institute for
Medical
Technology
Assessment

The value of real-world data in reimbursement decisions of oncology drugs

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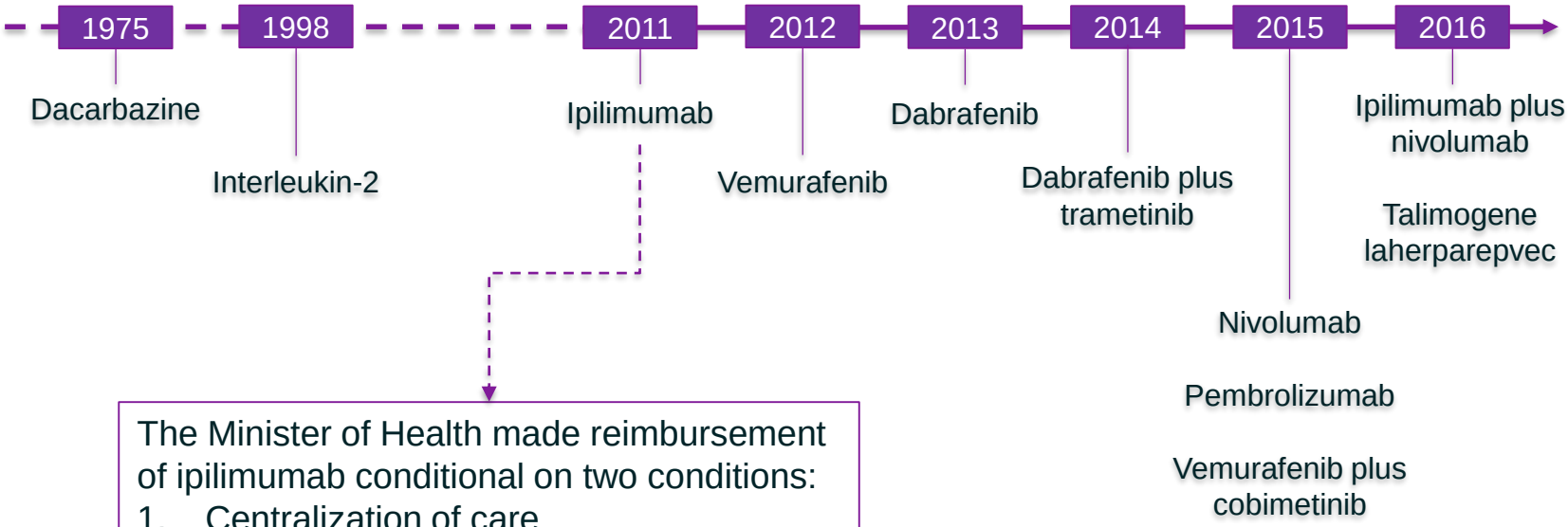
Reimbursement decisions of drugs in The Netherlands

Efficacy-effectiveness gap

	Clinical research	Clinical practice
Population		
Sources	Randomized controlled trial (RCT)	Real-world data Patient registry Electronic hospital records Administrative claim database
Clinical outcome	Efficacy	Effectiveness
Internal validity	↑	↓
External validity	↓	↑

Dutch Melanoma Treatment Registry



The Minister of Health made reimbursement of ipilimumab conditional on two conditions:

1. Centralization of care
2. Set-up of a nationwide, population-based registry: the **Dutch Melanoma Treatment Registry**

