4.37: MEMOIR & The Emperor Has No Clothes (a Critique of Cancer Care) with Dr. Christopher Booth

Season	4
Type	Plenary Session

We Discuss:

- MEMOIR [1:23]
- Dr. Christopher Booth Lecture [9:00]
- The Emperor Has No Clothes [13:00]
- Value [15:30]
- History [27:18]
- Time toxicity [33:00]
- Moonshots [42:00]
- Moving forward [50:00]

Plenary Session 4.37 Show Notes

Overview

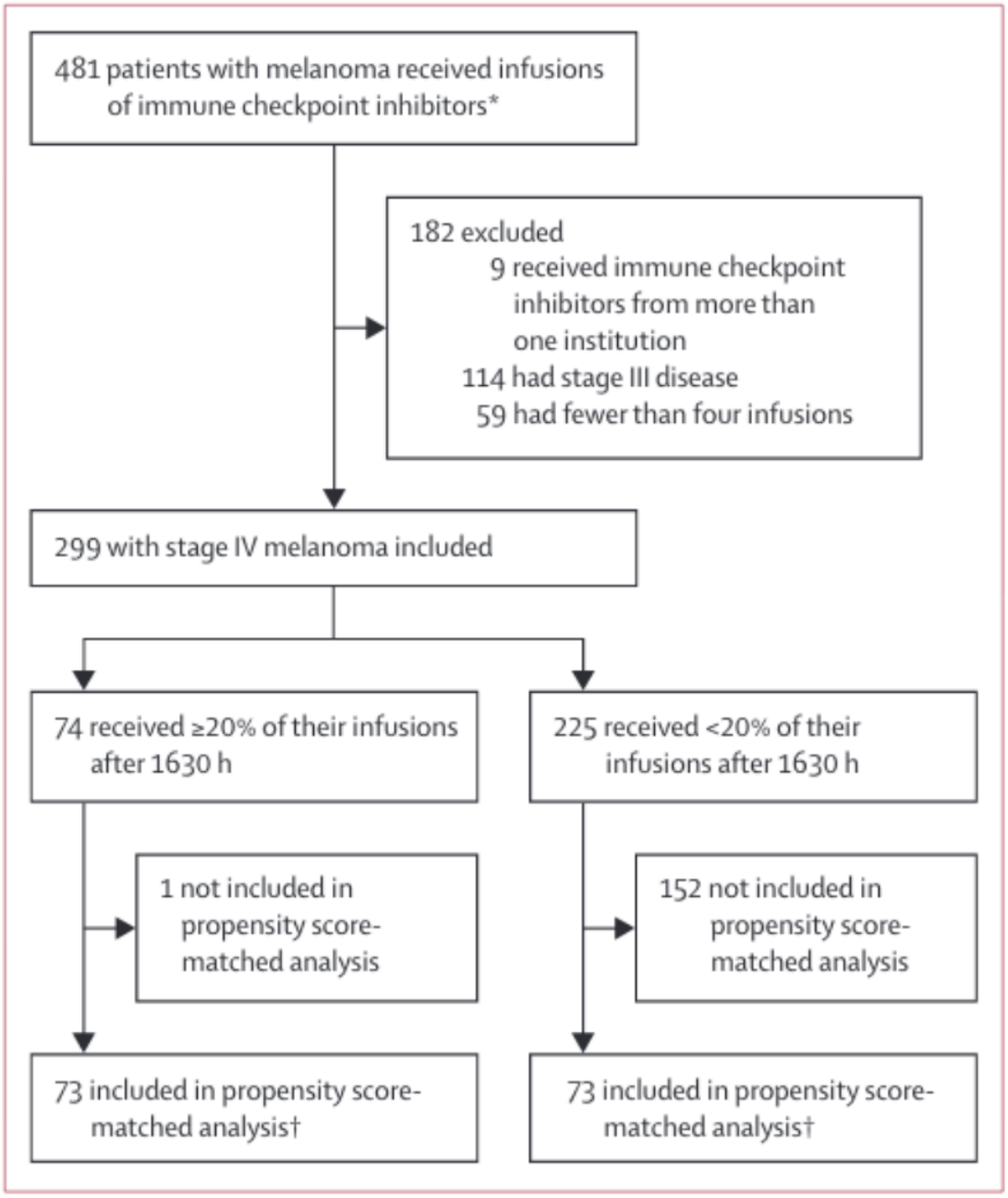
Trial Monologue

- **MEMOIR [1:23]**

- 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
  - Qian et al., *The Lancet Oncology*

> ⚕️ *“The dependence of the adaptive immune system on circadian rhythm is an emerging field of study with potential therapeutic implications. We aimed to determine whether specific time-of-day patterns of immune checkpoint inhibitor infusions might alter melanoma treatment efficacy.” - Qian et al.*

- Study design



Qian et al.

