La ricerca clinica e traslazionale nel carcinoma polmonare

Real World Data

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Disclosures

Dr Alessio Cortellini

Within the last 2 years I received

Grants for consultancies/advisory boards: MSD, OncoC4, Roche, Regeneron, BMS, Amgen, Daiichi Sankyo, Astrazeneca, Access Infinity, Ardelis Health, Alpha Sight, Capvision, Techspert.

Speaker fees: Astrazeneca, Roche, Pierre-Fabre, MSD, SANOFI/Regeneron.

Writing/Editorial activity: BMS, MSD.

Travel support: Sanofi, MSD, Roche

Funding (to institution): International Association for the Study of Lung Cancer

AGENDA

- Real-world evidence (RWE): definition and characteristics.
- RWE examples: “effectiveness” study, special/underrepresented populations, new insight/hypothesis.
- Pitfalls of RWE, beware of selection bias.
- RWE, decision making and health technology assessment (HTA).

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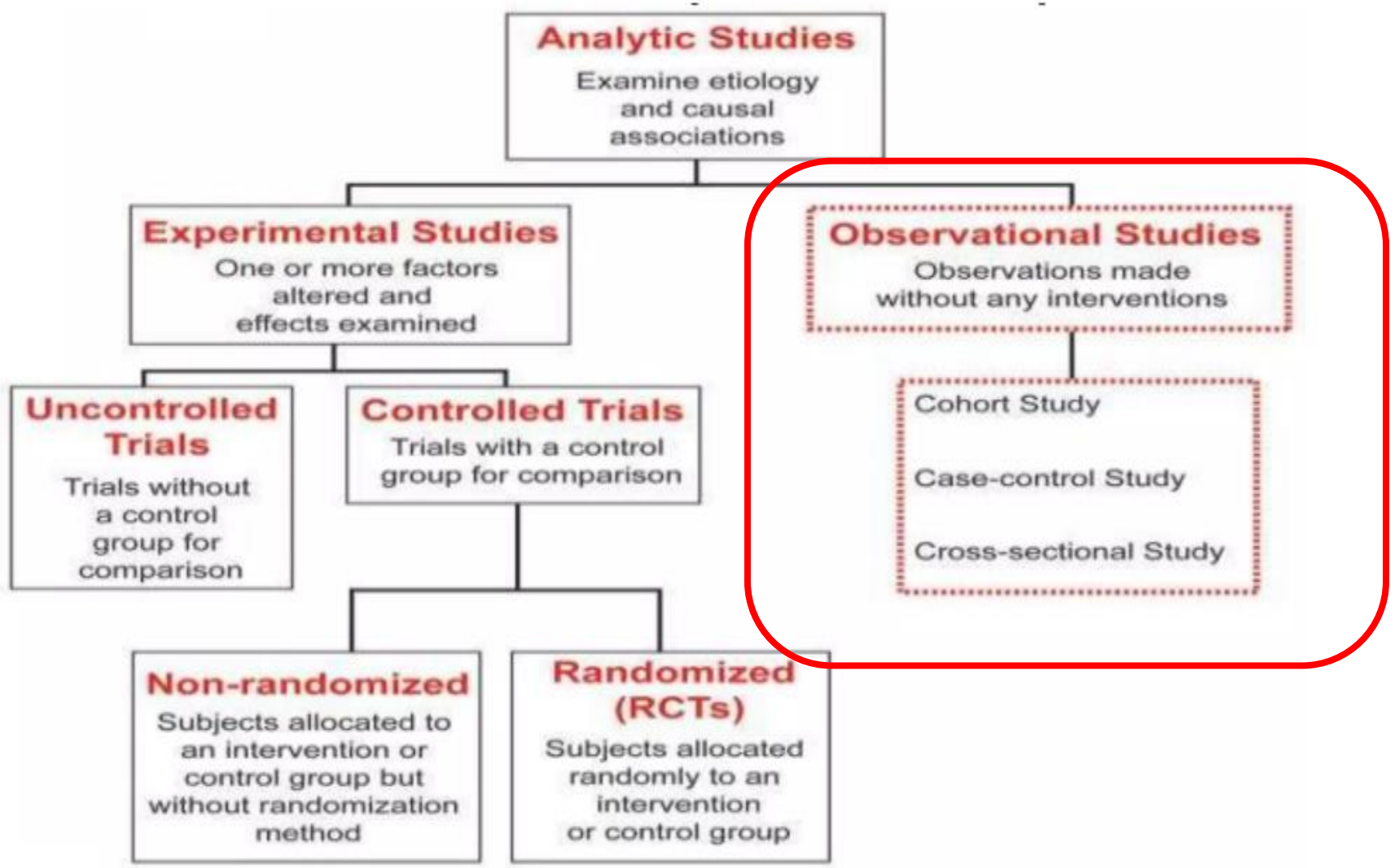
Interventional vs Observational



RWE: definition and Key characteristics

- Health care information derived from multiple sources outside traditional clinical trial settings (HER, claims and billing data, registries).

- Complement to Traditional Trials and provides insights that are often more generalizable, addressing limitations related to the controlled environment and selected populations ("effectiveness" vs efficacy).

- It can inform therapeutic development, quality improvement, safety surveillance, generate data on special populations.

- Can generate valuable insights and new research hypothesis.

- Proper use of RWE requires rigorous data management and careful methodological approaches: challenges such as selection bias, data quality concerns, and confounding factors to ensure robust, reliable conclusions.

Rachel E. Sherman; NEJM 2016

RWE: definition and Key characteristics

- **Primary:** data collected for a specific aim/hypothesis (mainly prospective)

- **Secondary:** data collected without a specific aim or for a different aim (only retrospective).

- Can be “descriptive” (cannot be generalized) or **analytical** (with a hypothesis and a group of interest).

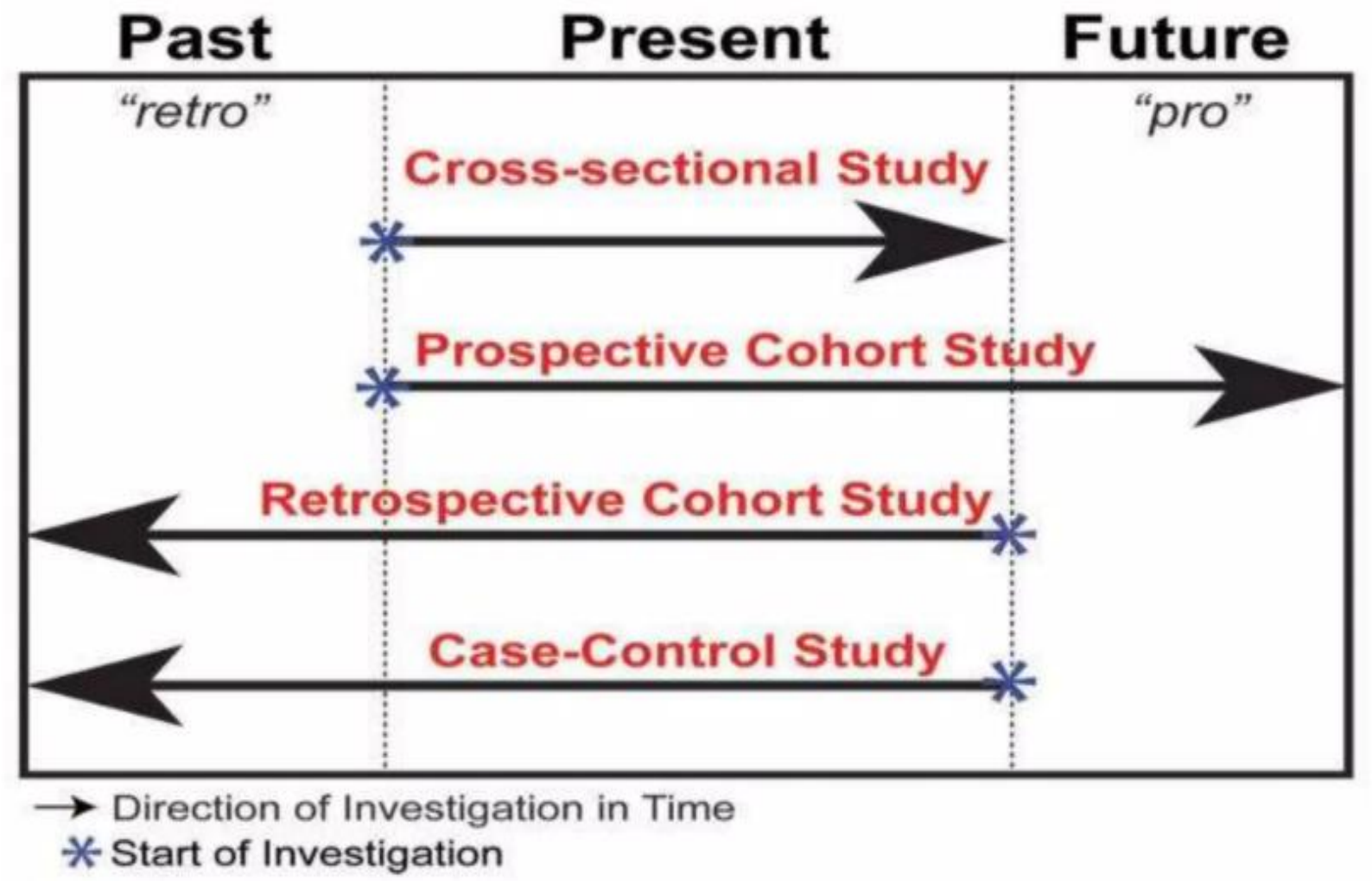
- Case-control study: two existing groups differing in outcomes are identified and compared on the basis of some supposed causal attribute.

- Cross-sectional study: involves data collection from a population, or a representative subset, at one specific point in time.

- Longitudinal study: co-relational research study that involves repeated observations of the same variables over long periods of time.

- Cohort study: a particular form of longitudinal study where a group of patients is closely monitored over a span of time.

Temporal design of observational studies



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RWE & effectiveness: the “pembro story”

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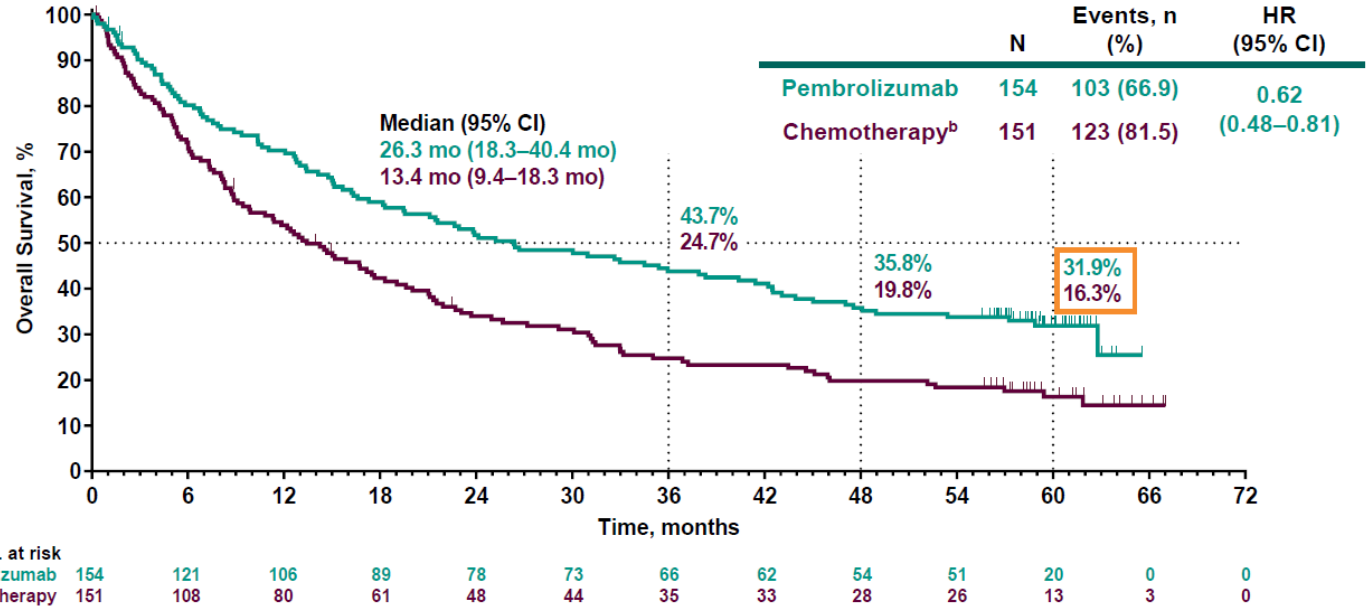
Overall Survival[a]



[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

KN024 exclusion criteria

- *EGFR* mutation and *ALK* translocations
- ECOG performance status of ≥2
- Unstable CNS metastases*
- Any medical condition requiring immune-suppressant
- Pre-existing Autoimmune Disease
- Steroids (pred >10 mg)
- Active ILD
- Life expectancy shorter than 3 months
- HIV/ Viral Hep / Tubercolosis

*Stable brain mets were allowed

Brahmer JL ESMO 2020; 1. Reck M, et al. *J Clin Oncol* 2021; 39(21):2339–49. 2. Reck M, et al. *J Clin Oncol* 2019; 37(7):537–46.

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RWE - Italian experience

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Real-world cohort from 34 institutions (Italy, Switzerland, UK)

- Patients treated from Jan 2017 to Oct 2019.
- 1st data lock: Feb 2020
- 2nd data lock: Set 2020

Cancer Immunology, Immunotherapy (2020) 69:2209–2221
https://doi.org/10.1007/s00262-020-02613-9

ORIGINAL ARTICLE

Clinicopathologic correlates of first-line pembrolizumab effectiveness in patients with advanced NSCLC and a PD-L1 expression of ≥ 50%

Alessio Cortellini[1,2] · Marcello Tiseo[3,4] · Giuseppe L. Banna[5] · Federico Cappuzzo[6] · Joachim G. J. V. Aerts[7] · Fausto Barbieri[8] · Raffaele Giusti[9] · Emilio Bria[10,11] · Diego Cortinovis[12] · Francesco Grossi[13] · Maria R. Migliorino[14] · Domenico Galetta[15] · Francesco Passiglia[16] · Daniele Santini[17] · Rossana Berardi[18] · Alessandro Morabito[19] · Carlo Genova[20] · Francesca Mazzoni[21] · Vincenzo Di Noia[22] · Diego Signorelli[23] · Alessandro Tuzi[24] · Alain Gelibter[25] · Paolo Marchetti[9,25,26] · Marianna Macerelli[27] · Francesca Rastelli[28] · Rita Chiari[29] · Danilo Rocco[30] · Stefania Gori[31] · Michele De Tursi[32] · Giovanni Mansueto[33] · Federica Zoratto[34] · Matteo Santoni[35] · Marianna Tudini[36] · Erika Rijavec[13] · Marco Filetti[9] · Annamaria Catino[15] · Pamela Pizzutilo[15] · Luca Sala[12] · Fabrizio Citarella[17] · Russano Marco[17] · Mariangela Torniai[18] · Luca Cantini[7,18] · Giada Targato[27] · Vincenzo Sforza[19] · Olga Nigro[24] · Miriam G. Ferrara[10,11] · Ettore D'Argento[10] · Sebastiano Buti[3] · Paola Bordi[3] · Lorenzo Antonuzzo[21] · Simona Scodes[6] · Lorenza Landi[6] · Giorgia Guaitoli[8] · Cinzia Baldessari[8] · Luigi Della Gravara[30] · Maria Giovanna Dal Bello[20] · Robert A. Belderbos[7] · Paolo Bironzo[16] · Simona Carnio[16] · Serena Ricciardi[14] · Alessio Grieco[14] · Alessandro De Toma[23] · Claudia Proto[23] · Alex Friedlaender[37] · Ornella Cantale[5] · Biagio Ricciuti[38,39] · Alfredo Addeo[37] · Giulio Metro[40] · Corrado Ficorella[1,2] · Giampiero Porzio[1,2]

