Dansk Lunge Cancer Gruppe
Årsmøde 22.09.2022

Immunterapi til danske patienter med avanceret NSCLC – Langtidsoverlevelse og kliniske aspekter

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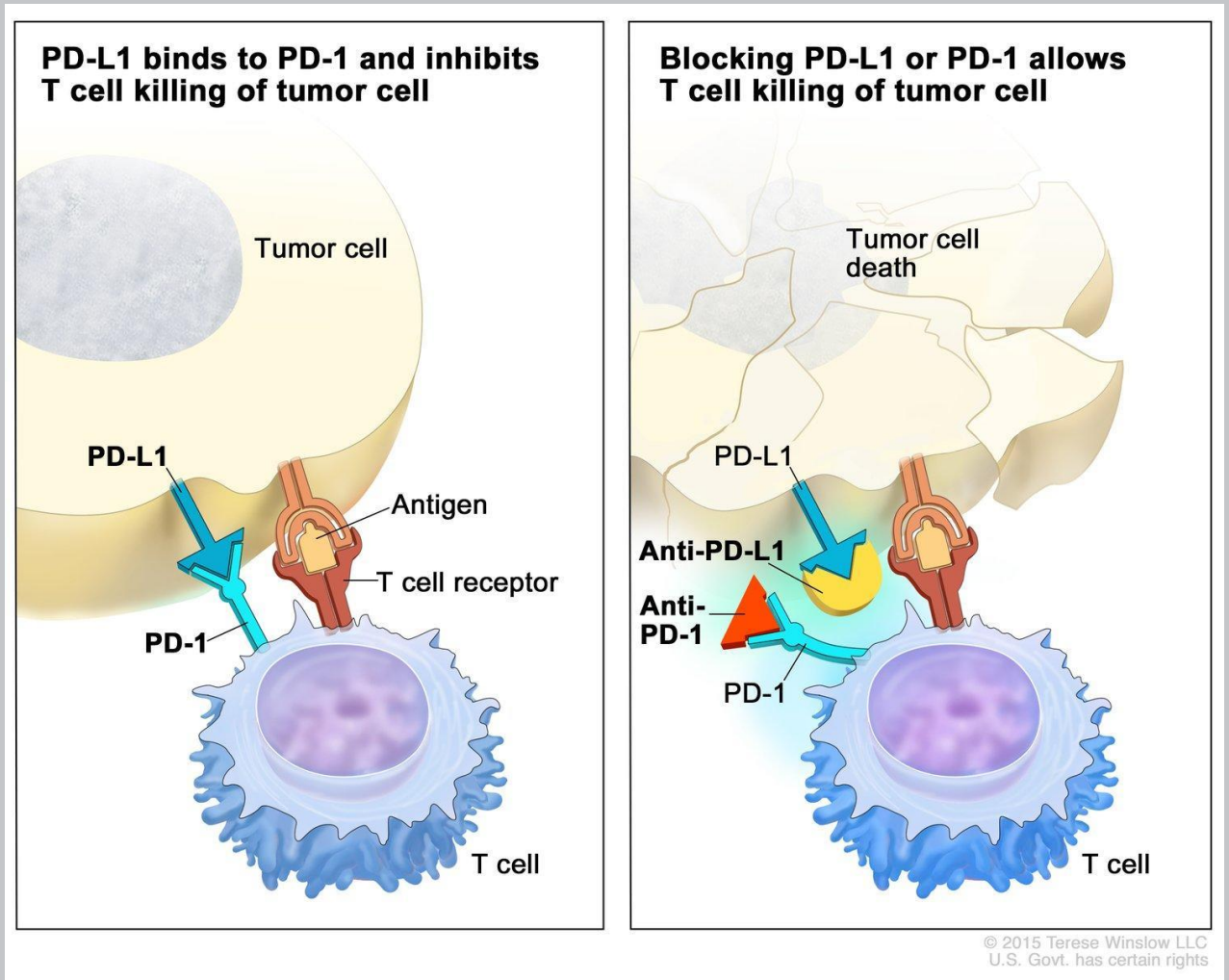
IMMUN CHECKPOINT HÆMMERE



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PUBLIKATIONER

cancers

MDPI

Article

Nationwide Survival Benefit after Implementation of First-Line Immunotherapy for Patients with Advanced NSCLC—Real World Efficacy

Mette T. Mouritzen [1,2,3,*], Andreas Carus [1,2,3], Morten Ladekarl [1,2,3], Peter Meldgaard [4], Anders W. M. Nielsen [4], Anna Livbjerg [4], Jacob W. Larsen [5], Halla Skuladottir [5], Charlotte Kristiansen [6], Kim Wedervang [7], Tine Schytte [8,9,10], Karin H. Hansen [8,9,10], Anne-Cathrine Østby [11], Malene S. Frank [11,12], Jakob Lauritsen [11,13], Jens B. Sørensen [12,13], Seppo W. Langer [12,13], Gitte F. Persson [12,14], Jon L. Andersen [14], Johanna M. C. Frary [15], Lars B. Drivsholm [15], Charles Vesteghem [2,3,16], Heidi S. Christensen [2,3,16], Birgitte Bjørnhart [8,9,10,†] and Mette Pøhl [13,†]

ACTA ONCOLOGICA
https://doi.org/10.1080/0284186X.2021.2023213

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ORIGINAL ARTICLE

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Clinical features affecting efficacy of immune checkpoint inhibitors in pretreated patients with advanced NSCLC: a Danish nationwide real-world study

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MOTIVATION

- Forbedret overlevelse efter ICI?
- RCT’er = daglig klinisk praksis?
- Underrepræsenterede patientgrupper?
- ICI behandlingsforløb?
- Prædiktive eller prognostiske patient karakteristika?