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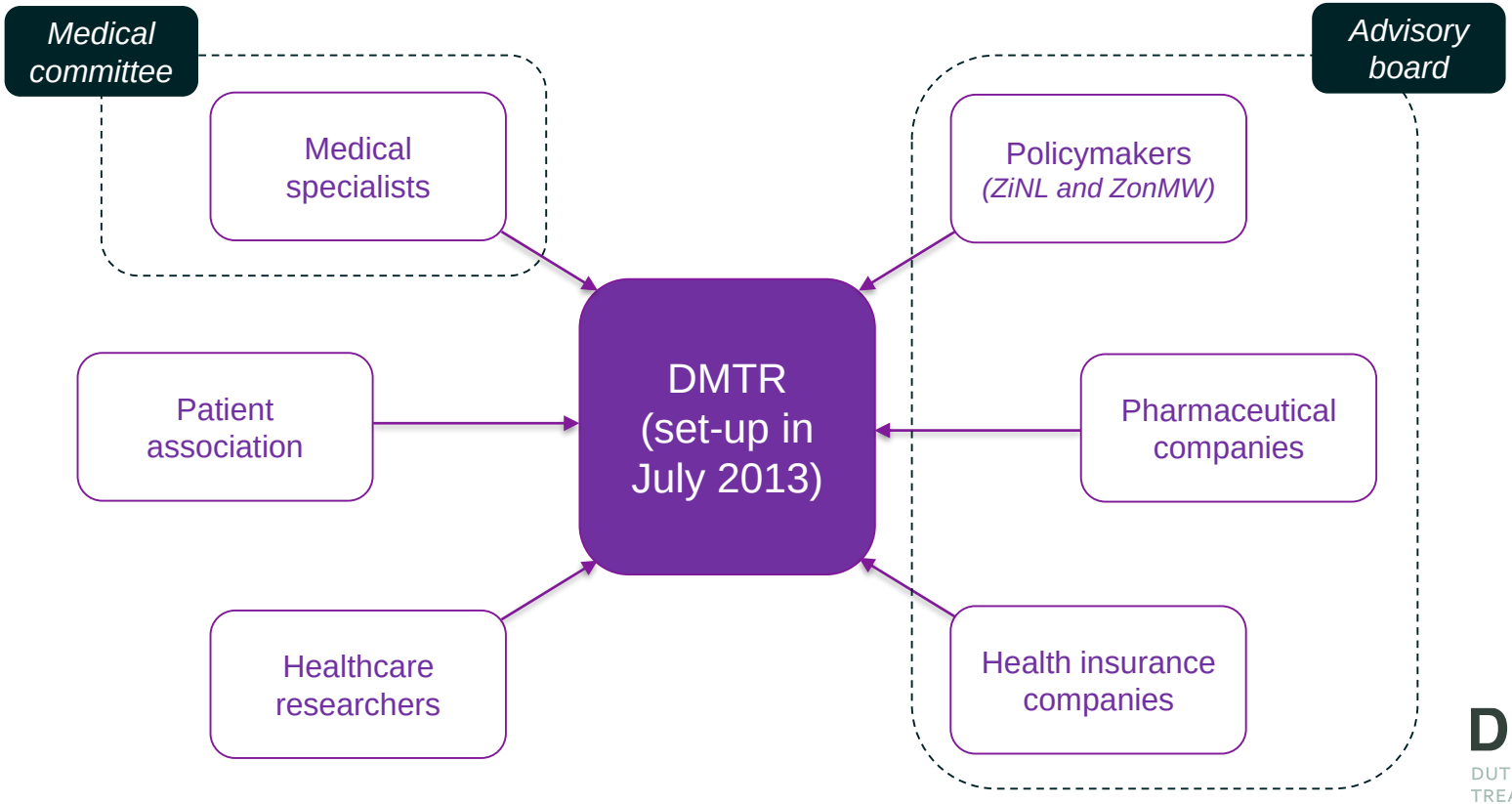
Set-up and structure of the DMTR



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Aims of the DMTR

1. Clinical auditing to improve melanoma care

2. Improving transparency of melanoma care using a set of quality indicators*

**Established by the medical specialists, patient association, and ZiNL*

3. Providing insights into real-world outcomes and costs

4. Creating a platform for research

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DMTR dataset

Patient population

All patients diagnosed with unresectable stage IIIC or IV melanoma

Data collection started in September 2013

- Retrospective cohort: July 2012 – June 2013
- Prospective cohorts: from July 2013 *(ongoing)*

Data

- Patient and tumor characteristics
- Treatment patterns
- Adverse events
- Clinical outcomes
- Healthcare resource use
- Quality of life (EQ-5D and FACT-M)
- Informal care (RUQ-M)
- Productivity losses (RUQ-M)

Example: real-world use, safety, and survival of ipilimumab[1]

Background

2010: phase III RCT[2,*] in previously-treated patients

**Ipilimumab (3 mg/kg) with or without gp100 versus gp100 alone*

2011: phase III RCT[3,*] in treatment-naive patients

**Ipilimumab (10 mg/kg) plus dacarbazine versus dacarbazine alone*

Reimbursement of ipilimumab became available in The Netherlands in 2012 for previously-treated patients and in 2014 for treatment-naive patients

[1]Jochems, Anouk, et al. "Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in The Netherlands." *Anti-cancer drugs* 29.6 (2018): 572-578.
[2]Hodi, F. Stephen, et al. "Improved survival with ipilimumab in patients with metastatic melanoma." *New England Journal of Medicine* 363.8 (2010): 711-723.
[3]Robert, Caroline, et al. "Ipilimumab plus dacarbazine for previously untreated metastatic melanoma." *New England Journal of Medicine* 364.26 (2011): 2517-2526.