1026 patients

- 51.6% elderly (≥ 70 anni)
- 10.3% Never smokers
- Poor PS: *17% PS2 e 0.4% PS3*
- 24.2% Squamous histology
- 17.6% CNS mets
- 31.8% Bone mets
- 15.4% Liver mets
- 24.5% Baseline steroids, including high dose *(>10 mg pred or eq/day)*
- 16.4% received palliative RT within prior 30 days (mostly to the bone)
- 6.9% *EGFR* unknown
- 8.2% *ALK* unknown

Cortellini A, et al. Cancer Immunol Immunother 2020

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RWE - Italian experience

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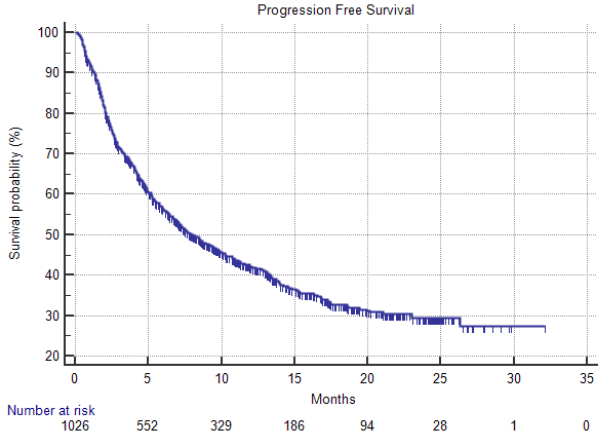
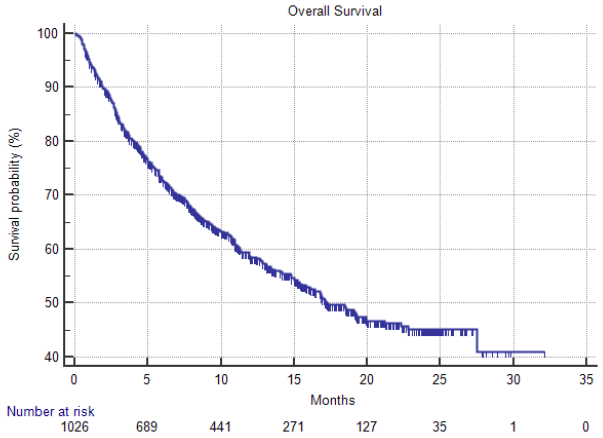
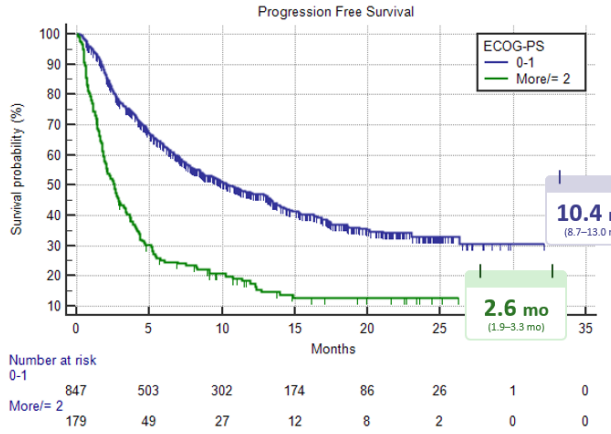
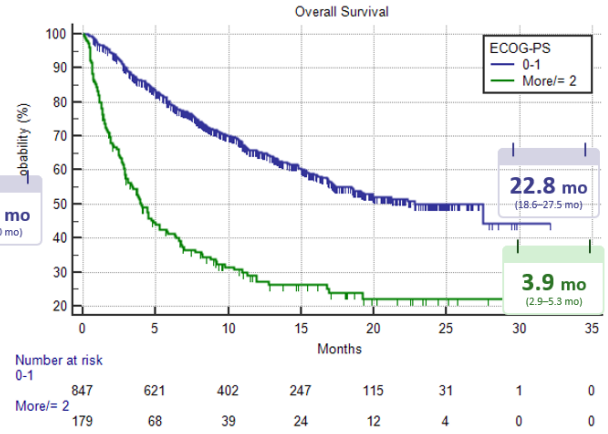
PFS 7.9 months (95%CI: 6.9-9.5)



OS 17.2 months (95%CI: 15.3-22.3)







Median FUP: 22.7 months

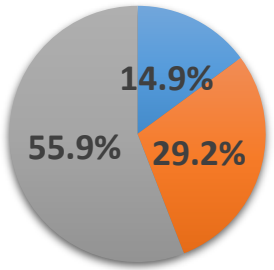
Updated study population:
974 patients

Did not experience disease progression
•**296 patients**

678 patients

~56%

Did not received further treatments
•**379 patients**



Pembrolizumab ByPD Switched approach

Cortellini A, et al. Cancer Immunol Immunother 2020; Cortellini A, et al. Eur J of Cancer 2021

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RWE - 5years outcome

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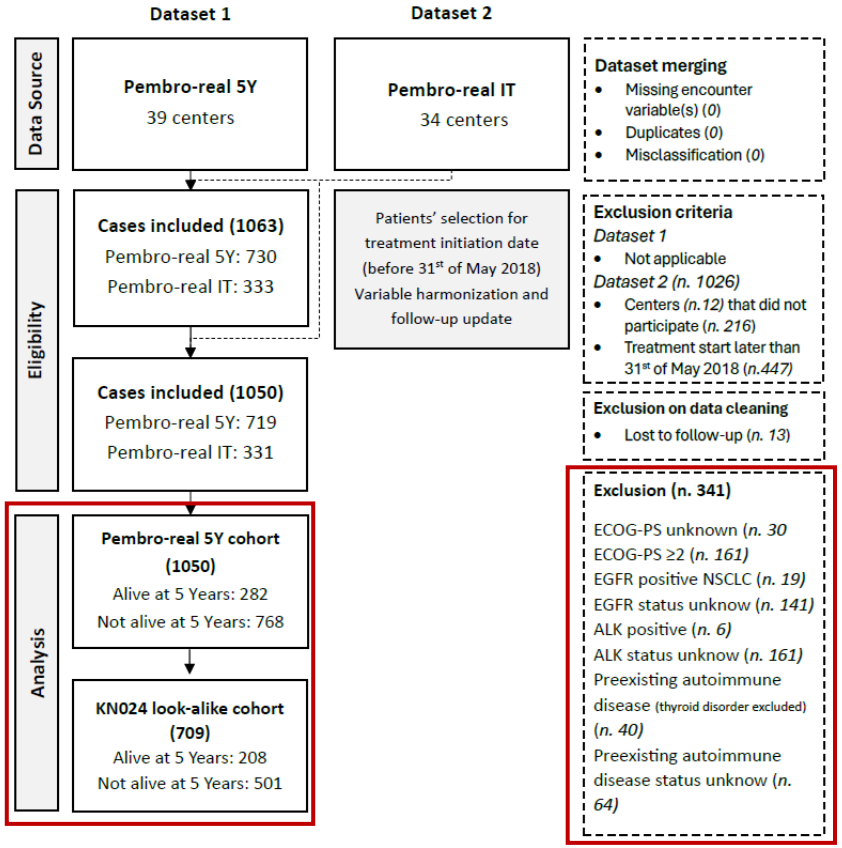

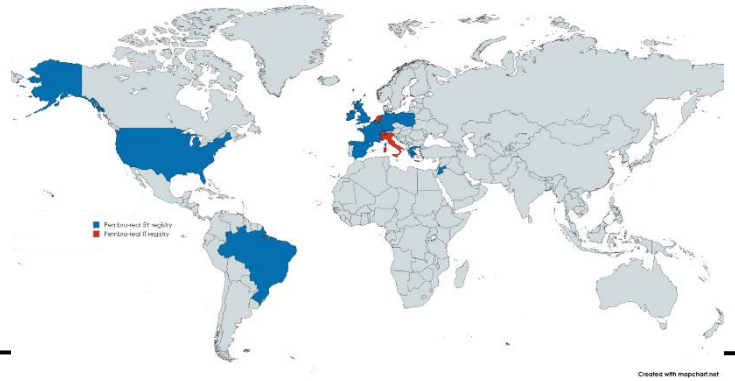

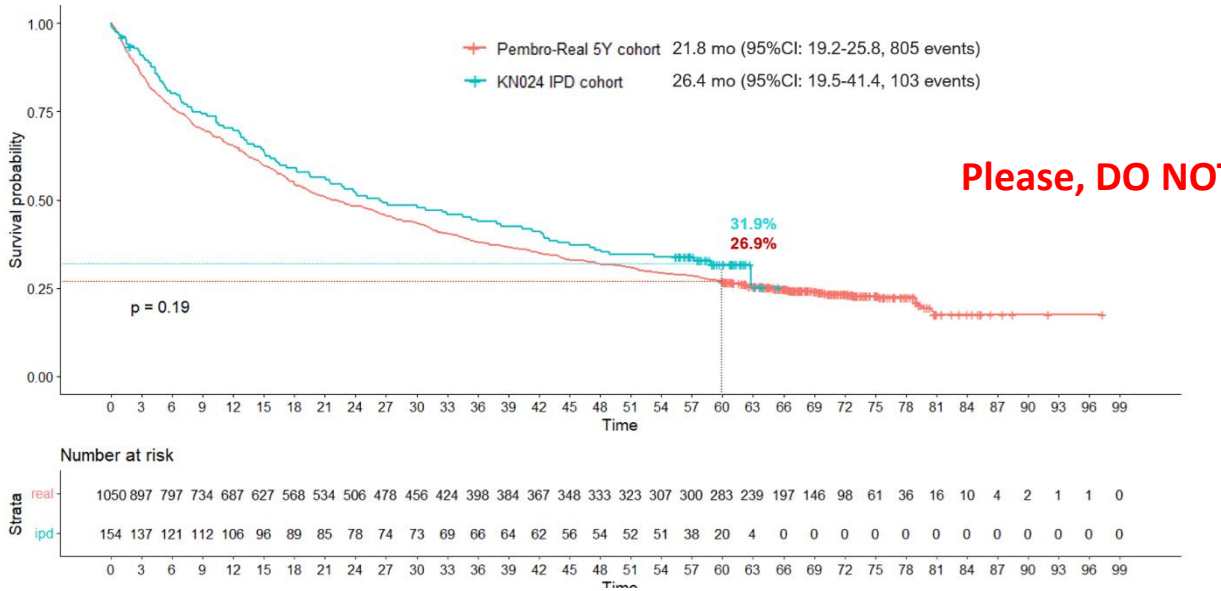

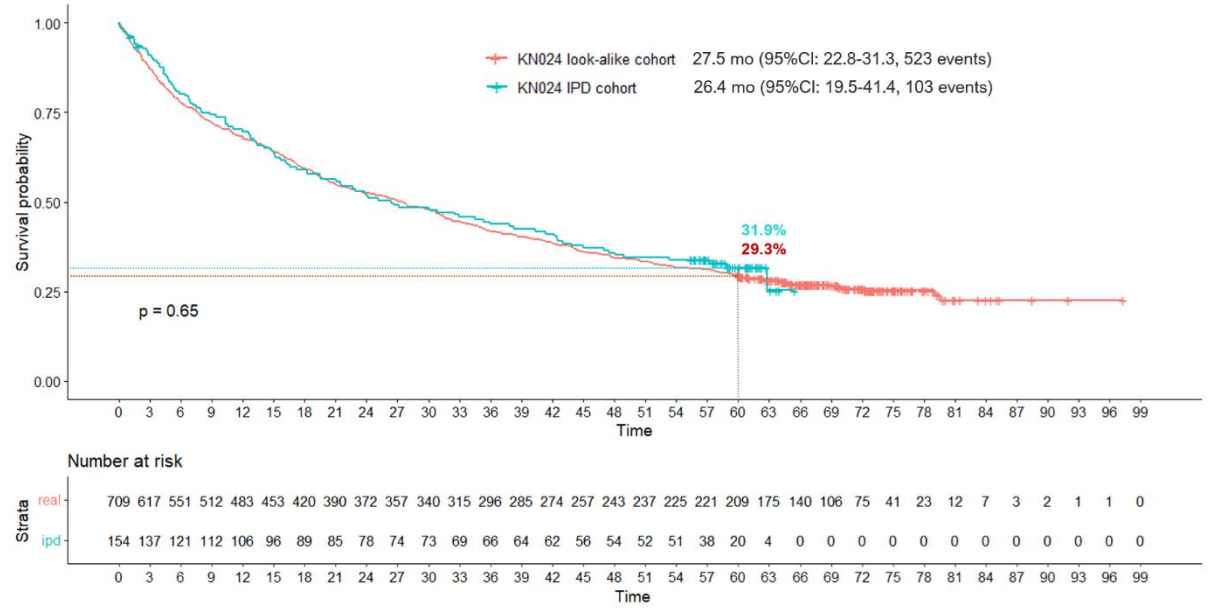

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RWE - 5years outcome

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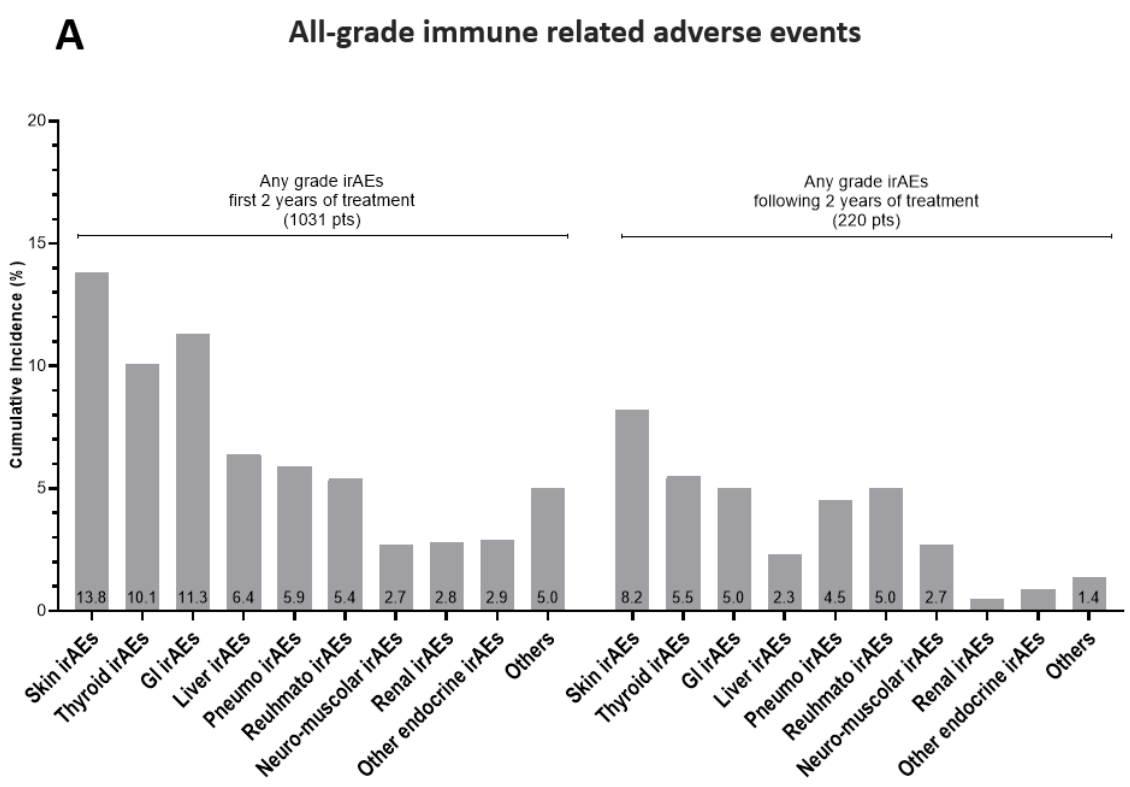