METODE

Advanced NSCLC
1L treatment

DLCR
All patients
January 2013 – October 2018

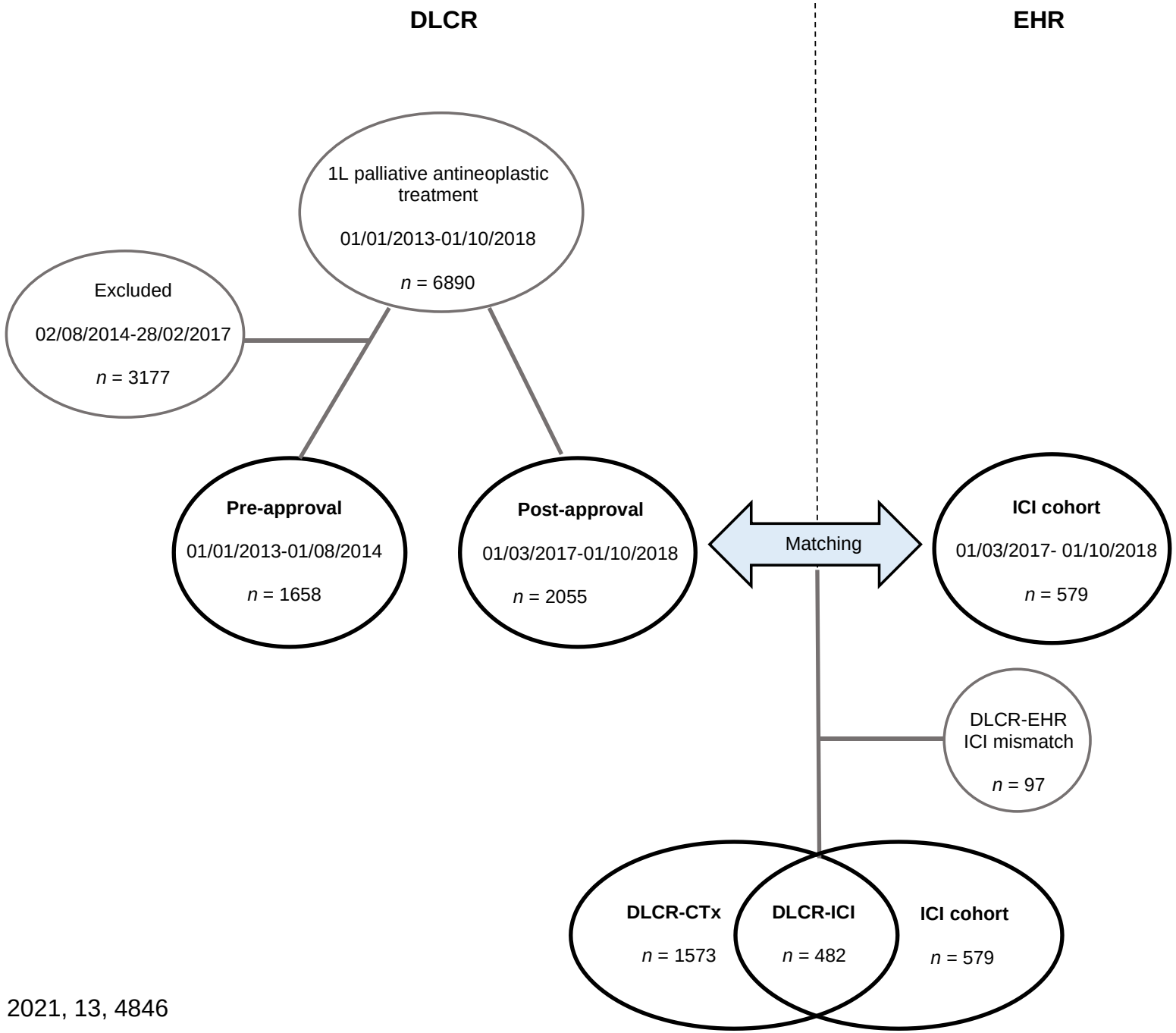
+

EHR
ICI-treated patients
March 2017 – October 2018

Advanced NSCLC
≥2L ICI

EHR
September 2015 – October 2018

METODE 1L



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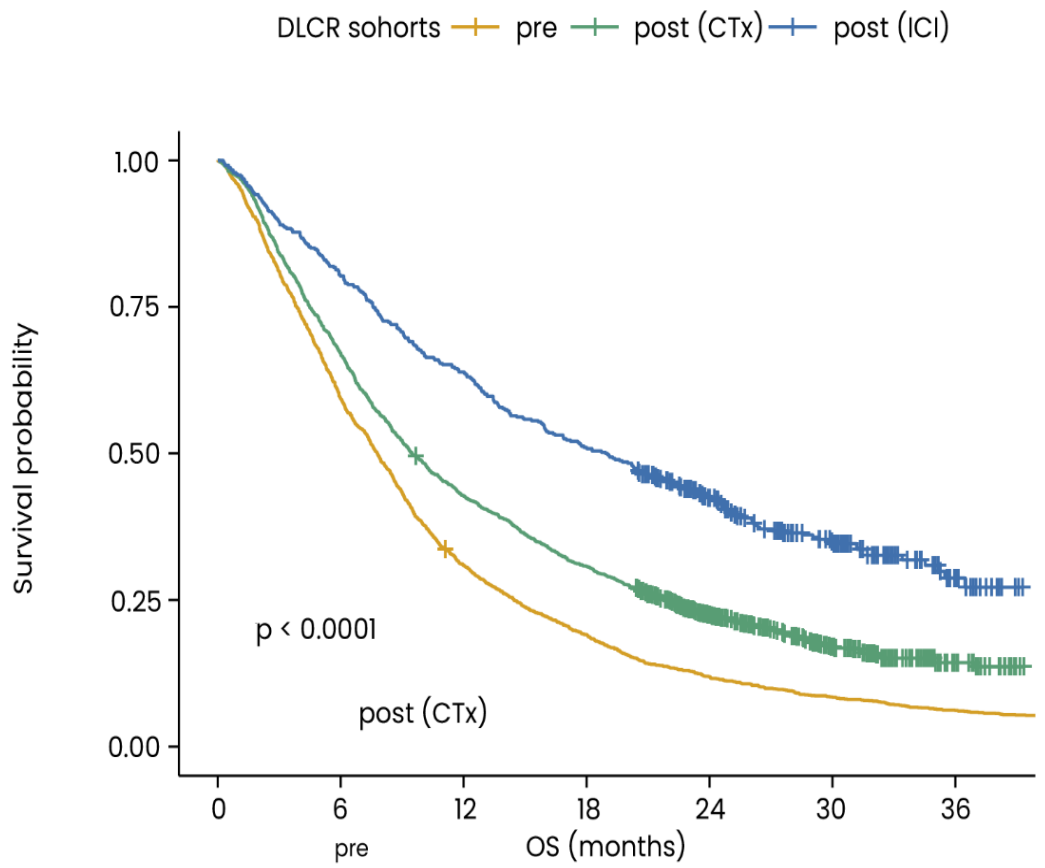
OVERLEVELSE FØR OG EFTER ICI GODKENDELSE



DLCR cohorts	n (%)	mOS (months) (95% CI)	1-year OS (%) (95% CI)	2-year OS (%) (95% CI)	3-year OS (%) (95% CI)
Pre-approval cohort	1,658 (100)	7.8 (7.4 – 8.2)	31 (29 – 33)	12 (10 – 14)	6 (5 – 7)
Post-approval cohort	2,055 (100)	11.0 (10.2 – 11.9)	48 (46 – 50)	27 (25 – 29)	18 (16 – 20)
CTx	1,573 (77)	9.5 (8.9 – 10.3)	43 (40 – 45)	22 (21 – 25)	14 (12 – 17)
ICI	482 (23)	19.0 (16.0 – 22.0)	64 (60 – 68)	42 (38 – 47)	29 (24 – 35)

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BASELINE KARAKTERISTIKA 1L ICI

Baseline characteristics	n (%)
