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Developing a core outcome set for (stage IV) melanoma trials – results of a systematic review

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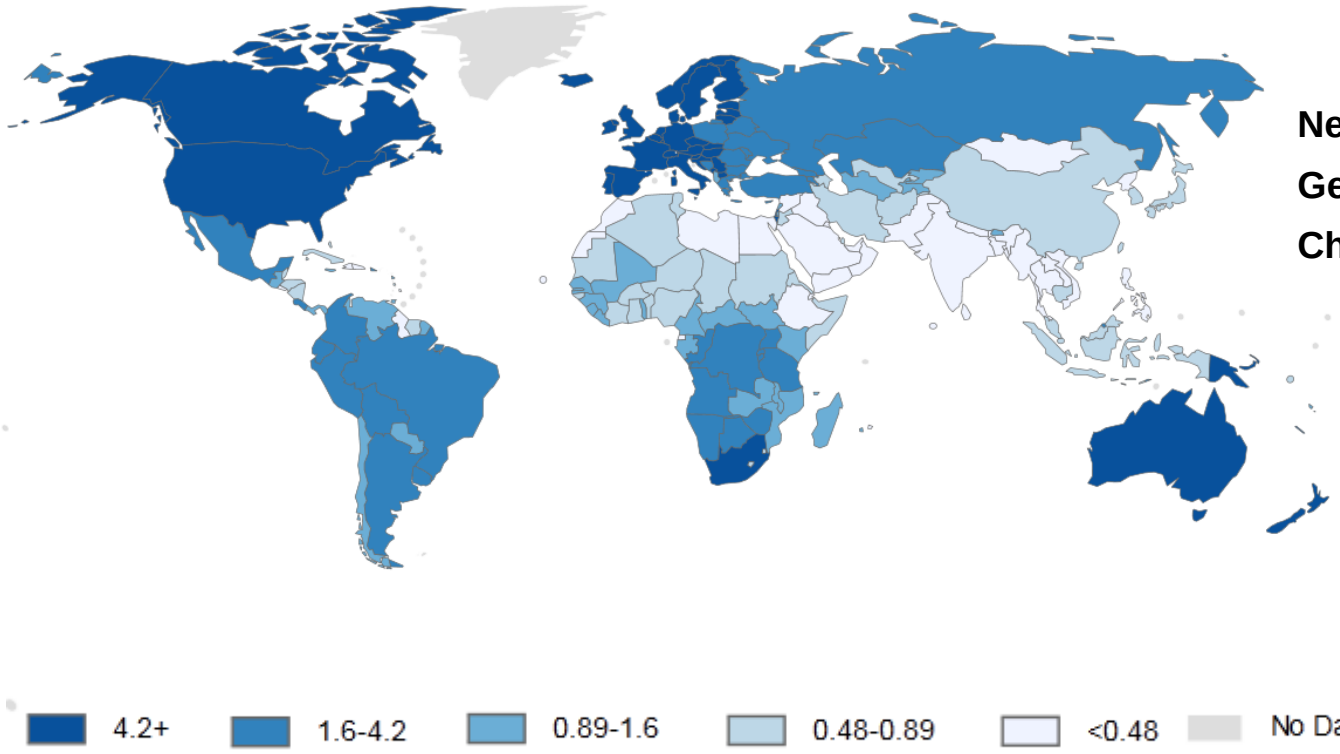
Annual Cochrane Skin Group Meeting 2015
Dresden, 17th March

Global statistics – Melanoma of the skin in 2012

- 232,130 (120,649 men, and 111,481 women)
- Worldwide age-standardized incidence rate (per 100,000):



New Zealand: 35.84 (ASR)

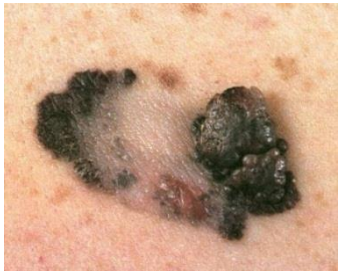
Germany: 11.43 (ASR)

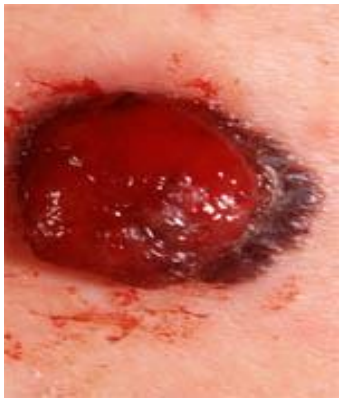
China: 0.55 (ASR)

GLOBOCAN (IARC) 2012

Stages of melanoma

- The system most often used to stage melanoma is the American Joint Commission on Cancer (AJCC)
- Stage grouping - The staging of melanoma depends on the following:
  - The thickness of the tumor
  - Whether the tumor is ulcerated (has broken through the skin)
  - Whether the tumor has spread to the lymph nodes and if the lymph nodes are joined together (matted).
  - Whether the tumor has spread to other parts of the body → Stage IV melanoma.