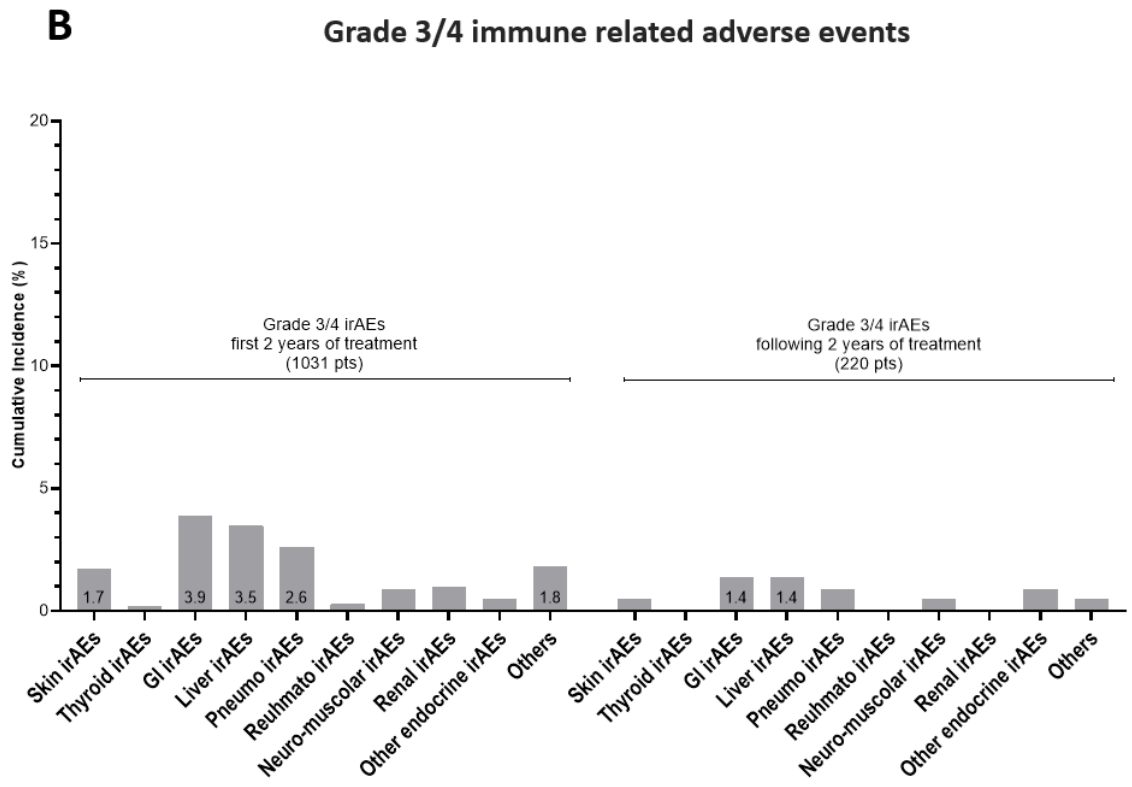

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RWE & safety in special populations: ICI in AIDs

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The Oncologist®

Immuno-Oncology

Clinical Outcomes of Patients with Advanced Cancer and Pre-Existing Autoimmune Diseases Treated with Anti-Programmed Death-1 Immunotherapy: A Real-World Transverse Study

Alessio Cortellini,[a,b] Sebastiano Buti,[c] Daniele Santini,[d] Fabiana Perrone,[c] Raffaele Giusti,[e] Marcello Tiseo,[c] Melissa Bersanelli,[c] Maria Michiara,[c] Antonino Grassadonia,[f] Davide Brocco,[g] Nicola Tinari,[f] Michele De Tursi,[f] Federica Zoratto,[h] Enzo Veltri,[h] Riccardo Marconcini,[i] Francesco Malorgio,[j] Carlo Garufi,[j] Marco Russano,[d] Cecilia Anesi,[d] Tea Zeppola,[d] Marco Filetti,[e] Paolo Marchetti,[e,k] Andrea Botticelli,[e] Gian Carlo Antonini Cappellini,[k] Federica De Galitiis,[k] Maria Giuseppa Vitale,[l] Roberto Sabbatini,[l] Sergio Bracarda,[m] Rossana Berardi,[n] Silvia Rinaldi,[n] Marianna Tudini,[o] Rosa Rita Silva,[o] Annagrazia Pireddu,[p] Francesco Atzori,[p] Rita Chiari,[q] Biagio Ricciuti,[q] Daniela Iacono,[r] Maria Rita Migliorino,[r] Antonio Rossi,[s] Giampiero Porzio,[a,b] Katia Cannita,[b] Valeria Ciciarelli,[t,b] Maria Concetta Fargnoli,[t,b] Paolo Antonio Ascierto,[u] Corrado Ficorella[a,b]

Table 2. List of pre-existing autoimmune disease and immunosuppressant treatments

AIDs and treatments	*n* (%)	Specifications
Pre-existing AIDs	85	
Thyroid disorders	51 (60)	10 GBD, 51 hypothyroidism after AIT
Dermatologic	14 (16.4)	11 PSO, 2 vitiligo, 1 lichen planus
Rheumatologic	10 (11.8)	2 PMR, 2 SLE, 4 AR, 1 vasculitis
Gastrointestinal/hepatic	4 (4.7)	3 CD, 1 PSC
Neurologic	1 (1.2)	1 AI optic neuritis
Nephrologic	1 (1.2)	1 membranous glomerulonephritis
Multiple site	4 (4.7)	1 GBS and PSO, 1 MG and AIT, 1 PSO and AIT, 1 scleroderma and AIT
Clinically active AIDs	15	
Dermatologic	6 (40)	6 PSO
Rheumatologic	6 (40)	4 RA, 2 PMR
Gastrointestinal	2 (13.3)	2 CD
Multiple site	1 (6.6)	1 scleroderma and AIT
Treatment of AIDs		
Corticosteroids	11 (73.3)	4 PSO, 1 scleroderma and AIT, 3 RA, 2 PMR, 1CD
Other immunosuppressants	3 (20)	1 RA, 2 PSO
Combinations	1 (6.6)	1 CD

Abbreviations: AIDs, autoimmune diseases; AIT, autoimmune thyroiditis; CD, Crohn's disease; GBD, Graves-Basedow disease; GBS, Guillain-Barre syndrome; MG, myasthenia gravis; PMR, polymyalgia rheumatica; PSC, primary sclerosing cholangitis; PSO, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Cortellini A, et al. Oncologist 2019

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RWE & safety in special populations: ICI in AIDs

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irAEs of any grade—univariate analysis			
Variable (comparator)	Events ratio	Incidence (95% CI)	*p* value
Overall	322/751	42.9 (38.3–47.8)	
Pre-existing AIDs			
Yes	56/85	65.9 (49.7–85.5)	<.0001
No	266/666	39.9 (35.2–45.0)	
Inactive AID (No AIDs)	45/70	64.3 (46.8–86.0)	.0001
Active AID (No AIDs)	11/15	73.3 (44.9–92.2)[a]	.0402

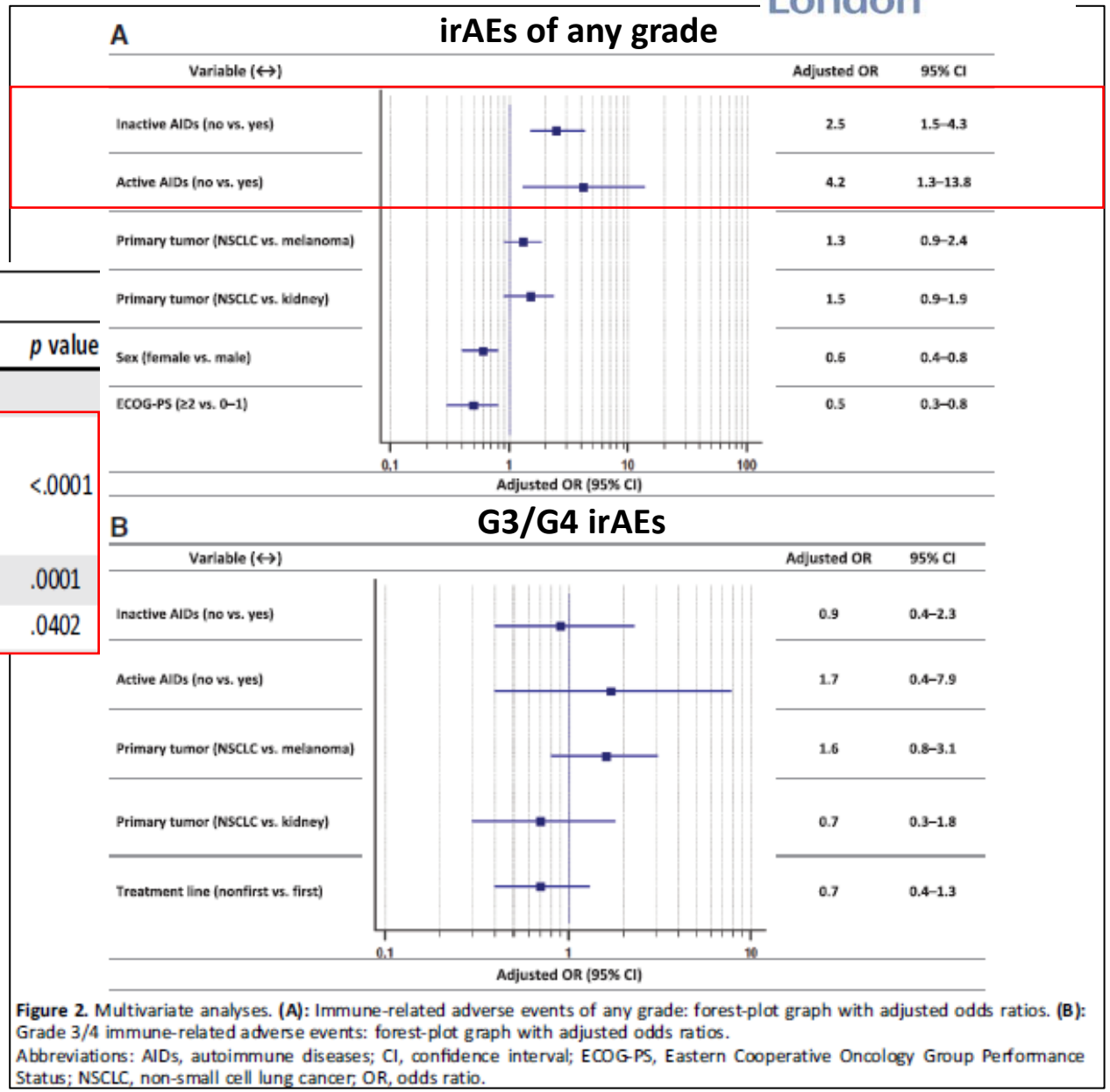
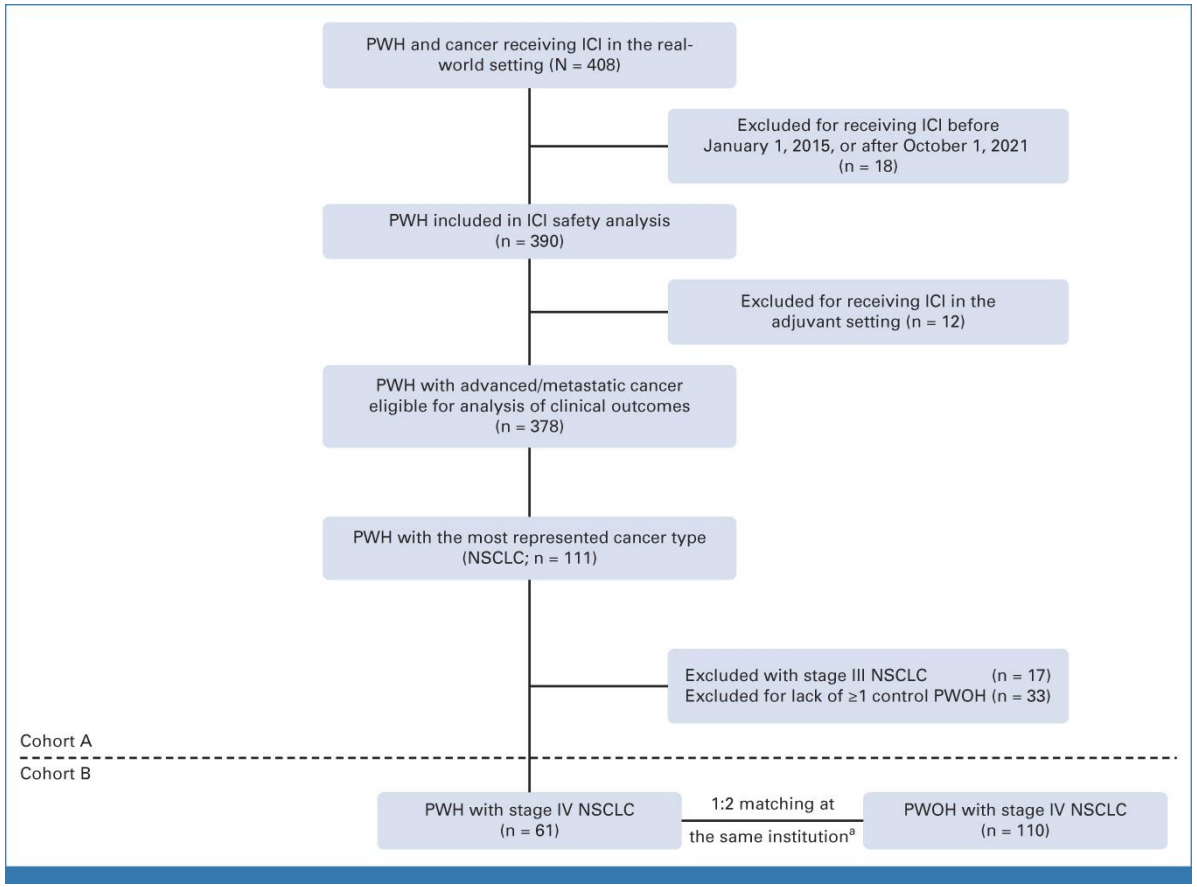
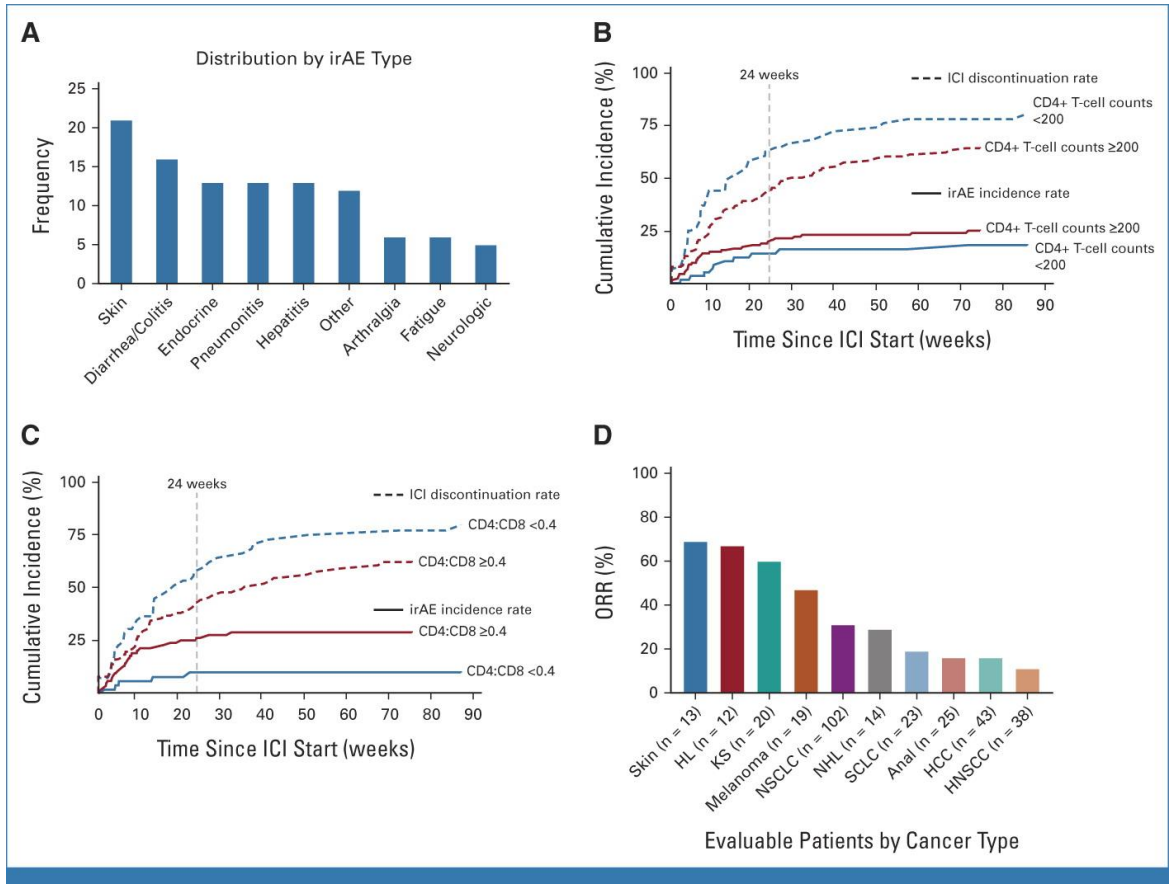