All patients	579
Age, median years (range)	70 (45–88)
<75	441 (76)
≥75	138 (24)
Sex	
Male	246 (42)
Female	333 (58)
ECOG performance status	
0	194 (34)
1	295 (51)
≥2	90 (15)
CCIS	
0 (none)	217 (37)
1 (mild)	169 (29)
2 (moderate)	103 (18)
3+ (severe)	90 (16)
Smoking status	
Current	189 (33)
Former	343 (59)
Never	26 (4)
Unknown	21 (4)
TNM stage and metastatic sites	
III	109 (19)
IV[a]	470 (81)
Brain	38 (7)
Bone	162 (28)
Liver	63 (11)
Adrenal	86 (15)
Distant lymph nodes	174 (30)
NSCLC histopathology	
Adenocarcinoma	409 (71)
Squamous cell carcinoma	135 (23)
Other[b]	35 (6)
PD-L1	
Negative	3 (0.5)
≥1% and <50%	20 (3.5)
≥50%	552 (95.3)
Unknown	4 (0.7)
Prior treatment with curative intention	
Surgery +/- adj. CTx	39 (7)
CRT	46 (8)
Surgery and CRT	16 (3)
None	478 (82)
Prior palliative RT[c]	
Yes	71 (12)
No	508 (88)

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BASELINE KARAKTERISTIKA ≥2L ICI