Stage IV melanoma

- Disease stage of melanoma at diagnosis is the major determinant of prognosis and survival
- Prognosis is associated with the thickness of the primary tumor, involvement of lymph node, presence of ulceration, and presence of distant metastases (Balch et al. 2001)
- Median survival of patients with stage IV disease is < 9 months with a mean 1-year survival rate of 25.5% (Korn et al. 2008)
- Existing Cochrane Reviews investigating effects of chemotherapy (Sasse et al. 2013) and systemic treatments (Crosby et al. 2013) for metastatic malignant melanoma/ metastatic cutaneous melanoma defined the following outcomes:
  - Survival (overall survival, median survival, progression free survival)
  - Response rates (secondary)
  - Treatment morbidity (secondary), and
  - Quality of life (secondary)

Aim of the systematic review

1) To systematically assess which **outcome domains** have been used as endpoints in **randomized and open-label extension trials** to investigate the **efficacy of interventions** for **stage IV melanoma.**

2) To systematically assess how the reported **outcome domains** were **defined**.

3) To systematically assess which **outcome measurement instruments** have been used to measure the reported outcome domains.

4) To systematically assess **outcome reporting bias** of all studies included.

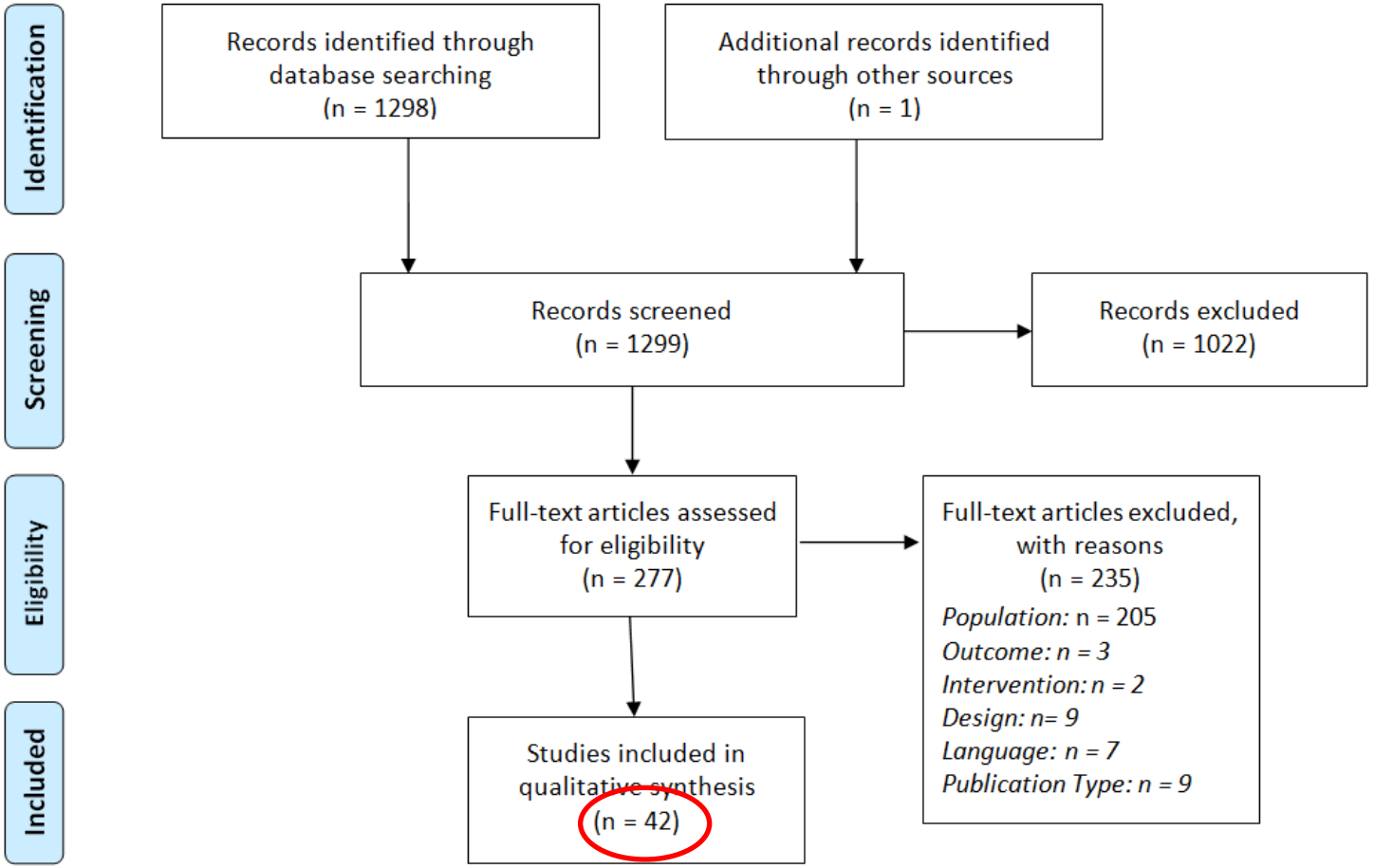
Methods

- Systematic literature search in CENTRAL (up to April 2014)
- Inclusion and exclusion criteria:

	Inclusion	Exclusion
P	Patients of all ages with stage IV cutaneous melanoma.	All others
I	All recommended interventions for metastatic melanoma stage IV (surgery, drug therapy, radiotherapy)	Adjuvant therapies
C	All	---
O	Outcome domains (patient-reported, physician assessed)	Laboratory outcomes, biological marker, predictors of outcomes
S	Randomized controlled trials and open-label extension of RCTs (at least phase II)	All others

- Outcome reporting bias was assessed by the Cochrane Collaboration's risk of bias tool (Domain "Selective Outcome Reporting")