Figure 2. Multivariate analyses. **(A):** Immune-related adverse events of any grade: forest-plot graph with adjusted odds ratios. **(B):** Grade 3/4 immune-related adverse events: forest-plot graph with adjusted odds ratios.
Abbreviations: AIDs, autoimmune diseases; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; OR, odds ratio.

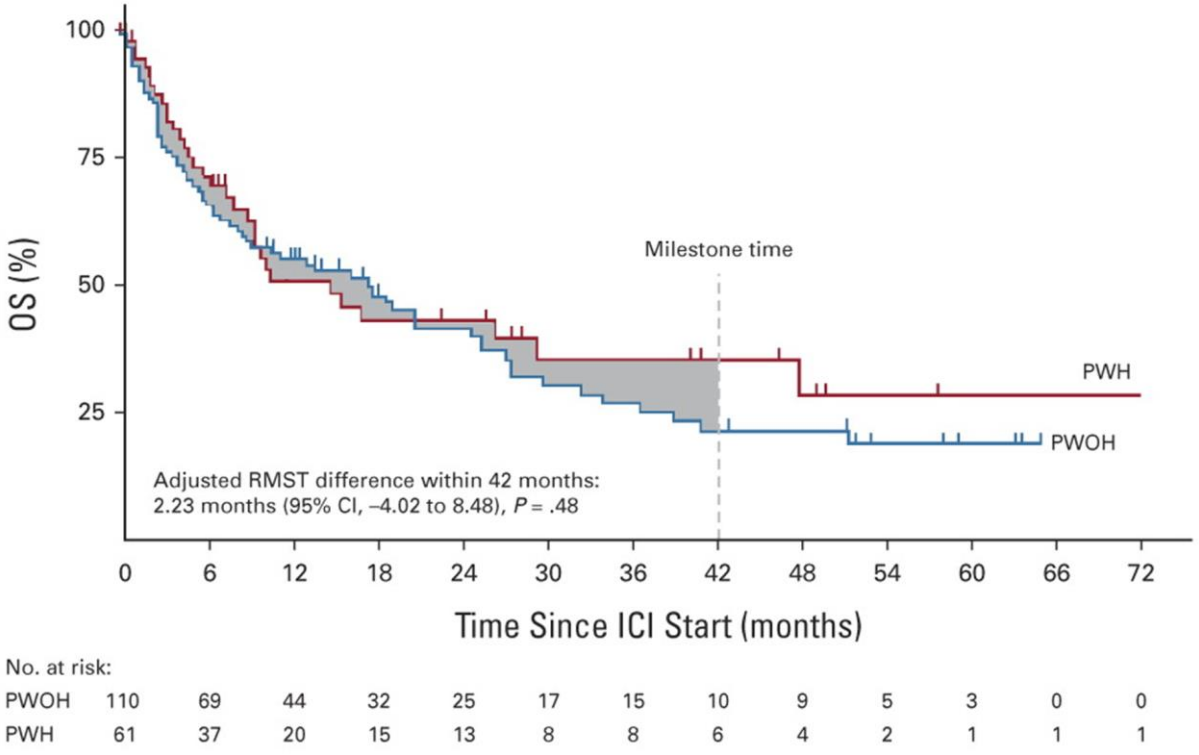
Cortellini A, et al. Oncologist 2019

RWE & safety in special populations: HIV



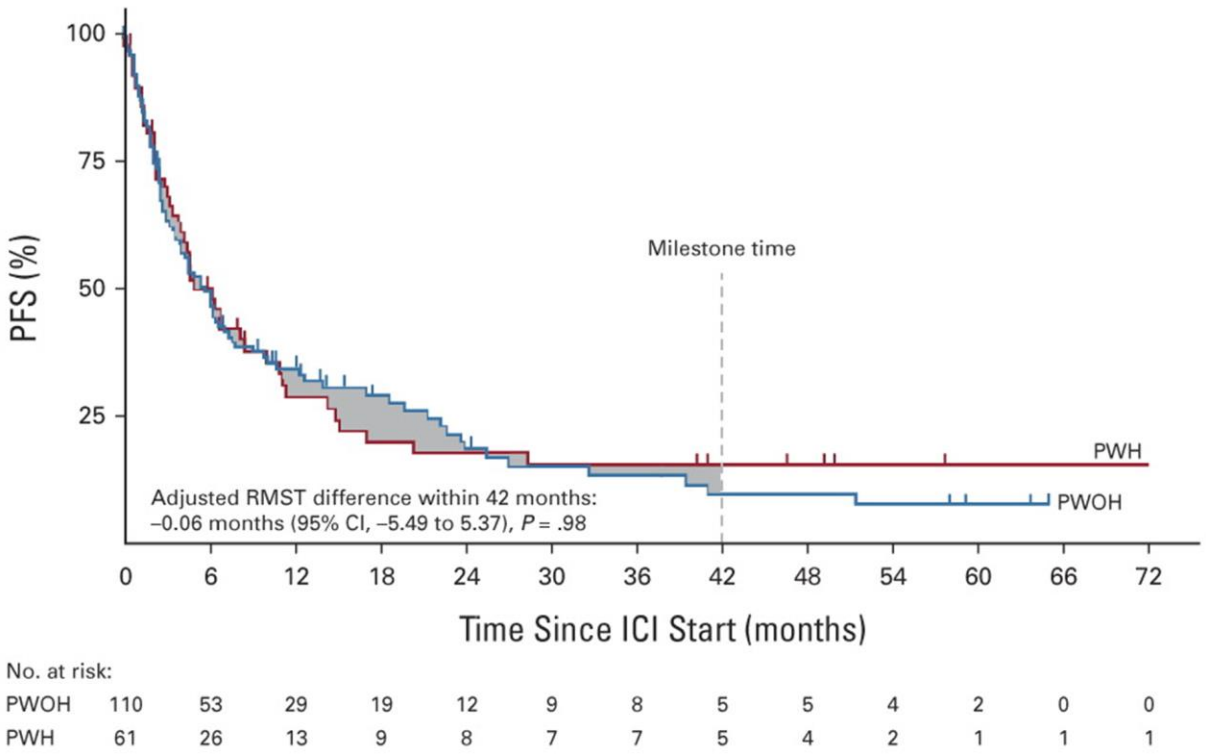


RWE & safety in special populations: HIV



No. at risk:

PWOH	110	69	44	32	25	17	15	10	9	5	3	0	0
PWH	61	37	20	15	13	8	8	6	4	2	1	1	1



No. at risk:

PWOH	110	53	29	19	12	9	8	5	5	4	2	0	0
PWH	61	26	13	9	8	7	7	5	4	2	1	1	1

El Zarif T, J Clin Oncol 2023

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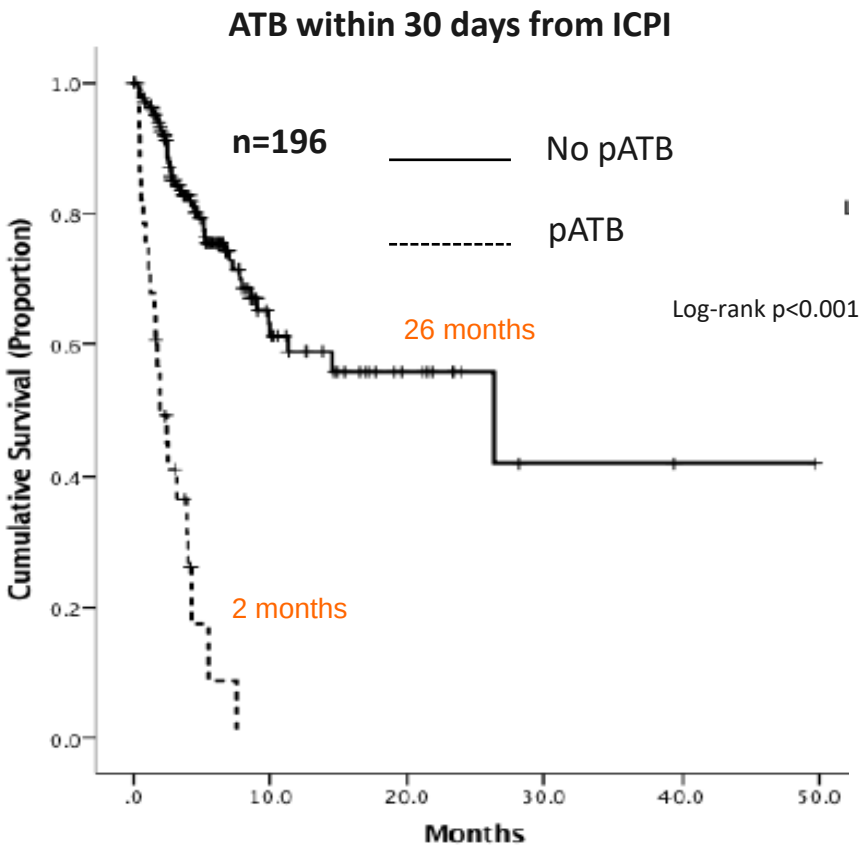
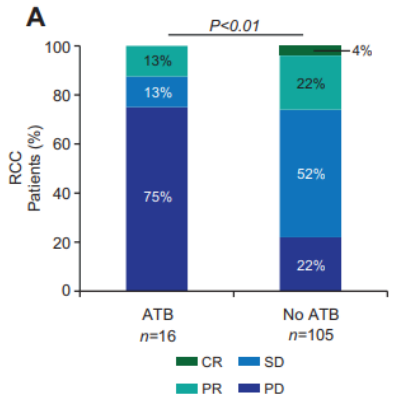
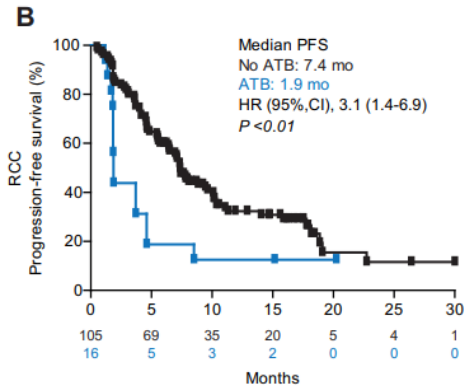
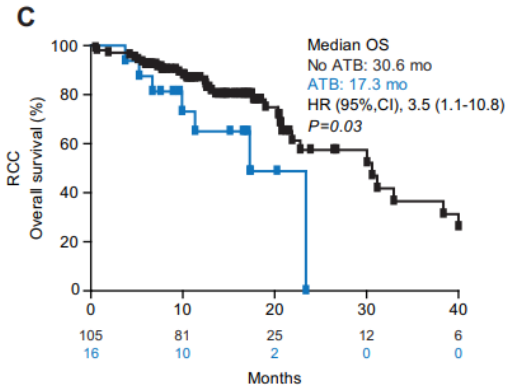
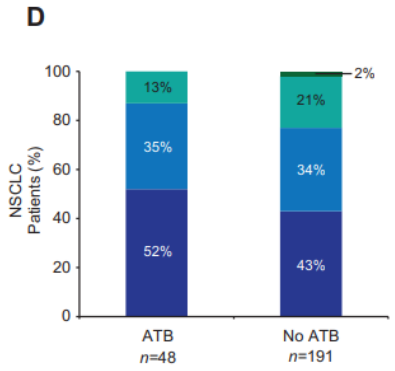
RWE & new insights: the "ATB story"