Baseline characteristics	*n* (%)
All patients	840 (100)
Sex	
Male	432 (51)
Female	408 (49)
Age, median; range	68; 22 – 89
Age	
<75 years	677 (81)
≥75 years	163 (19)
ECOG PS	
0	182 (22)
1	479 (57)
≥2	158 (19)
Missing	21 (2)
Charlson Comorbidity Index Score (CCIS)	
0 (no)	332 (40)
1 (mild)	207 (25)
2 (moderate)	154 (18)
≥3 (severe)	147 (17)
Smoking status	
Current	238 (28)
Former	535 (64)
Never	46 (6)
Unknown	21 (2)
TNM stage	
III	116 (14)
IV	724 (86)
Metastatic sites[a]	
Brain	95 (11)
Bone	221 (26)
Liver	133 (16)
Adrenal	127 (15)
Distant lymph nodes	233 (28)
NSCLC histopathology	
Adenocarcinoma	485 (58)
Squamous cell carcinoma	303 (36)
Other[b]	52 (6)
EGFR mutation	
No	537 (64)
Yes	25 (3)
Unknown	278 (33)
PD-L1 status	
Negative	72 (9)
≥1% and <50%	233 (28)
≥50%	290 (35)
Unknown	245 (29)

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BEHANDLING

1L	n (%)
All patients	579
Median number of cycles (range)	7 (1 – 41)
Median days on treatment[a] (range)	127 (1 – 826)
Ongoing ICI treatment[b]	38 (7)
ICI discontinuation	541 (93)
ICI discontinuation due to[c]:	
PD	250 (46)
Poor performance status	62 (11)
Two years of ICI[d]	39 (7)
IrAEs[e]	170 (31)
Pneumonitis	41 (8)
Hepatitis	31 (6)
Skin	10 (2)
Endocrinopathy	18 (3)
Diarrhea/colitis	37 (7)
Other[f]	52 (10)
IrAE only[g]	150 (28)
Other reasons	51 (9)
Hospitalization due to irAE	135 (23)
Grade 5 toxicity (death)	12 (2)

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Treatment characteristics ≥2L	*n* (%)
All patients	840 (100)
Treatment line	
2	536 (64)
3	205 (24)
4	68 (8)
≥5	31 (4)
Treatment	
Nivolumab	444 (53)
Pembrolizumab	396 (47)
Median number of ICI cycles[a]; range	
Nivolumab	6; 1–64
Pembrolizumab	6; 1–37
ICI treatment duration[a];	
Median days; range	98; 1–961
mTTD months; 95% CI	3.2; 2.8–3.6
Ongoing ICI treatment[b]	10 (1)
ICI discontinuation due to[c]:	
PD	461 (56)
Poor PS	126 (15)
irAEs[d]	179 (22)
Pneumonitis	47 (6)
Hepatitis	19 (2)
Skin toxicity	27 (3)
Endocrinopathy	15 (2)
Diarrhea/colitis	40 (5)
Other toxicity	51 (6)
irAEs only[e]	150 (18)
Other reasons[f]	145 (17)
Hospitalization due to irAEs	135 (16)
Death due to irAEs	8 (1)