Example: real-world use, safety, and survival of ipilimumab[1]

Aim

To evaluate the use, safety, and survival of ipilimumab in clinical practice

Patient population

All patients diagnosed with metastatic cutaneous melanoma who received ipilimumab in clinical practice *(registered in the DMTR between July 2012 and July 2015)*

807 patients received ipilimumab in clinical practice

- **344** (43%) treatment-naive patients
- **463** (57%) previously-treated patients

[1]Jochems, Anouk, et al. "Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in The Netherlands." *Anti-cancer drugs* 29.6 (2018): 572-578.

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Example: real-world use, safety, and survival of ipilimumab[1]

Baseline patient and tumor characteristics

	Treatment-naive patients (*n*=344)	Previously-treated patients (*n*=463)
Age, *yr*		
Median (95% CI)	64 (41-79)	60 (38-76)
Gender, *n* (%)		
Male	213 (62%)	264 (57%)
Female	131 (38%)	199 (43%)
Performance status (ECOG), *n* (%)		
0	213 (62%)	258 (56%)
1	89 (26%)	129 (28%)
≥2	12 (3%)	14 (3%)
Unknown	30 (9%)	62 (13%)
LDH level (U/L), *n* (%)		
Normal (≤250)	261 (76%)	334 (72%)
Elevated (>250)	72 (21%)	119 (26%)
Unknown	11 (3%)	10 (2%)
AJCC M-stage, *n* (%)		
M0-M1b	95 (28%)	91 (20%)
M1c	243 (71%)	365 (79%)
Unknown	6 (2%)	7 (2%)
Brain metastases, *n* (%)		
No	264 (77%)	329 (71%)
Yes	75 (22%)	123 (27%)
Unknown	5 (1%)	11 (2%)

In RCT[3]: 58 years

Excluded in RCT[3]

In RCT[2]: 47%

A real-world study by Kelderman *et al.* (2014) showed that patients with a normal LDH level are more likely to benefit from ipilimumab[4]

In RCTs: 63%[3] and 61%[2]

In RCT[3]: 57%

Excluded in RCT[3]

In RCT[2]: 21%

[1]Jochems, Anouk, et al. "Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in The Netherlands." *Anti-cancer drugs* 29.6 (2018): 572-578.
[2]Hodi, F. Stephen, et al. "Improved survival with ipilimumab in patients with metastatic melanoma." *New England Journal of Medicine* 363.8 (2010): 711-723.
[3]Robert, Caroline, et al. "Ipilimumab plus dacarbazine for previously untreated metastatic melanoma." *New England Journal of Medicine* 364.26 (2011): 2517-2526.
[4]Kelderman, Sander, et al. "Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma." *Cancer Immunology, Immunotherapy* 63.5 (2014): 449-458.

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Example: real-world use, safety, and survival of ipilimumab[1]

Drug use

	Treatment-naive patients (*n*=344)	Previously-treated patients (*n*=463)
Number of ipilimumab cycles, *n* (%)		
1	17 (5%)	56 (12%)
2	45 (13%)	66 (14%)
3	42 (12%)	55 (12%)
4	240 (70%)	286 (62%)
Reason for premature discontinuation, *n* (%)		
No premature discontinuation	240 (70%)	286 (62%)
Planned in advance	3 (1%)	5 (1%)
Progression	49 (14%)	117 (25%)
Toxicity	45 (13%)	41 (9%)
Patient choice	1 (0%)	1 (0%)
Death	4 (1%)	9 (2%)
Other	2 (1%)	2 (0%)
Unknown	0 (0%)	2 (0%)
Number of systemic treatments after ipilimumab, *n* (%)		
0	168 (49%)	258 (56%)
1	132 (38%)	132 (29%)
≥2	44 (13%)	73 (16%)

In RCT[3]: 37%

In RCT[2]: 64%

In RCT[3]: 46% progression and 36% toxicity

Most patients in the RCT received chemotherapy after ipilimumab, whereas most patients in our real-world study received one of the new drugs

In RCT[3]: 55%

[1]Jochems, Anouk, et al. "Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in The Netherlands." *Anti-cancer drugs* 29.6 (2018): 572-578.
[2]Hodi, F. Stephen, et al. "Improved survival with ipilimumab in patients with metastatic melanoma." *New England Journal of Medicine* 363.8 (2010): 711-723.
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Example: real-world use, safety, and survival of ipilimumab[1]