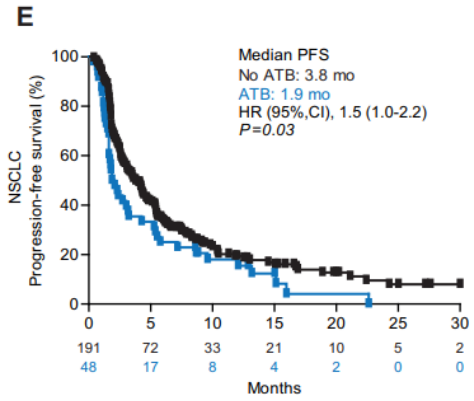


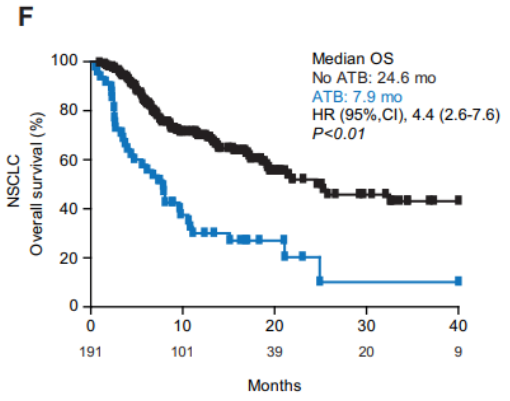












Pinato DJ, et al. JAMA oncol 2019; Derosa L et al. Ann Oncol 2019

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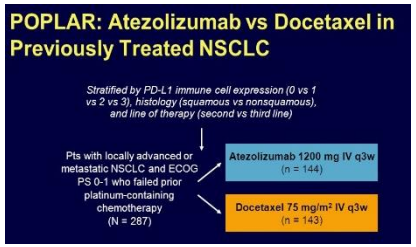
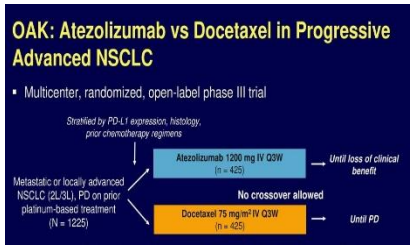
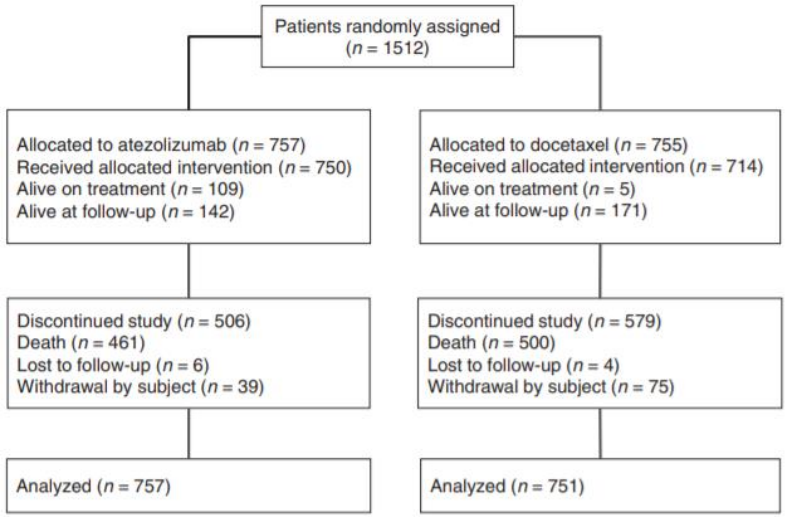
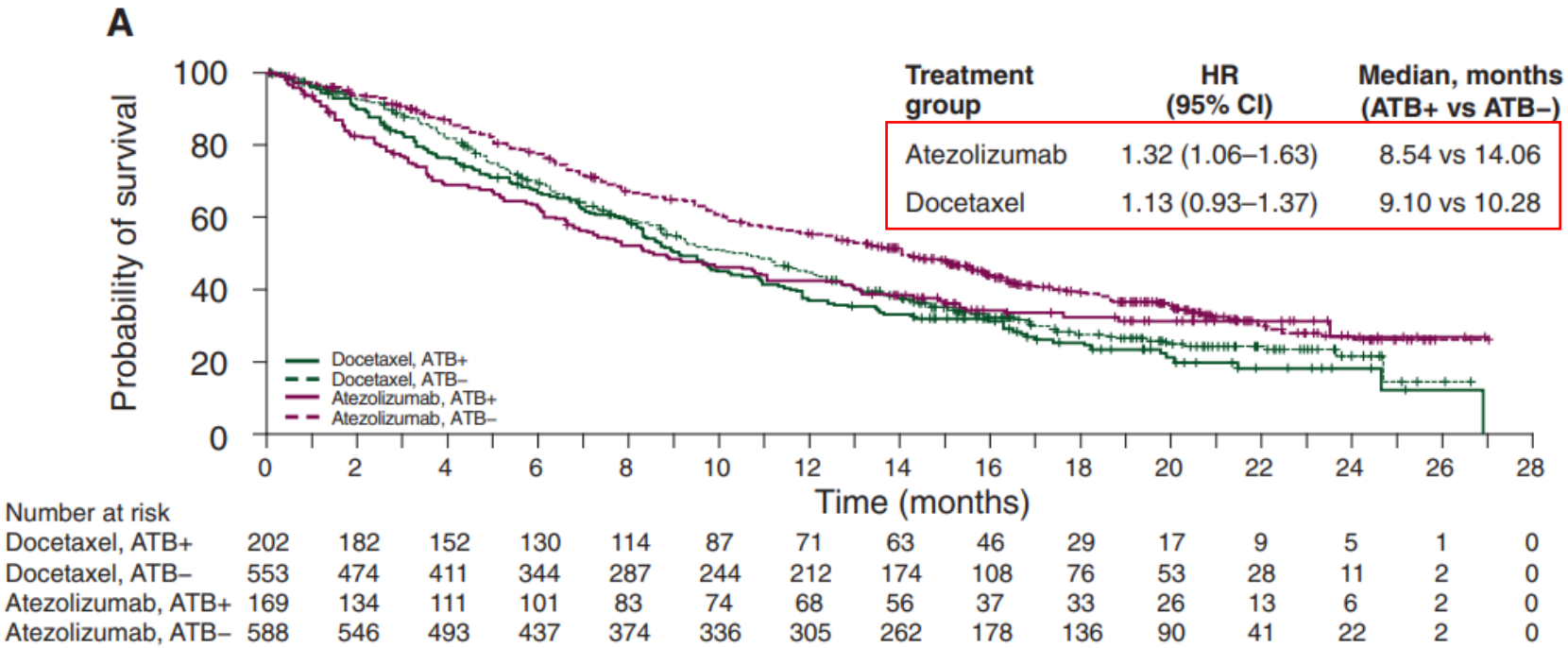
RWE & new insights: the "ATB story"





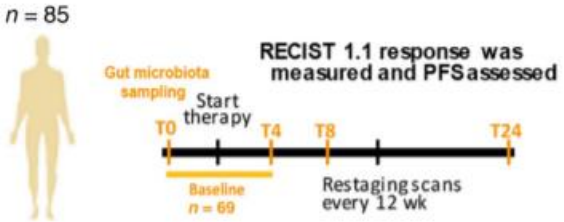


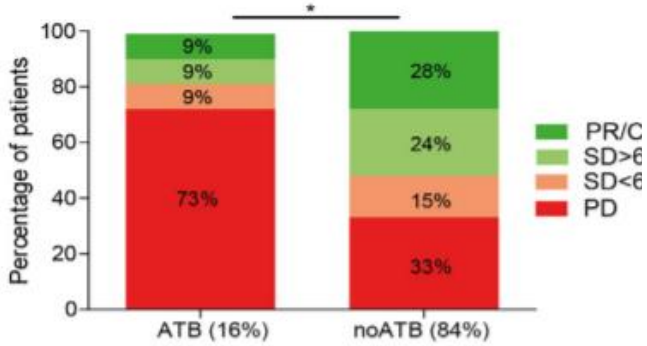


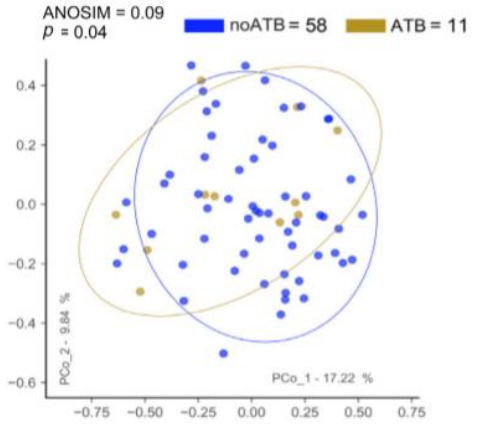
Chalabi M, et al. Ann Oncol 2020

"ATB story": mechanistic evidence

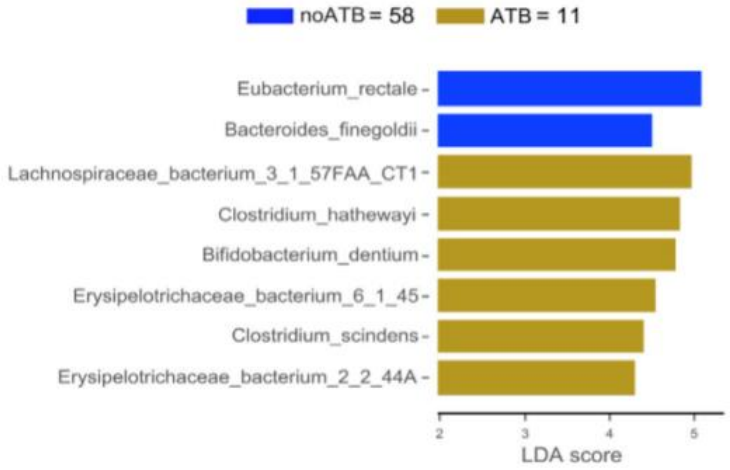
NIVOREN trial
NCT03013335





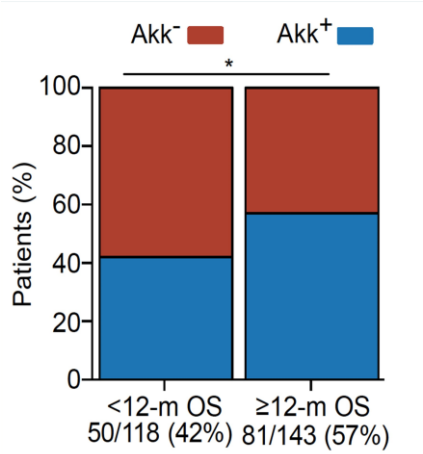


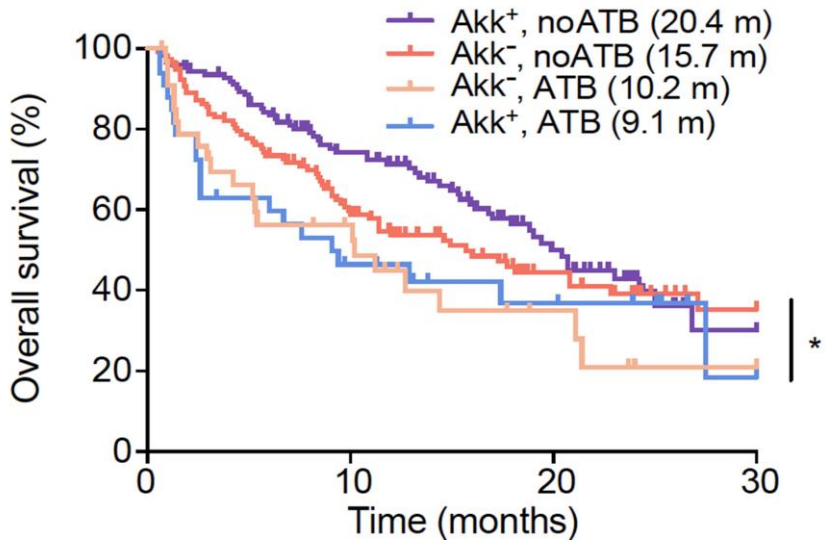
Between-sample DIVERSITY ordination plot



Most discriminant species for each cohort

Pts with NSCLC treated with ICI





De Rosa L, et al. Eur Ur. 2020; Derosa L, ASCO 2021

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AGENDA

- Real-world evidence (RWE): definition and characteristics.
- RWE examples: “effectiveness” study, special/underrepresented populations, new insight/hypothesis.
- **Pitfalls of RWE, beware of selection bias.**
- RWE, decision making and health technology assessment (HTA).

Rachel E. Sherman; NEJM 2016

RWE: beware of selection bias!

- Basically seen in all observational studies, depends on the manner in which the study population is selected.

- Mainly given to the differential distribution of measurable (**and unmeasurable**) variables across the subgroups.

- Mitigation strategies:

    - Clear definition of the study population and group(s) of interest.

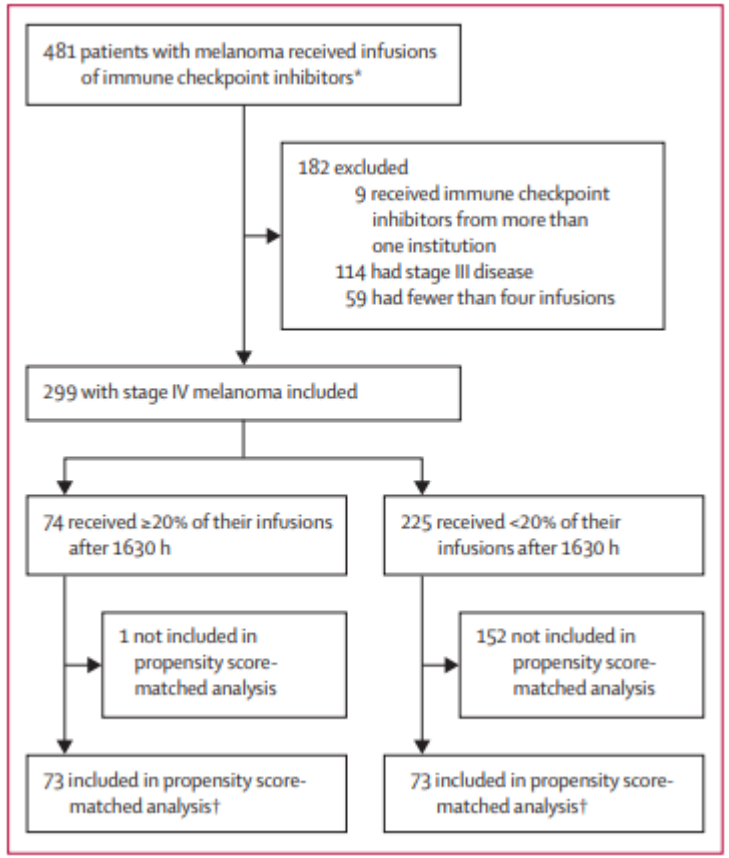
    - Choice of the right comparison (exposed vs unexposed) -> similar as much as possible.

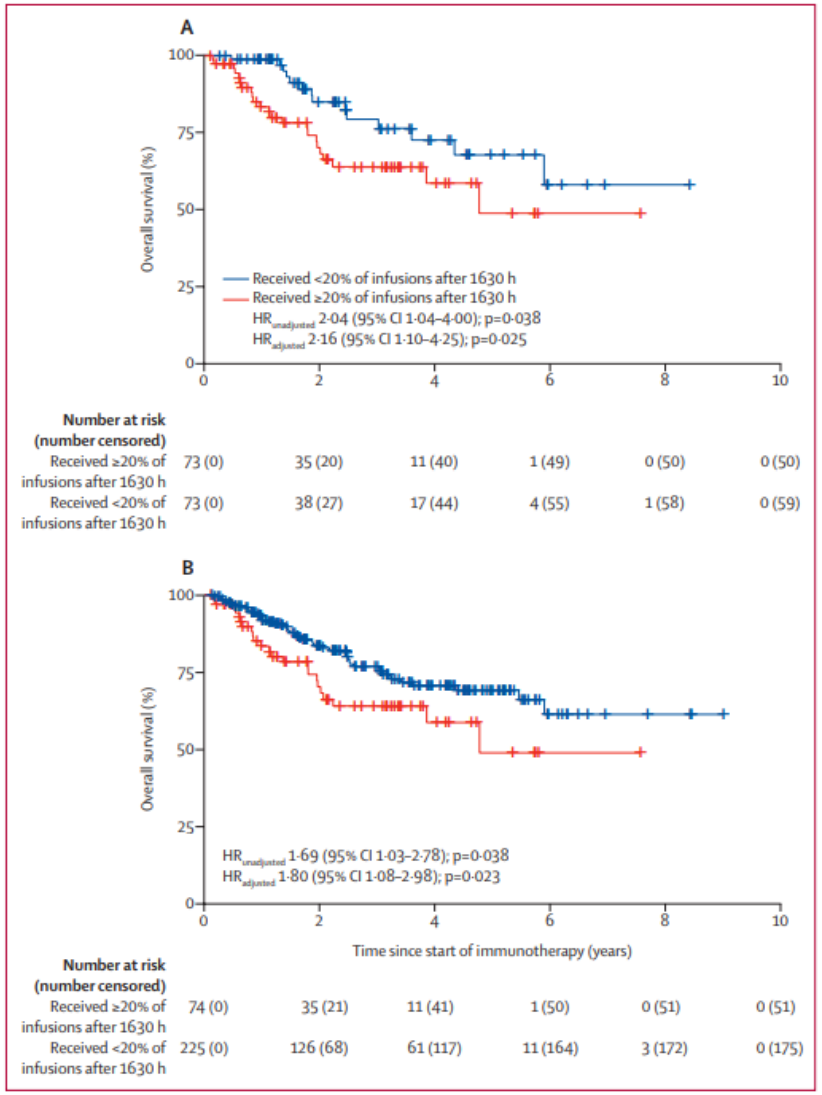
    - Multivariable analysis and matching strategies (depending on the outcomes/observations).