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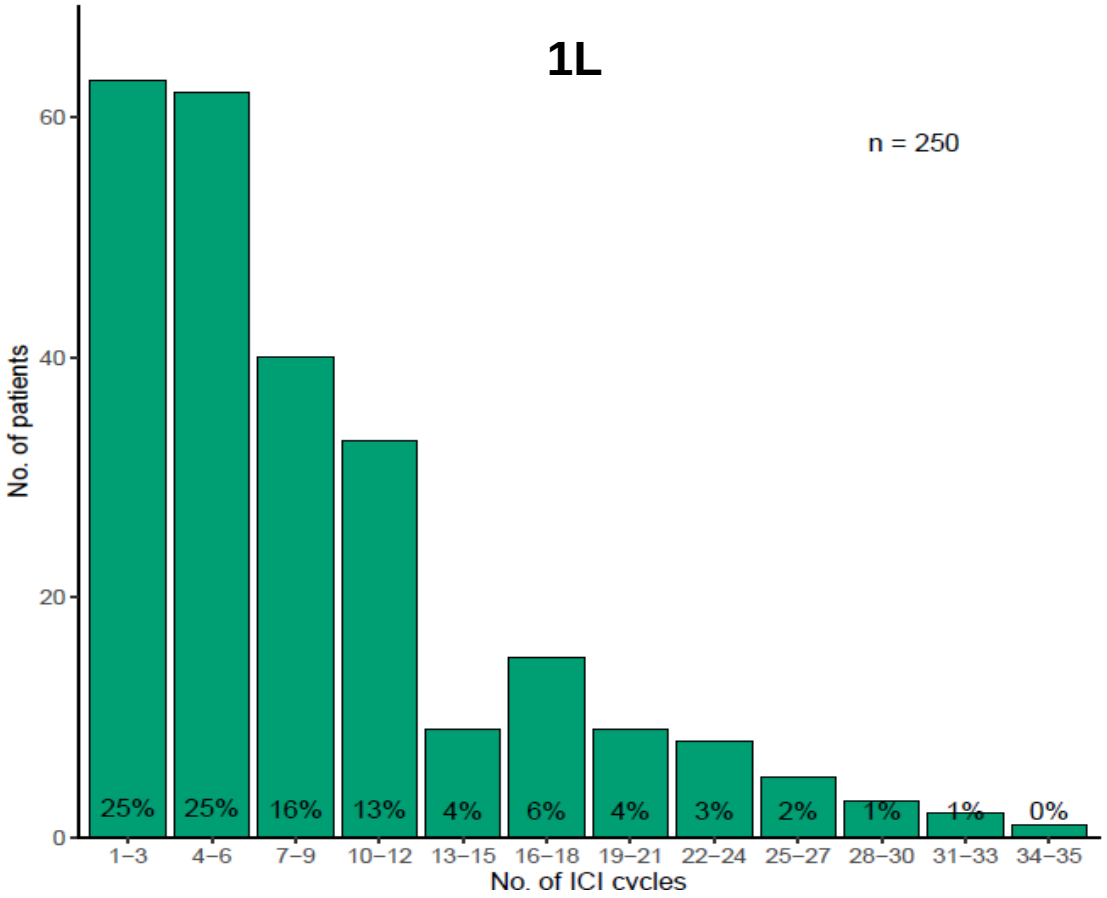
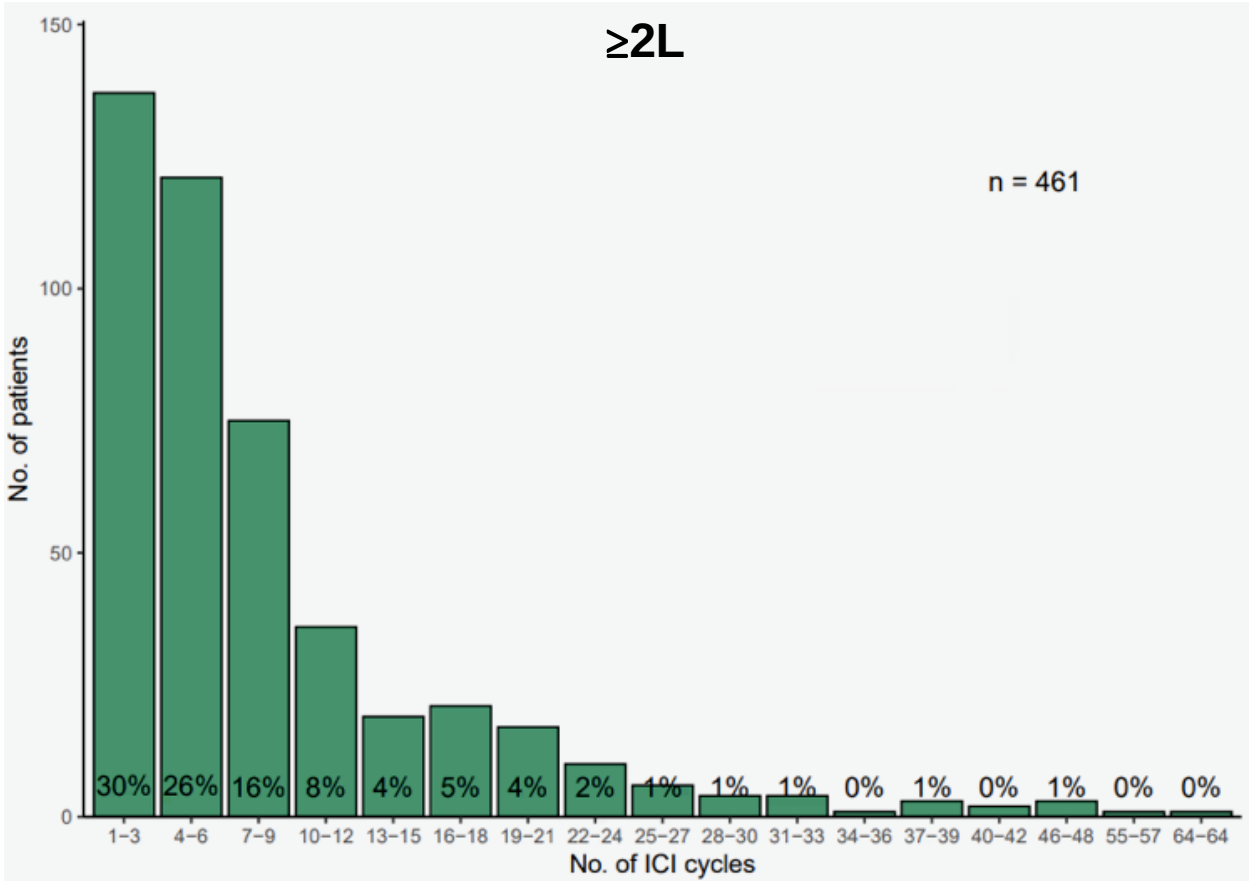
PROGRESSION SOM ÅRSAG TIL ICI OPHØR