Results – *study selection (PRISMA Statement* Moher et al. 2009*)*



Results – *general study description*

Publication period	1972 - 2013
Countries of study conduction (number of studies)	Not reported: 18 Europe: 9 USA: 6 Multiple countries: 8 Australia: 1
Study design (number of studies)	RCTs: 27 Open-label extension trials: 15
Number of participants (at clinical baseline)	Range: 25 – 859 Cumulative frequency: 6499
Differentiation between primary and secondary outcome	31 of 42 studies included (74%)
Number of outcomes reported in each study	Min. 2, max. 8 (median = 4)

Results – *reported outcome domains as study endpoint*

(n=42 studies)

Reported outcomes	Number of studies
Safety/Toxicity/Tolerability	**42**
Overall survival	**36**
Progression-free survival	**30**
Time to disease progression	**10**
Response	
Objective (tumor) Response/ objective clinical response	23
Response Rate/ Overall Response Rate/Clinical Response	16
Response duration/ time to response	12
Duration of objective tumor response	1
Clinical benefit rate	1
Immune response	1
Clinical antitumor response	1
Others:	
Objective remission	1
Rate of stability	1

Results – *definitions used for outcome domains*

Safety/Toxicity/Tolerability (42 of 42 studies)

Definitions used	Number of studies
Adverse events	29
Not reported	9
Side effects and adverse events	1
Side effects	1
Frequency of dose reductions and withdrawals due to adverse events	1
For each toxicity that was reported, was at least possibly related to treatment, the percentage of patients who reported any level of severity was determined along with the percentage of patients who reported a grade 3 level of severity	1

→ 27/42 studies used the National Cancer Institute Common Toxicity Criteria

→ 9/42 studies did not report the outcome measurement instrument

→ 6/42 studies used other outcome measurement instruments (such as WHO criteria)

Results – *definitions used for outcome domains*

Overall survival (OS) (36 of 42 studies)