    - DESCRIBE! DESCRIBE! DESCRIBE! Patients' characteristics to draw conclusions.

RWE: beware of selection bias!

Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): a propensity score-matched analysis of a single-centre, longitudinal study





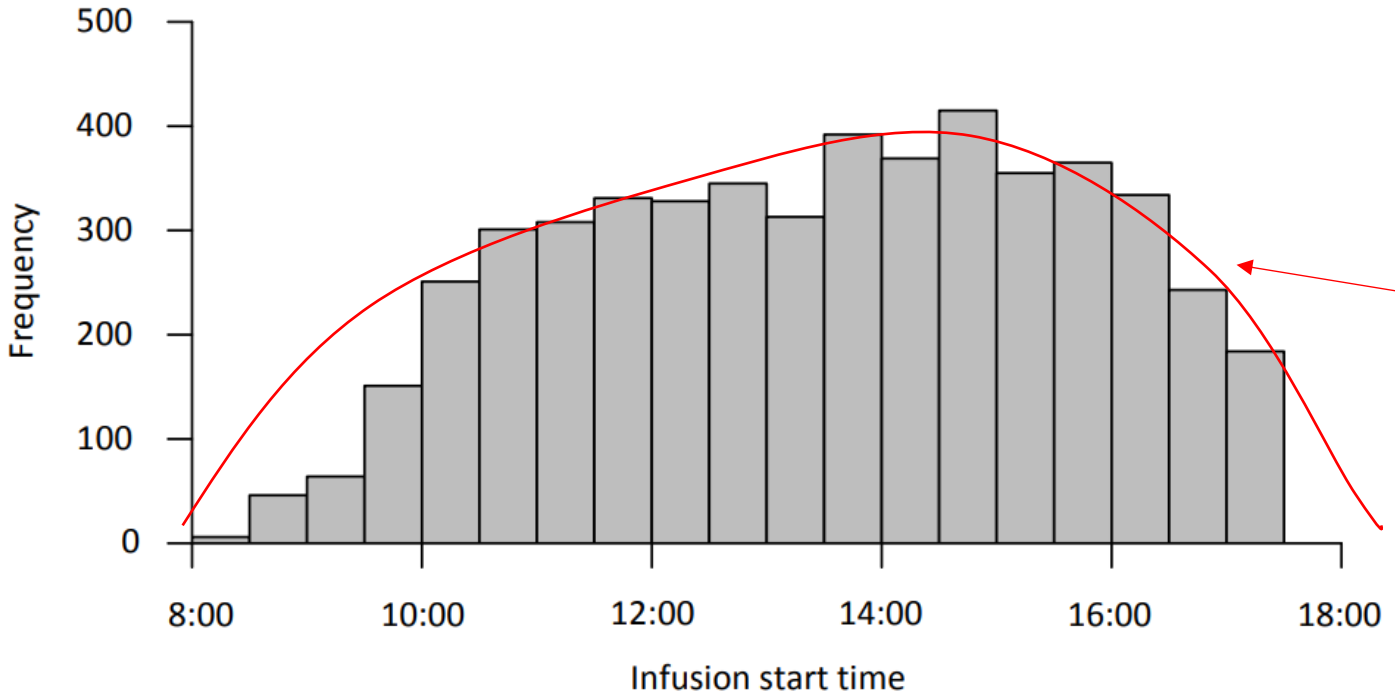
Quian DC, Lancet Oncol 2022

RWE: beware of selection bias!

	Propensity score-matched		Unmatched		
	≥20% of infusions after 16:30 (n=73)	<20% of infusions after 16:30 (n=73)	≥20% of infusions after 16:30 (n=74)	<20% of infusions after 16:30 (n=225)	p value
Number of ICI infusions					0.073
4–10	46 (63)	33 (45)	46 (62)	105 (47)	
11–15	13 (18)	15 (21)	13 (18)	45 (20)	
16–20	7 (10)	11 (15)	8 (11)	28 (12)	
≥ 21	7 (10)	14 (19)	7 (9)	47 (21)	

Arbitrary grouping

Mischievous p-value



«Gaussian» distribution

Figure S2: Frequency plot of immunotherapy infusion start times.

Quian DC, Lancet Oncol 2022

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RWE: beware of selection bias!

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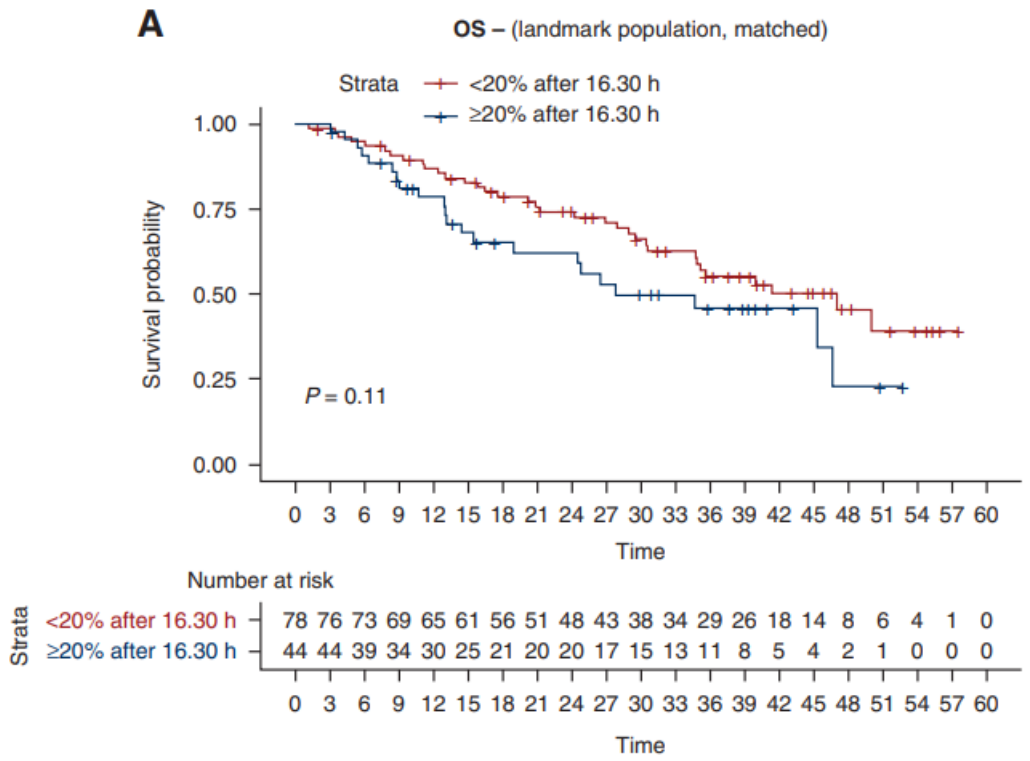
	Overall population 262 N° (%)	Overall population <20% after 16.30h N=195 (%)	Overall population ≥20% after 16.30h N=67 (%)	P value
Number cycles				
Median (Range)	6 (1-55)	8 (1-55)	5 (1-42)	P=0.0201
1-3	82 (31.3)	59 (30.3)	23 (34.3)	P=0.0009
4-10	86 (32.8)	53 (27.2)	33 (49.3)	
11-15	24 (9.2)	19 (9.7)	5 (7.5)	
16-20	21 (8.0)	20 (10.3)	1 (1.5)	
≥21	49 (18.7)	44 (22.6)	5 (7.5)	
AGE, (years)				
Median (range)	69 (42-96)	69 (45-92)	68 (42-96)	P = 0.5050
< 70 years old	143 (54.6)	103 (52.8)	40 (59.7)	P = 0.3300
≥ 70 years old	119 (45.4)	92 (47.2)	27 (40.3)	
Biological sex				
Male	131(50.0)	101 (51.8)	30 (44.8)	P = 0.3225
Female	131 (50.0)	94 (48.2)	37 (55.2)	
ECOG-PS				
0 - 1	210 (80.2)	158 (81.0)	52 (77.6)	P = 0.5464
> 2	52 (19.8)	37 (19.0)	15 (22.4)	
Histology				
Adenocarcinoma	208 (79.4)	153 (78.5)	55 (82.1)	P = 0.7192
Squamous	35 (13.4)	28 (14.4)	7 (10.4)	
Carcinoma NOS/others	19 (7.3)	14 (7.2)	5 (7.5)	
Smoking status				
Never smokers	19 (7.3)	18 (9.4)	1 (1.5)	P = 0.0335
Former/current smokers	240 (92.7)	174 (90.6)	66 (98.5)	
Missing	3	3	-	
CNS metastases				
No	199 (76.0)	150 (76.9)	49 (73.1)	P = 0.5321
Yes	63 (24.0)	45 (23.1)	18 (26.9)	
Bone metastases				
No	178 (67.9)	137 (70.3)	41 (61.2)	P = 0.1711
Yes	84 (32.1)	58 (29.7)	26 (38.8)	
Liver metastases				
No	231 (88.2)	172 (88.2)	59 (88.1)	P = 0.9747
Yes	31 (11.8)	23 (11.8)	8 (11.9)	
PD-L1 TPS				
50-89%	121 (46.2)	90 (46.2)	31 (46.3)	P = 0.9870
≥ 90%	141 (53.8)	105 (53.8)	36 (53.7)	
EGFR mutational status				
Wild type	250 (99.2)	187 (99.4)	63 (98.4)	P = 0.4441
Mutant ¥	2 (0.8)	1 (0.6)	1 (1.6)	
Unknown	10	7	3	
Other actionable biomarkers				
KRAS mutations	98 (48.8)	71 (49.3)	27 (47.4)	P = 0.5844
BRAF V600E	8 (4.0)	4 (2.8)	4 (7.0)	
Met exon_14 skipping	5 (2.5)	3 (2.1)	2 (3.5)	
Others*	8 (4.0)	5 (3.5)	3 (5.3)	
None identified	82 (40.8)	61 (42.4)	21 (36.8)	
Unknown	61	51	10	
Median TMB (mut/mega-base)				
Median (range)	10.6 (0-26.0)	10.6 (2.3-56.2)	10.6 (0-26.0)	P = 0.8214
Available patients	141	96	45	



Cortellini A, et al. Annals of Oncolgy 2022

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RWE: beware of selection bias!

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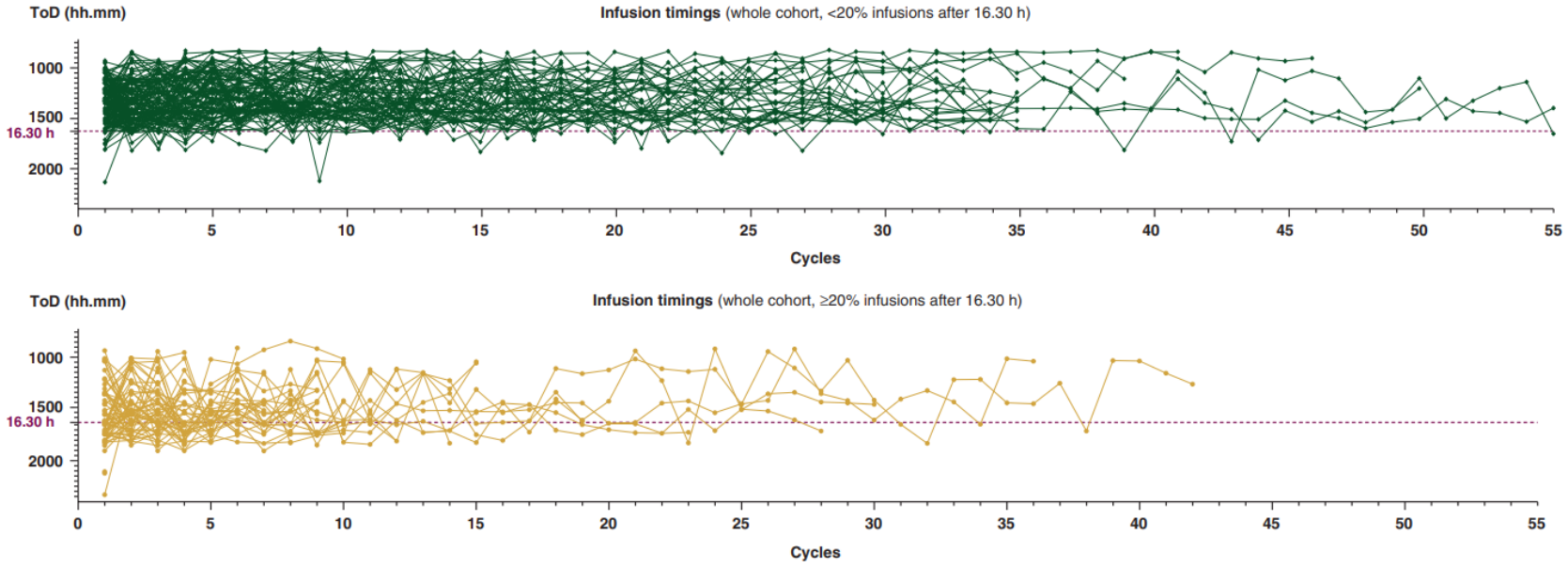

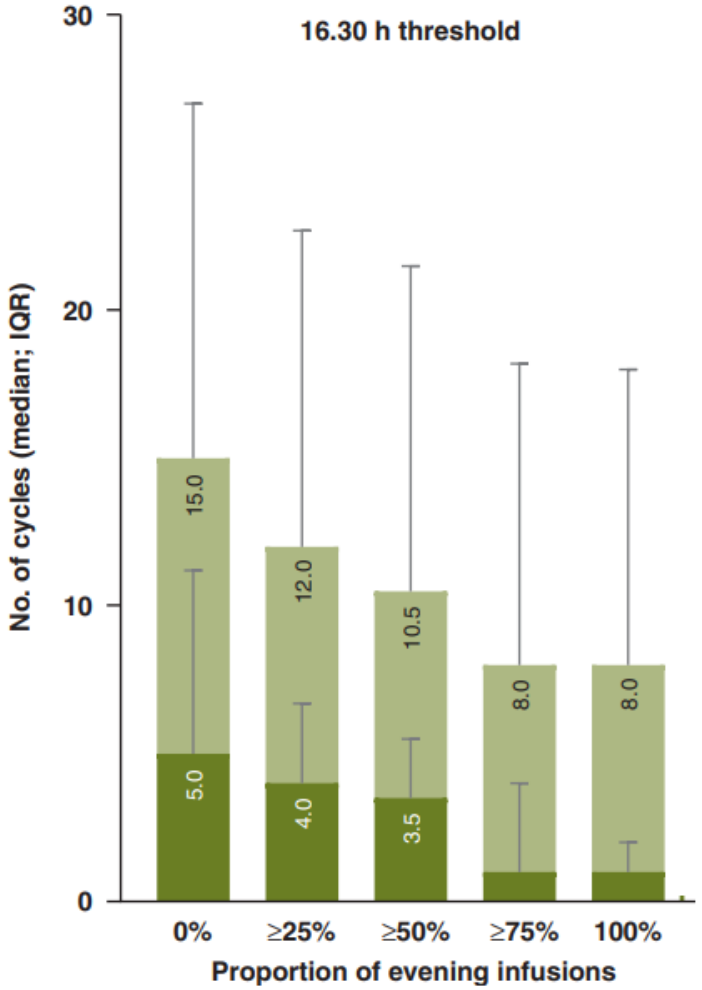

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RWE: beware of selection bias!