- OS Results

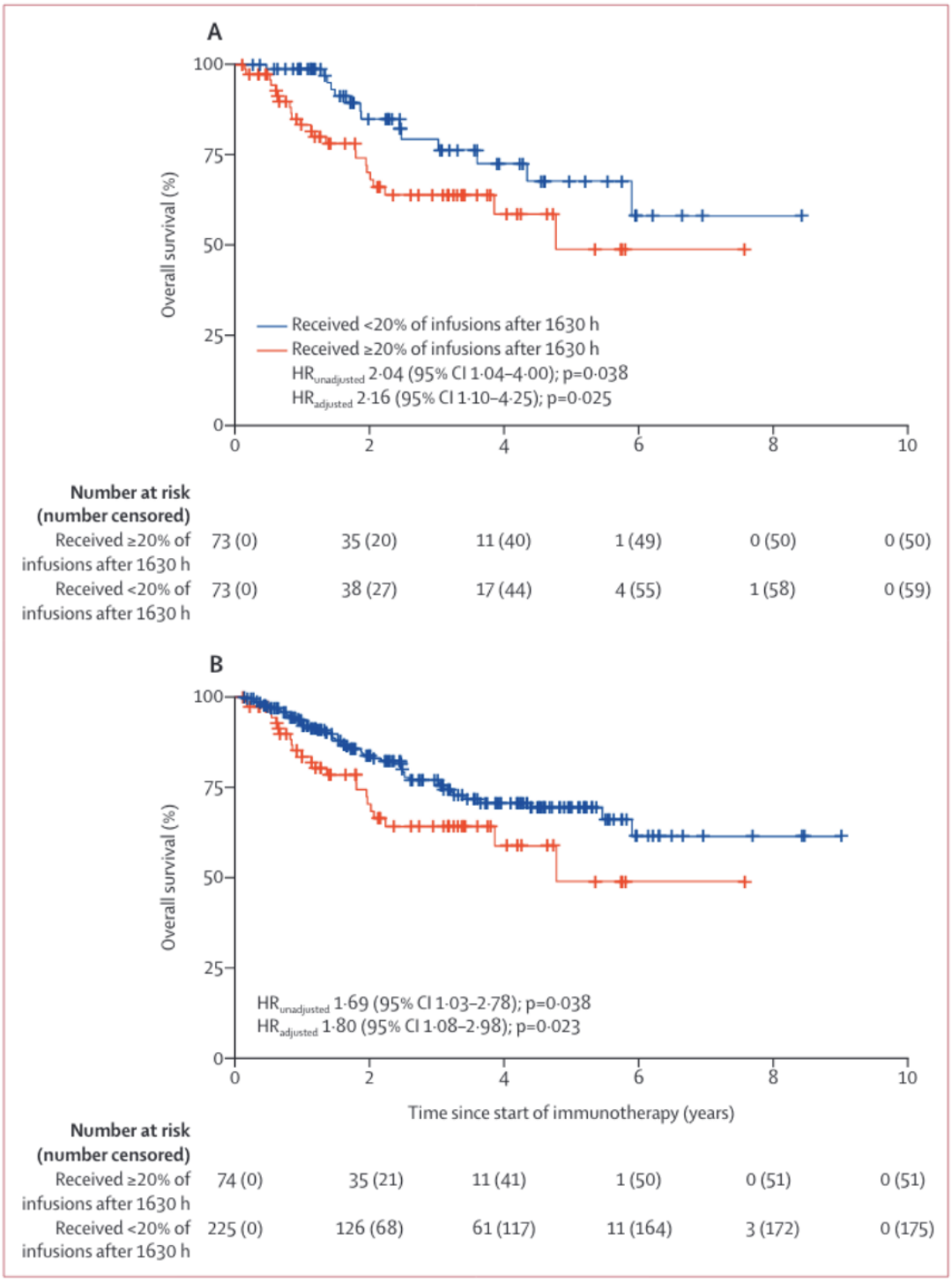


Figure 2: **Overall survival for propensity score-matched groups (A) and unmatched groups (B)**

Qian et al.