Grade 3/4 immune-related adverse events

	Treatment-naive patients (*n*=344)	Previously-treated patients (*n*=463)
Number of adverse events, *n* (%)		
0	245 (71%)	366 (79%)
1	82 (24%)	78 (17%)
≥2	17 (5%)	19 (4%)
Adverse events reported, *n* (%)		
Adrenal insufficiency	5 (1%)	10 (2%)
Bone marrow suppression	2 (1%)	3 (1%)
Colitis	55 (16%)	51 (11%)
Dermatologic	12 (3%)	4 (1%)
Gastrointestinal perforation	1 (0%)	1 (0%)
Hepatic	3 (1%)	9 (2%)
Hypophysitis	20 (6%)	18 (4%)
Neurologic	2 (1%)	3 (1%)
Thyroiditis	9 (3%)	6 (1%)
Uveitis	2 (1%)	1 (0%)
Other	9 (3%)	19 (4%)

In RCT[3]: 42%

In RCT[2]: 15%

Number of treatment-related deaths:
- Clinical practice[1]: *n*=0
- RCT previously-treated patients[2]: *n*=0
- RCT treatment-naive patients[3]: *n*=4

[1]Jochems, Anouk, et al. "Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in The Netherlands." *Anti-cancer drugs* 29.6 (2018): 572-578.
[2]Hodi, F. Stephen, et al. "Improved survival with ipilimumab in patients with metastatic melanoma." *New England Journal of Medicine* 363.8 (2010): 711-723.
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Example: real-world use, safety, and survival of ipilimumab[1]

Overall survival

	Treatment-naive patients (*n*=344)	Previously-treated patients (*n*=463)
Follow-up, *mo*		
Median (95% CI)	11.5 (10.5-12.4)	20.9 (17.4-22.7)
Overall survival, *mo*		
Median (95% CI)	14.3 (11.6-16.7)	8.7 (7.6-9.6)
Survival rates, %		
One-year	54%	38%
Two-year	39%	24%

In RCT[3]: 11.2 months

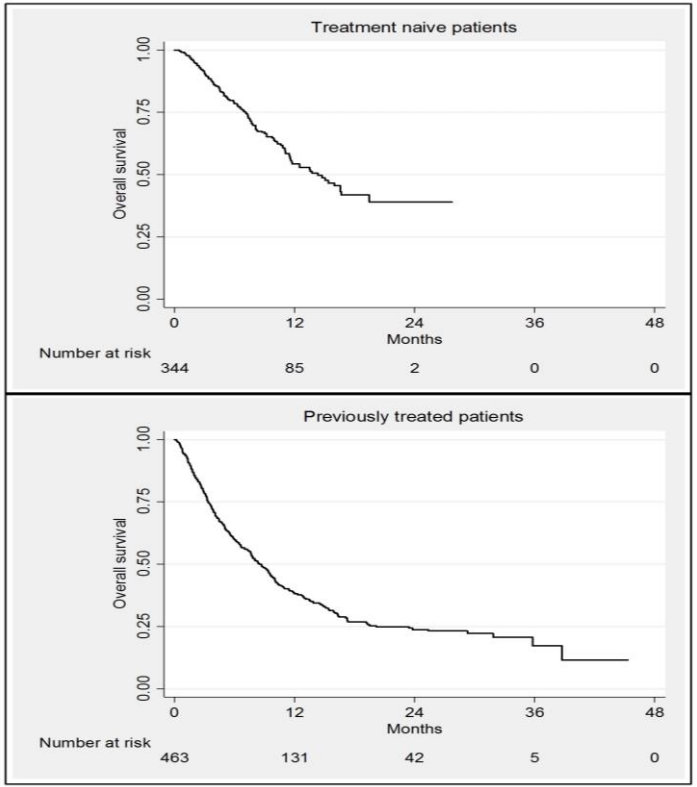
In RCT[3]: 47%

In RCT[3]: 29%

In RCT[2]: 10.1 months

In RCT[2]: 24%

In RCT[2]: 46%



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Value of real-world data in cost(-effectiveness) analyses

Resource use in a RCT may differ from resource use in clinical practice

Cost(-effectiveness) estimates based on real-world data will provide generalizable insights into the costs, cost drivers, and cost-effectiveness in clinical practice

The costs(-effectiveness) can not only be estimated for one treatment, but also for treatment sequences

A disease model based on real-world data may facilitate the comparison of the cost-effectiveness of different treatments and treatment sequences

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Challenges for using real-world data

Timelines

- Real-world outcomes may not be available at the time of the initial reimbursement decision

Correcting for confounders

- The effect of confounders is not eliminated in clinical practice
- Propensity score matching and multivariate regression analysis are methods to correct for confounders

Missing data

- The number of missing values often depends on the number of variables included in the analysis
- Complete case analysis, single imputation, and multiple imputation are methods to correct for missing data

Conclusion

“Real-world data can complement RCT data,

and may bridge the gap between clinical research and clinical practice”

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