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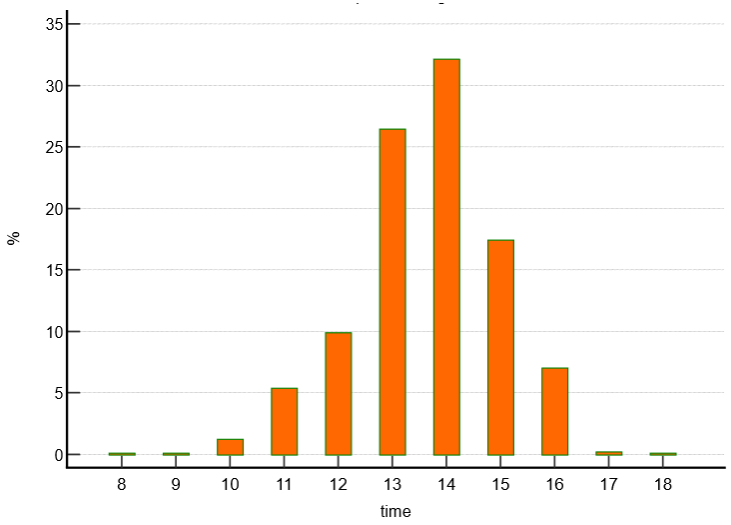
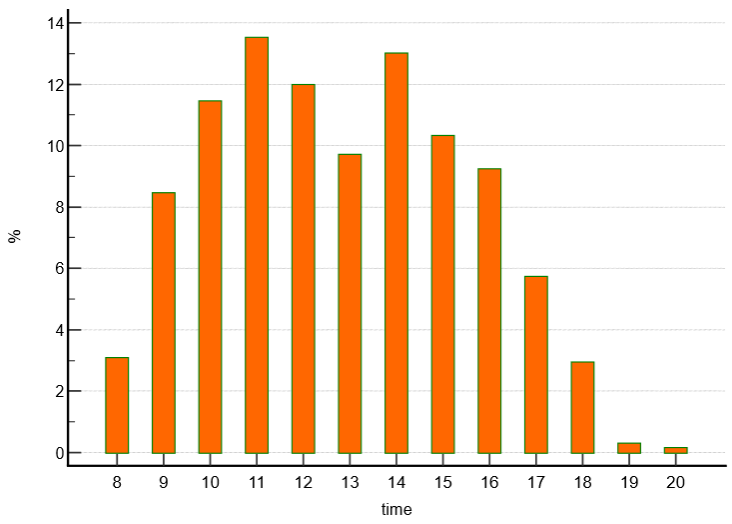
Imperial College London, distribution of time-of-day of infusion

Median: 14.12 (8.30-18.24)

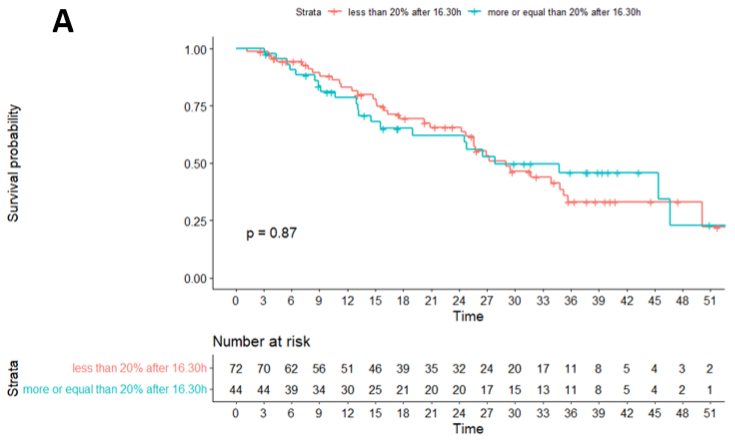


Dana Farber Cancer Centre, distribution of time-of-day of infusion

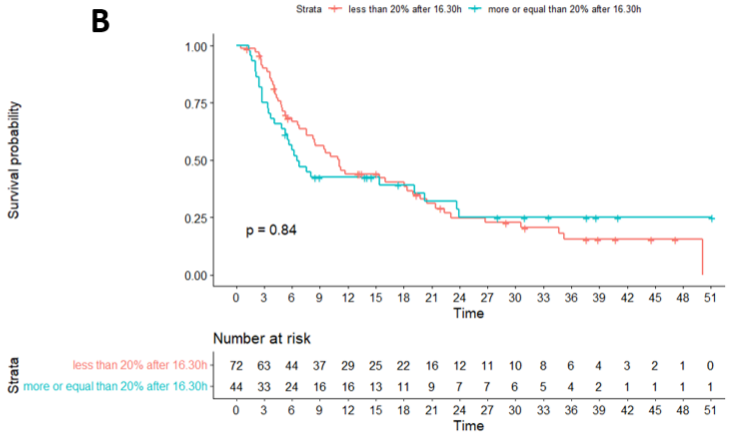
Median: 13.11 (8.14-23.32)



OS - (landmark population, matched-including N° of cycles)



PFS - (landmark population, matched-including N° of cycles)



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The down-side of RWE

Imperial College London

Covidence-assisted systematic "mapping" review of RWE on TT between 2020 and 2022 → **1251 studies included**!

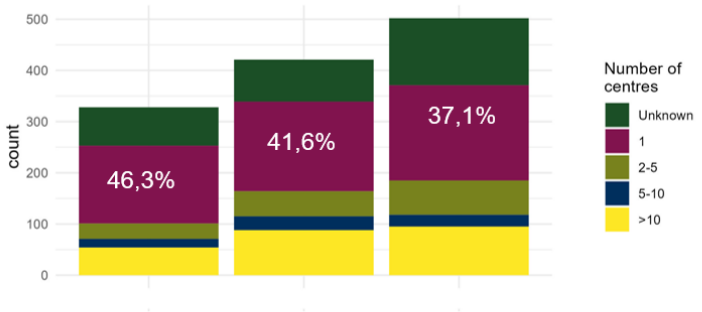
Overall "low quality" publications

- Number of centers / national-basis
- Data source
- IF

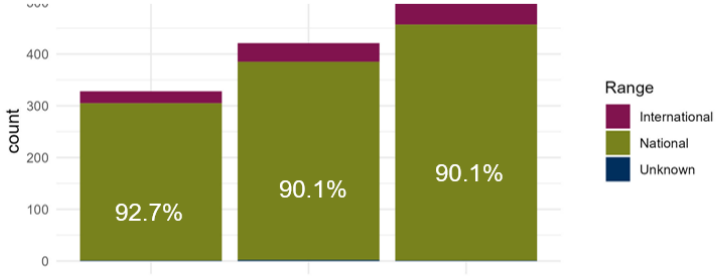
Assuming IF as the most reliable proxy

- **Region** (p=0.006)
- **>10 centres** (p=0.002)

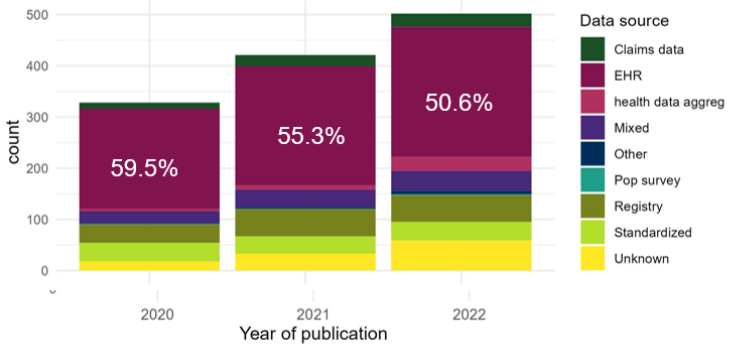
Number of center(s)



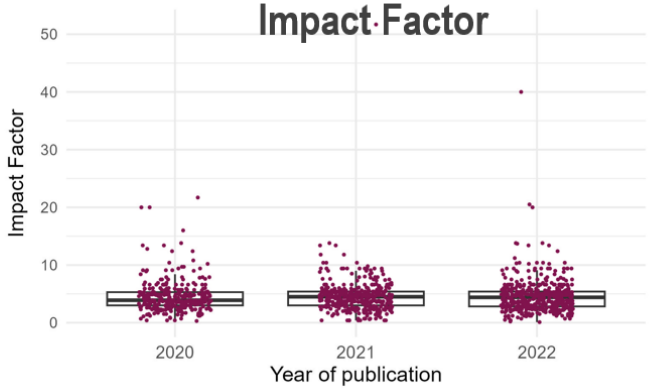
Study range



Data Source



Impact Factor



For the whole sample:

- Median IF 4,4 (3-5,3)
- Mean IF 4,6
- Min IF 0,1 and Max IF 51,7

Publication in:

- Specialized journals: 86%
- General medical journals: 8,6%
- Non medical journals: 5,4%

ADAPTED from Cortellini A, ESMO 2023; Pellat A, et al. ESMO 2023

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The down-side of RWE

Imperial College London

293 RWE studies for 45 drugs for FDA and EMA approved indications

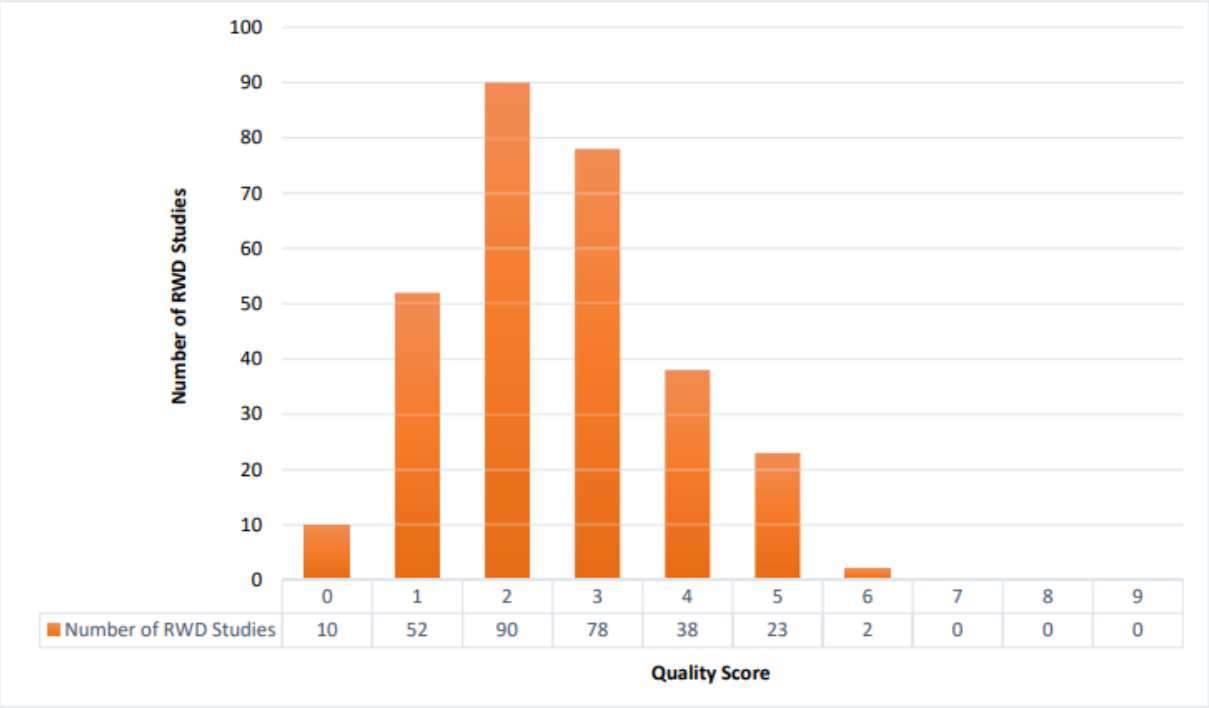

Fig. 1. Histogram of the distribution of total scores for RWD studies appraised using the Newcastle Ottawa Scale.

European Journal of Cancer 155 (2021) 136–144

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC

Original Research

Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study

Jemma M. Boyle [a,1], Gemma Hegarty [b,1], Christopher Frampton [c], Elizabeth Harvey-Jones [d], Joanna Dodkins [d], Katharina Beyer [e], Gincy George [e], Richard Sullivan [d,f], Christopher Booth [g,2], Ajay Aggarwal [a,d,f,*,2]

Newcastle Ottawa Scale (NOS) for cohort studies (0-9):

- **Selection of the study groups** (representativeness of the exposed and non-exposed cohorts, ascertainment of exposure, no outcome at baseline)
- **Comparability of groups** (for design and analysis)
- **Outcome** (assessment methodology, proper follow-up for all cohorts,

ADAPTED from Cortellini A, ESMO 2023; Boyle JM, et al. EJC 2021; Murad MH, BMJ Evid Based Med 2018; Wells G, The Ottawa Health Research Institute, 2011

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Improve reporting/quality is KEY

Imperial College London

35 reporting recommendations on:

- title,
- introduction,
- methods,
- results,
- discussion and conclusions,
- final considerations

ESMO Guidance for Reporting Oncology real-World evidence (GROW)

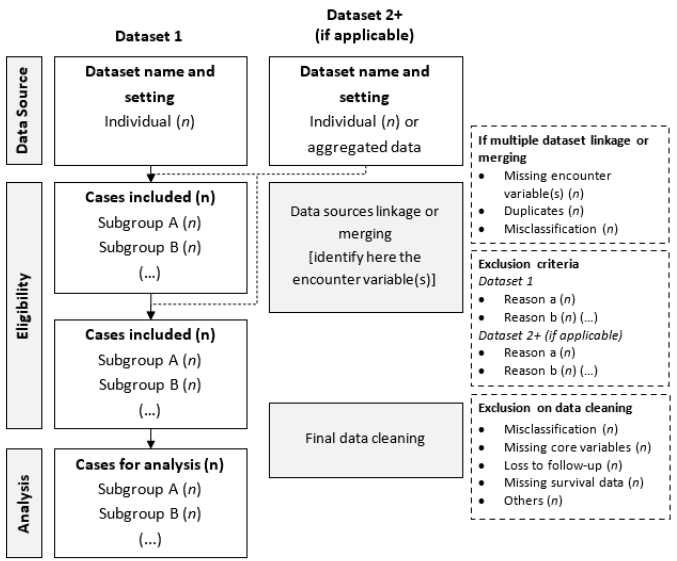
ESMO-GROW Checklist for Authors and Reviewers

This checklist integrates all ESMO-GROW recommendation and could be used by authors and reviewers when assessing the reporting standards of a real-world evidence study in Oncology.

For the the ESMO-GROW checklist, the following criteria are considered:
"Yes, fully reported" – The recommendation is adequately considered.
"Yes, partially reported" – The recommendation is considered, but some important details are missing.
"Not reported" – The recommendation is applicable for the case, but it was not considered.
"Not applicable" – The recommendation is not applicable for this study.