- Issues

1. The time of day at which someone receives their infusion is not determined randomly by the computer
    a. There are many confounding factors at play (e.g., socioeconomic status, disease burden, urgency of treatment, preference)
        i. For instance, if you have a younger person who has a tough social situation or other obligations
        ii. Occasionally, you will have a patient with an abundance of disease, and you will be quite concerned and want to have them treated quickly.
            1. This will have resulted in the creation of a schedule for the next morning → a blatant confounding factor
2. Propensity score matching cannot match on characteristics that are not measured
3. The absolute numbers of the overall trial (single center) are rather modest

> "The proof is you have to somehow experimentally, randomly assign people to a different strategy and show improved outcomes." - VP

- Takeaways
    - VP believes that the time of day has little effect on immunotherapy outcomes
        - It is much more likely a surrogate for the aforementioned confounders

> "You really want to test it in some randomized fashion if you believe this effect is real" - VP

Lecture from Dr. Christopher Booth

- **Introduction**
    - Dr. Booth is a Medical Oncologist, researcher, and Professor of Oncology at Queen's University

        - He earned his M.D. at Queen's University
            - He completed his postgraduate training in internal medicine and oncology at the University of Toronto

- **Art of oncology**

> “This is an issue that all of us in the cancer care ecosystem need to think about need to work collectively on. This is not just an issue that applies to low resource context, this is an issue that all of us must face as providers of cancer care.” - Dr. Booth

    - Benefits to patients
        - The art of oncology is the delivery of compassionate care
            - That compassionate care might include treatments, and if we're giving treatments, it should be treatments that make a real difference
                - However, on the flip side, there is growing concern and recognition that many of our new treatments offer small, and in some cases, no real benefit
    - The Emperor Has No Clothes [13:00]

Source

- Themes of this lecture
    1. There is a crisis in the value of cancer care.
    2. On the flip side, we should no longer settle for marginal and toxic therapies
        a. Our patients expect better and we can do better
    3. All of us need to speak up When we see elements of our cancer care system in which the emperor has no clothes

- **Value [15:30]**
    - The high price of anticancer drugs: origins, implications, barriers, solutions.
        - **Prasad V**, De Jesus K, Mailankody S; *Nat Rev Clin Oncol.*

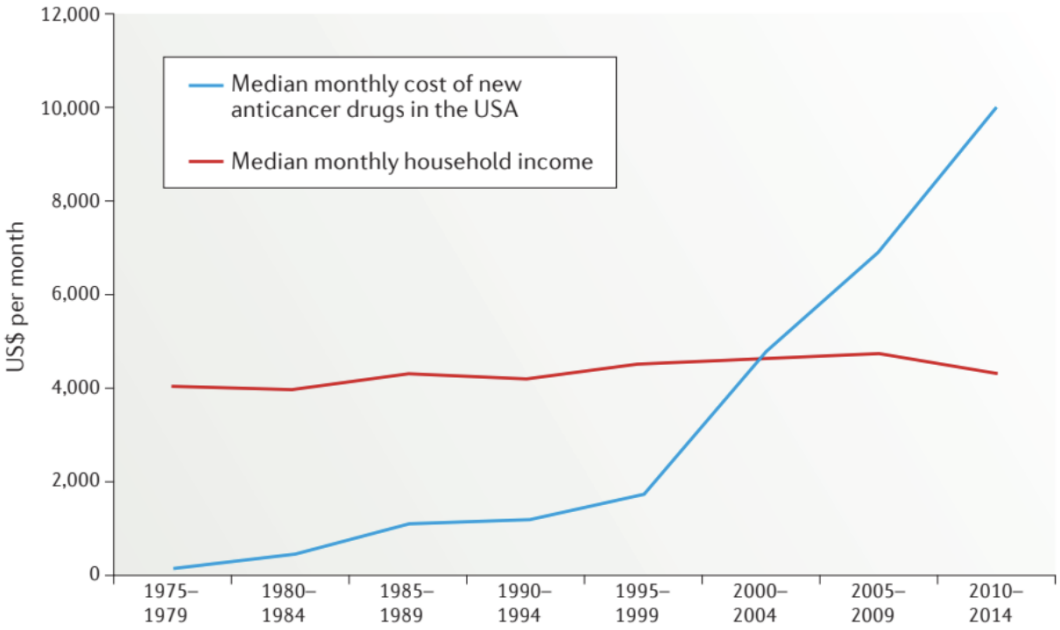


Figure 2 | **Median monthly launch price of a new anticancer drug, compared with median monthly household income from 1975–2014 in the USA.** Data on household incomes were obtained from the 2015 United States Census[133], and drug prices were obtained from Bach & Schnorr[134].

