningslinje*
Kopp HG et al. (310)	*2008*	*Review*		*Pallierende kemoterapi til STS*				*Generelt, anvendt til at sikre at relevant original litteratur er inkluderet i denne retningslinje*
Tascilar M et al.(311)	*2007*	*Review*		*Ifosfamid monoterapi*				*ORR 16%-55%* *OS 9-18 m*
Sleijfer S et al.(6)	*2005*	*Review*		*Doxorubicin*	*Doxorubicin + andre kemoterapeutika*			*ORR 16-27%* *OS 7.7 -12 m* *Begrænsende pga myelosuppression og cardiomyopati*
Bauer S et al.(69)	*2004*	*Review*		*Gemcitabin*	*Gemcitabin + andre kemeterapeutika*			*Effektiv ved angiosarkom evt ved LMS non-GI origin*
Bramwell VH et al.(7)	*2003*	*Review*		*Doxorubicin*				
Verma S et al. (41)	*2008*	*Review*		*Ifosfamid*				
Fury MG et al.(119)	*2005*	*Retrospektiv*		*Forskellige behandlinger*		*Angiosarkom (125)*		*Doxorubicin (12 pt) PFS 3.7 m* *Caelyx (11 pt) PFS 4.2 m*

								Paclitaxel (41 pt) 4.0 m *Gemcitabin (11 pt) 2.2 m* *Vinorelbine (6 pt) 3.1 m* *Ifosfamid (12 pt) 1.6 m*

PR: Partiel respons som svare til en reduktion i tumor volumen på 30% eller derover.
DCR: Disease contol rate som er patienter med partiel respons og stabil sygdom.
UPS: udifferentieret pleomorft sarkom
LMS: leiomyosarkom
DDLPS: dedifferentiret liposarkom
ASPA: alveolær soft part sarkom
CR: komplet respons
SD: stabil sygdom
PFR: progressions fri rate.
Pt: patienter
ORR: objektiv response rate (PR + CR)
ORRxxx: xxx er den behandling som outcome data relaterer til.
M: måneder

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8. Om denne kliniske retningslinje

Denne kliniske retningslinje er udarbejdet i et samarbejde mellem Danske Multidisciplinære Cancer Grupper (DMCG.dk) og Sundhedsvæsenets Kvalitetsinstitut. Indsatsen med retningslinjer er forstærket i forbindelse med Kræftplan IV og har til formål at understøtte en evidensbaseret kræftindsats af høj og ensartet kvalitet i Danmark. Det faglige indhold er udformet og godkendt af den for sygdommen relevante DMCG. Sekretariatet for Kliniske Retningslinjer på Kræftområdet har foretaget en administrativ godkendelse af indholdet. Yderligere information om kliniske retningslinjer på kræftområdet kan findes på: www.dmcg.dk/kliniske-retningslinjer

Retningslinjen er målrettet klinisk arbejdende sundhedsprofessionelle i det danske sundhedsvæsen og indeholder systematisk udarbejdede udsagn, der kan bruges som beslutningsstøtte af fagpersoner og patienter, når de skal træffe beslutning om passende og korrekt sundhedsfaglig ydelse i specifikke kliniske situationer.

De kliniske retningslinjer på kræftområdet har karakter af faglig rådgivning. Retningslinjerne er ikke juridisk bindende, og det vil altid være det faglige skøn i den konkrete kliniske situation, der er afgørende for beslutningen om passende og korrekt sundhedsfaglig ydelse. Der er ingen garanti for et succesfuldt behandlingsresultat, selvom sundhedspersoner følger anbefalingerne. I visse tilfælde kan en behandlingsmetode med lavere evidensstyrke være at foretrække, fordi den passer bedre til patientens situation.

Retningslinjen indeholder, ud over de centrale anbefalinger (kapitel 1 – quick guide), en beskrivelse af grundlaget for anbefalingerne – herunder den tilgrundliggende evidens (kapitel 3), referencer (kapitel 4) og anvendte metoder (kapitel 5).
Anbefalinger mærket A baserer sig på stærkeste evidens og anbefalinger mærket D baserer sig på svageste evidens. Yderligere information om styrke- og evidensvurderingen, der er udarbejdet efter "Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations", findes her:

Generelle oplysninger om bl.a. patientpopulationen (kapitel 2) og retningslinjens tilblivelse (kapitel 5) er også beskrevet i retningslinjen. Se indholdsfortegnelsen for sidehenvisning til de ønskede kapitler.

Retningslinjeskabelonen er udarbejdet på baggrund af internationale kvalitetskrav til udvikling af kliniske retningslinjer som beskrevet af både AGREE II, GRADE og RIGHT.

For information om Sundhedsstyrelsens kræftpakker – beskrivelse af hele standardpatientforløbet med angivelse af krav til tidspunkter og indhold – se for det relevante sygdomsområde: https://www.sst.dk/

Denne retningslinje er udarbejdet med økonomisk støtte fra Sundhedsstyrelsen (Kræftplan IV) og Sundhedsvæsenets Kvalitetsinstitut