Name of Author/Reviewer: Date: Title of Manuscript or Identifier: Recommendations	Yes, fully reported	Yes, partially reported	Not reported	Not applicable
1. Title				
1.1: Concisely include relevant key terms referring to the study type, study population, objectives, data sources and outcomes, depending on the study. Consider including the terms 'real-world' or 'observational'	◯	◯	◯	◯
2. Introduction				
2.1: Explain the scientific rationale for the research question(s), providing concise background information on previous core evidence from systematic reviews, meta-analyses, clinical trials and/or real-world evidence studies	◯	◯	◯	◯
2.2: Identify the gaps in evidence and explain why and how they can be suitably addressed by real-world evidence research. Specify the new evidence that is expected from the current study	◯	◯	◯	◯
2.3: Briefly introduce the aim(s) of the study	◯	◯	◯	◯
3. Methods				
Study objective(s), design, data sources and variables				
3.1: Provide the study research question(s) including a description of the patients or the object under study and the target outcome(s)	◯	◯	◯	◯
3.2: Provide the study objective(s) and consider classifying the type of research as descriptive and/or analytical (explanatory or predictive)	◯	◯	◯	◯
3.3: Provide relevant information to describe and classify the study design used to address the research question	◯	◯	◯	◯
3.4: Give a clear definition of the eligibility criteria used to select the patients or objects under study, particularly regarding cancer-related aspects	◯	◯	◯	◯
3.5: Report the specific type and purpose of real-world data source(s) used, providing a detailed description and the reason(s) why the source was considered appropriate for the study objectives	◯	◯	◯	◯
3.6: When multiple real-world data sources are used, provide details on interoperability, including identification of duplicated cases or data linkage from separate databases	◯	◯	◯	◯
3.7: Provide details and timings of source and study data management. Consider specifying methods of raw data collection, updates and completeness, data extraction, cleaning and/or quality controls and validation	◯	◯	◯	◯
3.8: Provide core details on database and/or study registration, governance, ownership, metadata and full data accessibility in the main text or supplementary material	◯	◯	◯	◯
3.9: Identify the data source of each core variable, its definition, if the variable was derived or coded, and describe how the derivation or coding was conducted and validated.	◯	◯	◯	◯
3.10: Specify the time points of core variables in relation to the cancer disease trajectory	◯	◯	◯	◯
3.11: Provide a complete list of core variables included in the study. Variables can be grouped as baseline characteristics, exposure and outcomes or endpoints	◯	◯	◯	◯
3.12: For biomarker-related studies, provide details on biomarker description, timing, and methods of assessment and analytical validation	◯	◯	◯	◯
Statistical analysis and artificial intelligence methods				
3.13: Summarise the main aspects of the statistical analysis	◯	◯	◯	◯
3.14: When applicable, provide details on the pre-planned sample size requirements and power of the study	◯	◯	◯	◯
3.15: Specify the pre-planned strategies to identify and mitigate the main sources of bias	◯	◯	◯	◯
3.16: Clearly distinguish prespecified from *post hoc* analyses, especially for subgroup analyses	◯	◯	◯	◯
3.17: Provide information on internal and external validity, as well as any sensitivity analyses	◯	◯	◯	◯
3.18: For analytical studies, the full version of the statistical analysis plan should be provided in the supplementary material, including a brief explanation of any amendments	◯	◯	◯	◯
3.19: When applicable, specify which machine learning, deep learning or alternative artificial intelligence method has been used	◯	◯	◯	◯
3.20: When reporting real-world data analysis with artificial intelligence (e.g. machine learning and deep learning) algorithms, include comprehensive aspects on data pre-processing techniques, feature engineering strategies and model development	◯	◯	◯	◯
3.21: Address the artificial intelligence model explainability and interpretability, and present the plan for integration into clinical practice, if applicable	◯	◯	◯	◯
3.22: When applicable, briefly describe the multidisciplinary team required for the study and explain how these needs were met	◯	◯	◯	◯

ESMO-GROW flowchart for real-world evidence studies in oncology



Castelo-Branco L, et al. Ann Oncol 2023

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AGENDA

- Real-world evidence (RWE): definition and characteristics.
- RWE examples: “effectiveness” study, special/underrepresented populations, new insight/hypothesis.
- Pitfalls of RWE, beware of selection bias.
- **RWE, decision making and health technology assessment (HTA).**

RWE, decision making and HTA

Registry-based response guided decision-making and guidelines (at international levels) during the COVID19 pandemic

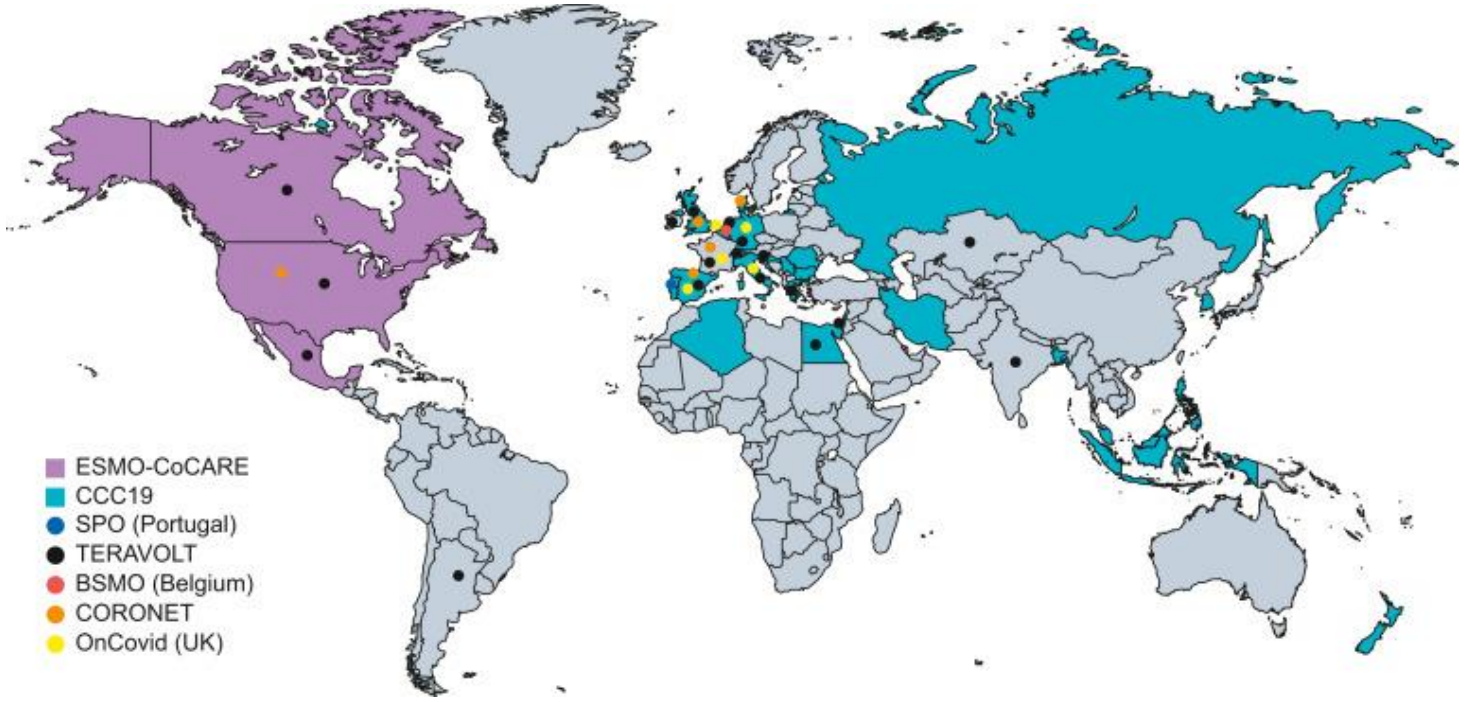


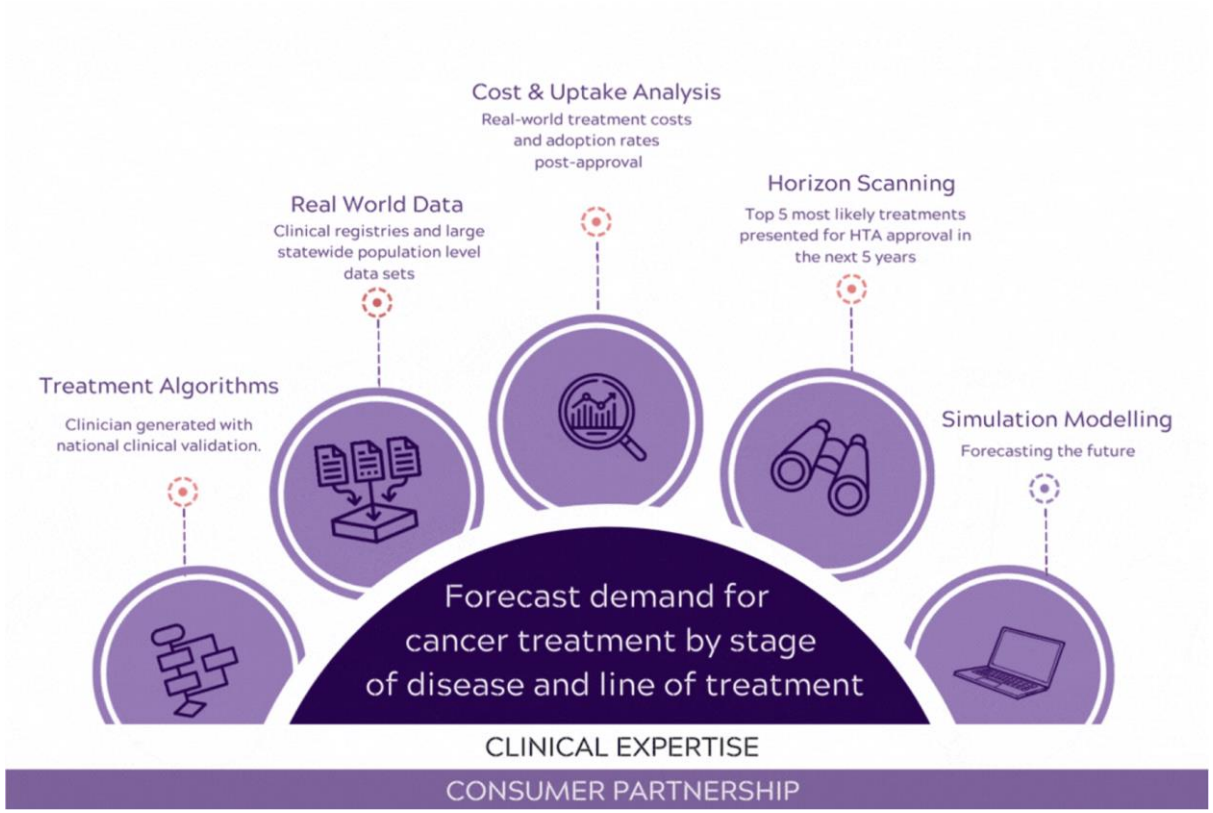
Table 1. Details of the collaborative real-world evidence groups working in cancer and COVID-19

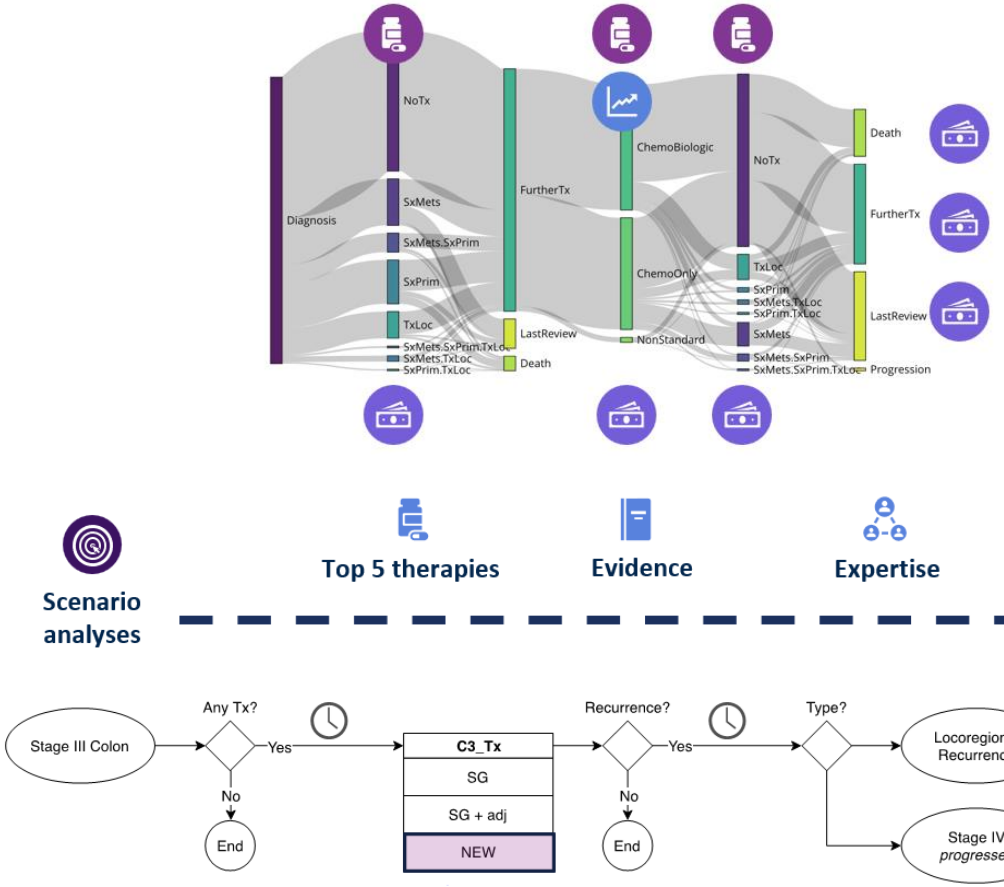
Name	Starting date	Geography	Number of participating centers	Number of patients included	Collaborations established
ESMO-CoCARE	March 2020	Europe Asia Africa	43	2366	CCC19 BSMO SPO OnCovid.UK CORONET
CCC19	March 2020	North America	120+	19 275	ESMO-CoCARE, OnCovid
OnCovid (UK)	February 2020	Europe	37	3820	ESMO-CoCARE CCC19 NCI
BSMO-COVID[a]	March 2020	Belgium	19	928	ESMO-CoCARE
OnCovid (Portugal)/SPO	March 2021	Portugal	10	276	ESMO-CoCARE
CORONET	March 2020	Europe, North America	18	1968	ESMO-CoCARE; various individual groups
TERAVOLT	March 2020	Europe America, North Africa Asia	92	1491	CCC-19

Castelo-Branco L, et. al. ESMO Open 2023; Desai A, et al. JAMA Oncol 2021

RWE, decision making and HTA

PRIMECAT: evidence-based forecasts of the population health economic impact of new cancer treatments in Australia to help HTA agencies in decision making/planning





RWE, decision making and HTA

EMA (2015) → patient registry initiative: to explore the expansion of the use of registries by supporting a systematic and standardized approach to the risk-benefit evaluation of drugs**.**

EMA Committee for Medicinal Products for Human Use (CHMP) requested specific registries as a condition of the marketing authorization for 9% of all products centrally authorized between 2005 and 2013.

Review of policies of 6 EU HTA agencies on the use of RWD (wide heterogeneity):

- **Initial reimbursement discussions** (IRDs) → accepted but generally not prioritized over RCTs
- **Pharmacoeconomic analyses** (PEAs) → frequently requested for cost-effectiveness evaluations
- **Conditional reimbursement schemes** (CRSs) → some agencies allow that, but large-scale CRS implementations/re-evaluations are rare

RWD faces challenges related to data quality, standardization, and methodological rigor, with potential biases impacting HTA decisions.

Olmo CA, et al. Clin Pharmacol Ther 2019; McGettigan P, et al. Drug Saf 2019; Jonker CJ, et al. Pharmacoepidemiol Drug Saf 2017; Makady A, Value Health. 2017

Conclusion

- RWE overall and in the context of lung cancer has an immense (partially un-used) potential.
- Can help confirming the “effectiveness” of a treatment.
- Can help with under-represented populations.
- Can help providing new insight/generating hypothesis
- Can Inform clinical decision making/regulatory level decision making
- Regulation, harmonization, standardization, quality and implementation are still points of concern.

Makady A, Value Health. 2017

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THANK YOU!

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