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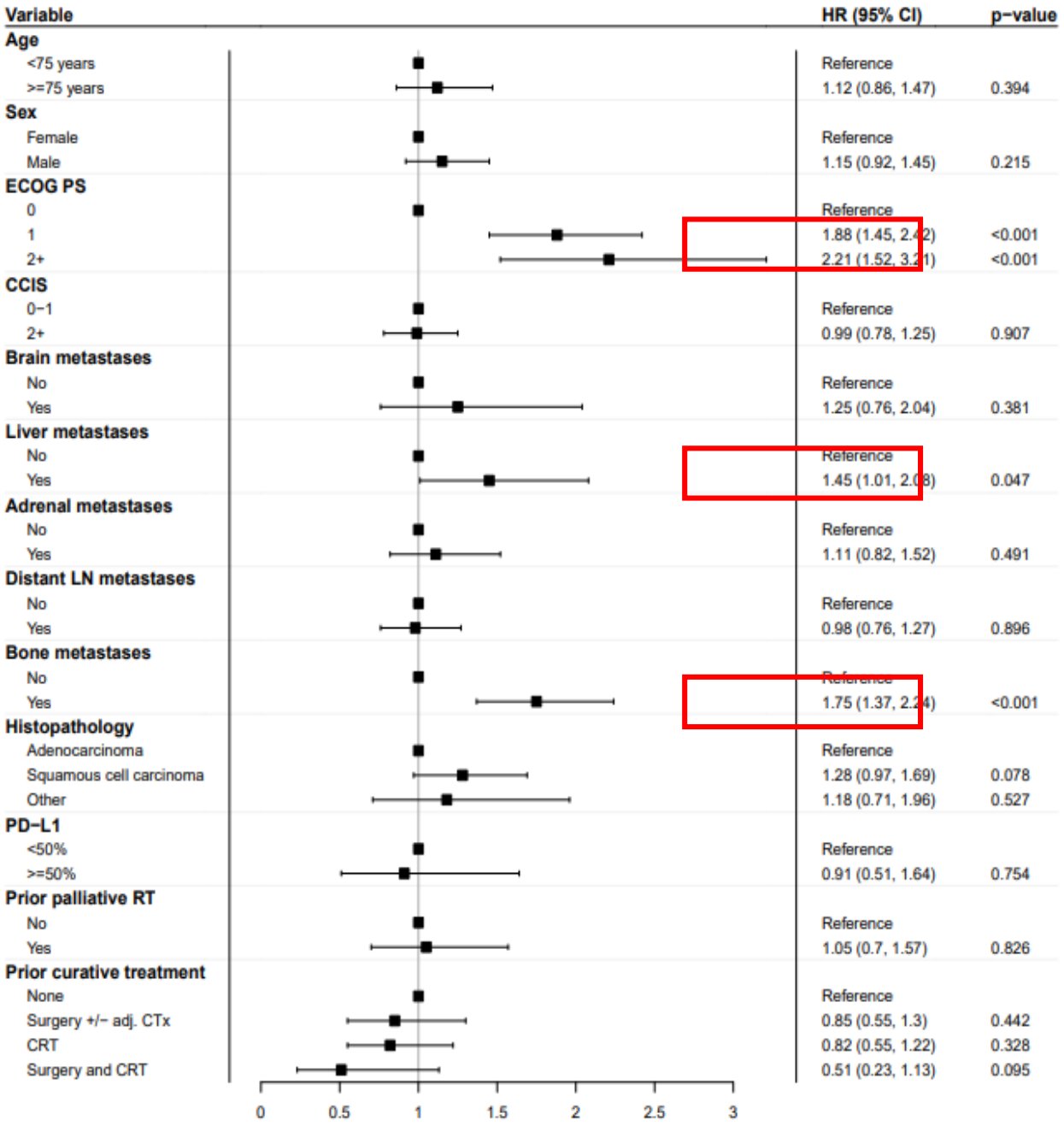