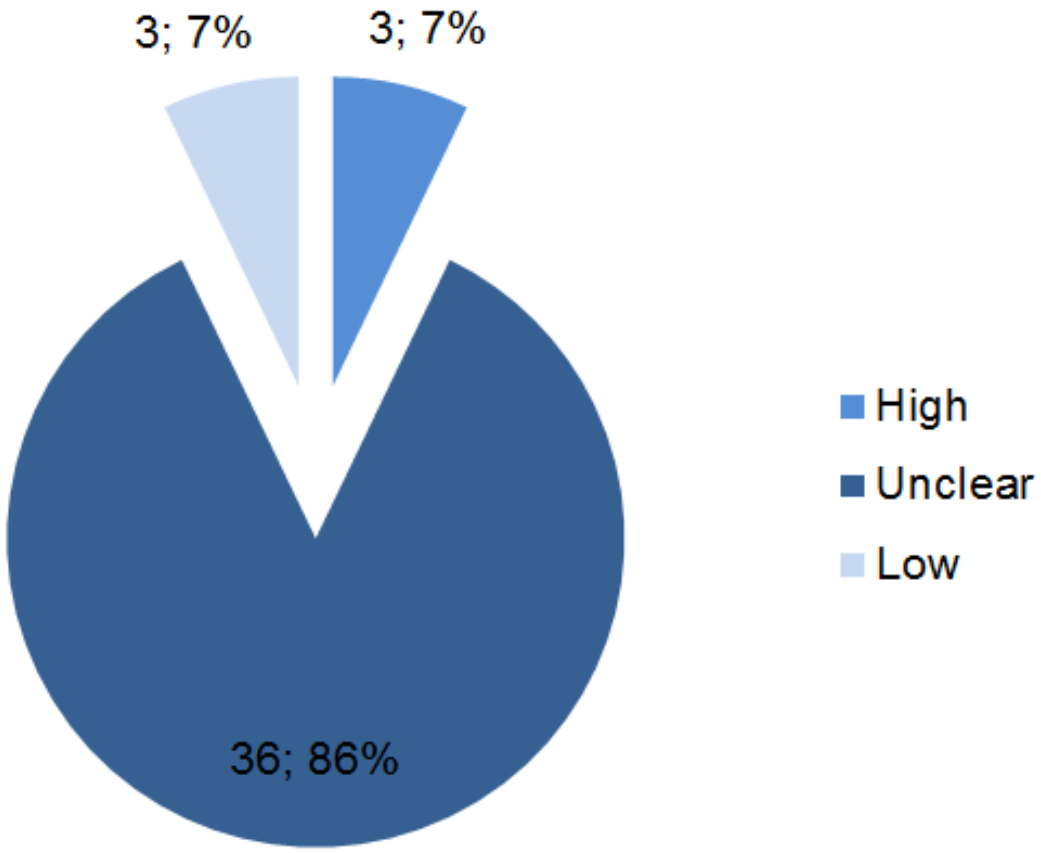
Definitions used	**Number of studies**
Date of randomization until death or last known date alive at the cutoff date	11
Not reported	9
Median OS: not specified	6
Time from the date of enrollment until the date of death due to any cause / Defined as the time from registration to death from any cause	3
Date of therapy began until death from any cause or censored at the date the patient was last known to be alive	2
Rate of 1-year OS	1
Days between the first study medication dose and the day of death, irrespective of the cause of death; median time to death	1
Time patient entered the study	1
From randomization until death or until date of last follow-up	1
From the initiation of the treatment to the date of death or the date of the last follow-up examination	1

Results – *definitions used for outcome domains*

Progression free survival (PFS) (30 of 42 studies)

Definitions used	Number of studies
Time from randomization to any type of progression or death from any cause	8
Not reported	7
Median PFS: not specified	3
6-month progression-free survival (PFS) rate/ PFS at 24 weeks	3
Time from registration to documentation of disease progression	2
Median PFS = interval of time since receiving first study drug to time of clinical or radiographic progression, or death due to any cause	1
Median PFS: time from random assignment to documented PD or death	1
Time elapsed from random assignment to start of new antitumor therapy , disease progression, or death	1
4-month progression free survival: time from the date of enrollment until the first date of documented disease progression	1
Time from randomization to the earliest date of documented PD, documented symptomatic deterioration, or death	1
From the date of randomization until the date of disease progression	1
The date of start of therapy to disease progression or death	1

Results – *Outcome reporting bias* (n=42 studies)



Discussion

- Outcomes are **partly not clearly stated and defined**
- Patient-reported outcomes (**PROs**) **were not reported**
- Unidimensional single items and composite scales vs. multidimensional composite scales vs. **quality indicators** – is the HOME Roadmap (Schmitt et al. 2014) (incl. COSMIN checklist) applicable for all future core outcome sets? Do we need a **methods group**?
- **Contents** (e.g. time frames; numerators and denominators) of measured outcome domains are **contradictory**
- Outcomes such as quality of life were not reported – How specific should a core outcome set for melanoma be (stage-specific?)

Many thanks for your attention.