1L ICI

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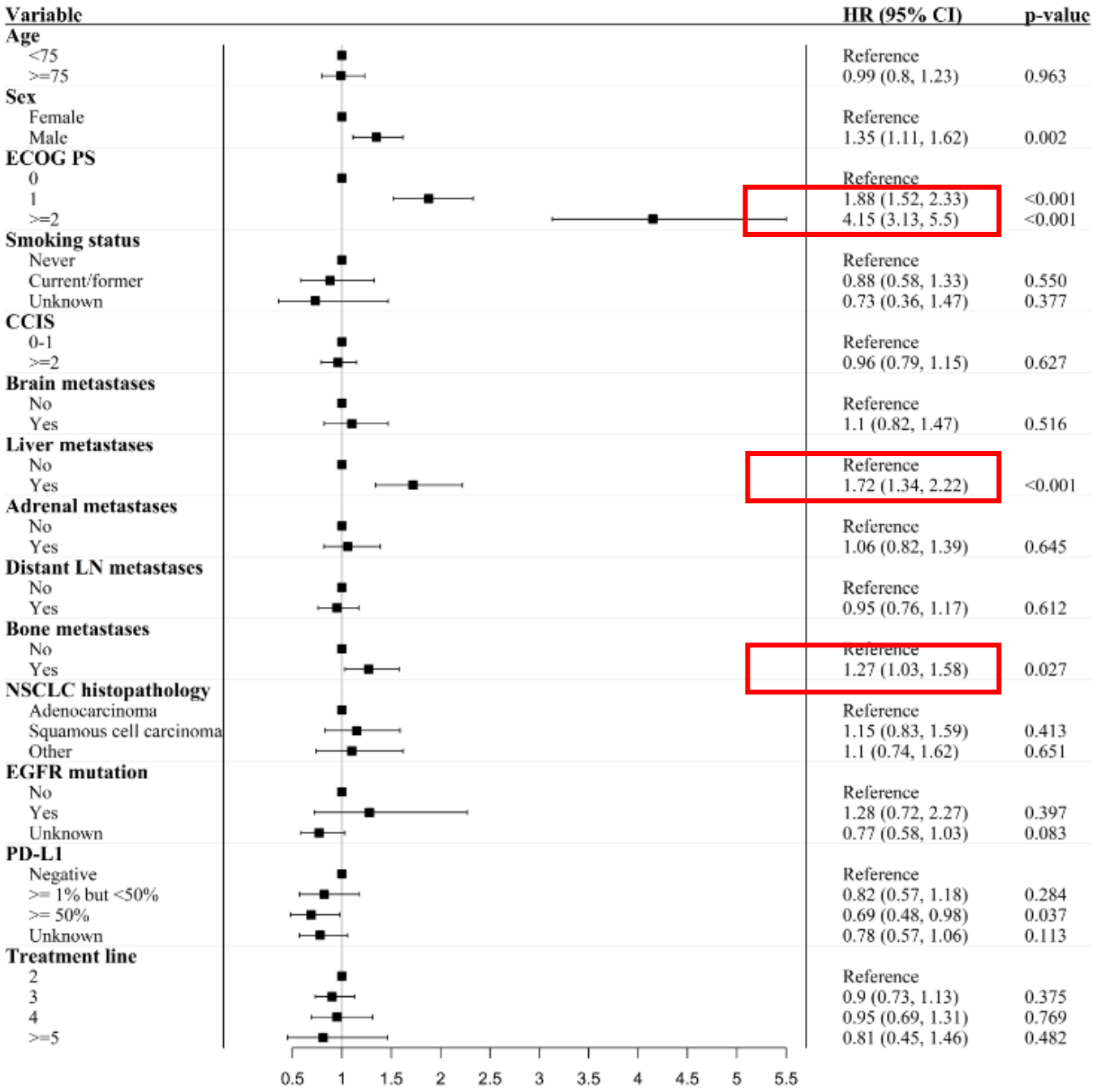

≥2L ICI

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SURVIVAL

1L ICI	**mOS** months	**mPFS** months
All patients	18.3	8.2
PS 0 (34%)	28.0	11.0
PS 1 (51%)	14.6	7.7
PS 2 (15%)	12.8	6.0

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≥2L ICI	**mOS** months	**mPFS** months
All patients	12.2	5.2
PS 0 (22%)	22.1	8.9
PS 1 (57%)	12.2	5.4
PS 2 (19%)	4.5	2.0

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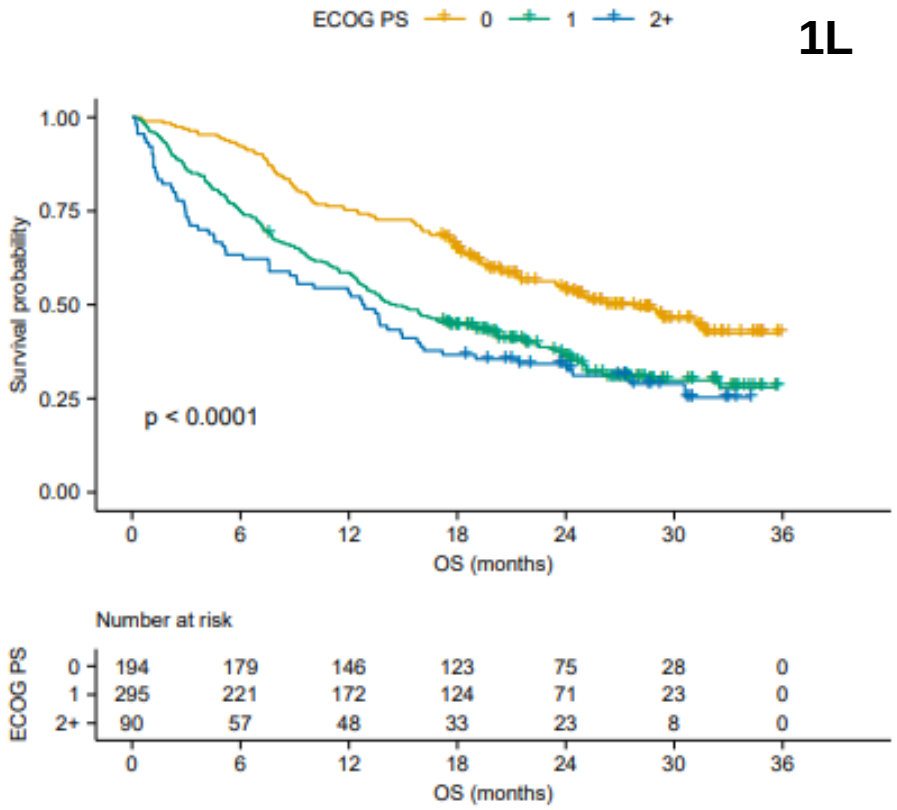
OVERLEVELSE OG PS

1L



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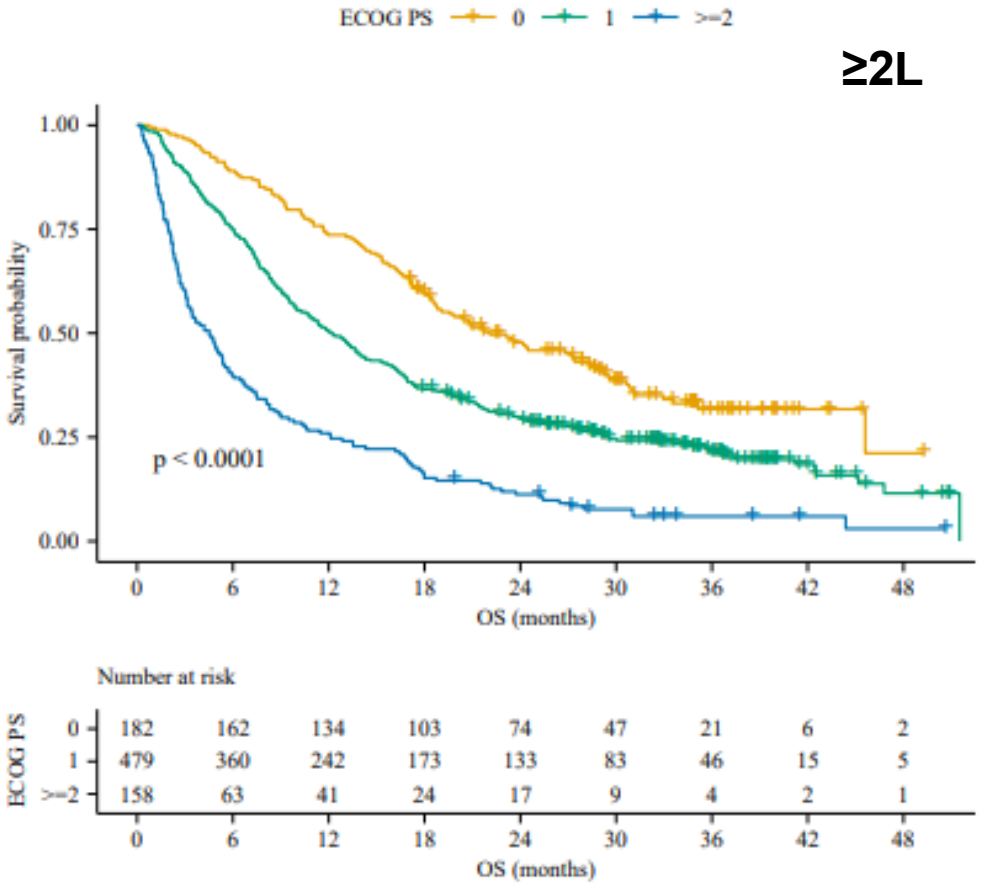
≥2L



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KONKLUSION

- Forbedret overlevelse efter ICI implementering
- Overlevelsen var lidt dårligere end i RCT'erne, undtaget patienter i PS 0
- Omkring 20% af patienter behandlet i daglig klinisk praksis var ≥75 år, i PS ≥2 og havde moderat/svær komorbiditet.
- Progression ses hos omkring 25% af alle patienter indenfor seks ICI behandlinger
- ICI ophør skyldtes PD hos 50%, dårlig PS hos 15% og immun-relaterede bivirkninger hos 20-30%
- PS ≥1 (og især PS ≥2), knogle- og levermetastaser var associeret med signifikant dårligere OS
- Nogle patienter i PS ≥2 bliver langtidsoverlevere efter ICI; grundige individuelle vurderinger

HVAD HAR VI LÆRT?

- Store nationale eller international real-world studier er vigtige når nye behandlinger indføres, for at vurdere effekten i daglig klinisk praksis
- Real-world evidens bør baseres på prospektive data, især gradering af bivirkninger
- De onkologiske data i DLCR er utilstrækkelige
- Resultater fra real-world studier (RWS) og RCT'er er vanskelige at sammenligne
- Rapportering af kendte prognostiske faktorer som fx. metastaser er vigtig i både RWS og RCT'er

FREMTIDIGE PERSPEKTIVER

- Tværregional, ensartet, real-time registrering i én fælles elektronisk patientjournal bør prioriteres højt
- Fortsat fokus på forbedring af onkologiske data i DLCR
- Detaljeret vurdering af PS: årsager til dårlig PS, frailty, komorbiditet som ikke er inkluderet i CCI, socioøkonomisk status, fysisk aktivitet, alkohol, behov for tidlig specialiseret palliative vurdering og indsats
- Internationale guidelines om RWS; studie design, data indsamling, definitioner af kovariater og endpunkter, statistiske metoder
- Primære resistensmekanismer hos patienter med tidlig PD bør fortsat undersøges
- Nye komplementære prædiktive biomarkører for ICI behandling

TAK FOR I DAG

Læge

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