- Temporal trends in oncology drug revenue among the world's major pharmaceutical companies: A 2010-2019 cohort study.
  - Meyers et al.; JCO

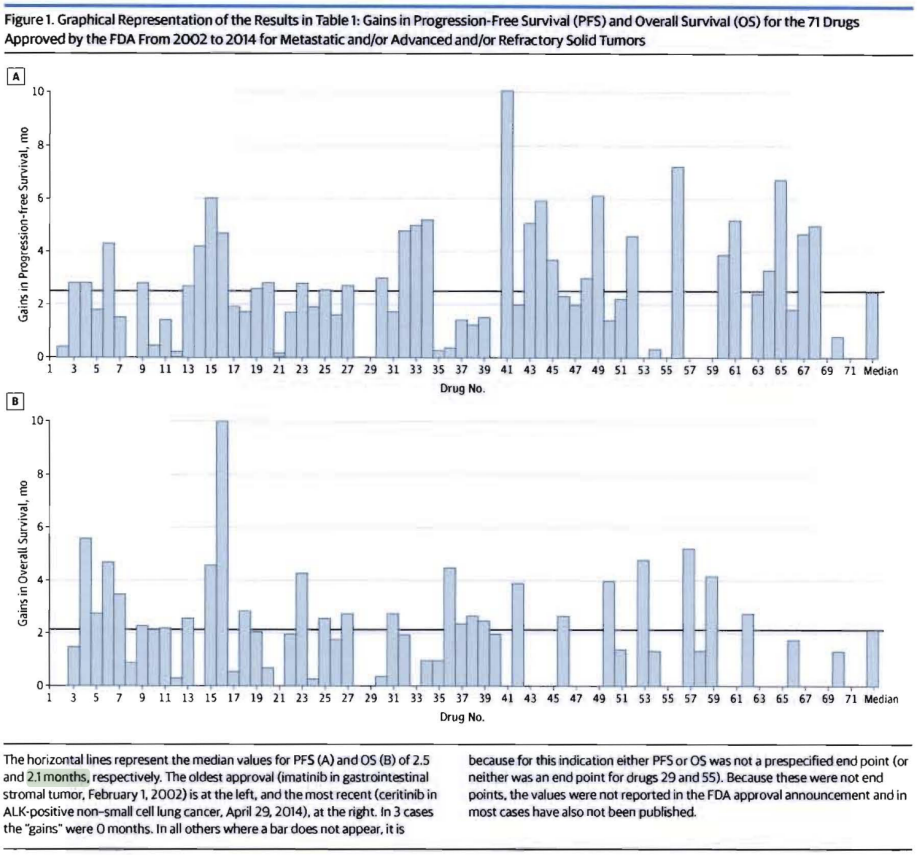
> "Has this massive reallocation of resources lead to a proportional improvement in the outcomes at the patient level at the population level? And I would argue the answer is no" - Dr. Booth

- Magnitude of benefit
  - What is the endpoint that was improved in the relevant trial?
    - Progression-free survival: meaningful or simply measurable?
      - Booth & Eisenhauer; *JCO*

> *“The last few years have seen an increase in the number of randomized controlled trials (RCTs) of new agents in metastatic solid tumors using progression-free survival (PFS) as the primary end point. Some trials showing improvement in PFS, without a corresponding increase in overall survival (OS), have led to approval of new drugs and/or changes in standard of care. This suggests a growing belief in the oncology community that delaying progression in metastatic disease is a worthy goal, even if OS is not improved. But is a new treatment that improves PFS really an advance for patients? Or is it only lowering the bar to declare active some of our much-heralded new molecular targeted therapies? We believe that as a community, this trend requires discussion and debate.” - Booth & Eisenhauer*

- It's worth remembering that response rate and PFS were designed to help early phase II/III trialists in the context of trial design
    - At no point were these two ever designed to inform RCTs
        - They certainly were not to inform clinical decision making
    - The most important primary endpoints of our randomized control trials should be overall survival and quality of life
- Patient perspectives of value of delayed disease progression on imaging (imaging PFS). A treatment trade-off experiment
    - Robinson et al.; *Journal of Cancer Policy*

- What is the effect size of that improvement?
    - Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture
        - Fojo et al.



Fojo et al.

- Do Contemporary Randomized Controlled Trials Meet ESMO Thresholds for Meaningful Clinical Benefit?
  - Del Paggio et al., *Annals of Oncology*

- **History [27:18]**
  - Evolution of the randomized controlled trial in oncology over three decades
    - Booth et al., *JCO*

Table 4. Results of Univariate and Multivariate Analysis for Variables Associated With RCT Author Strong Endorsement of the Experimental Arm

	Univariate Analysis			Multivariate Analysis		
Variable	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Decade						
1975-1984	Reference			—	—	—
1985-1994	1.4	0.6 to 3.3				
1995-2004	2.2	1.0 to 4.8	.06			
Disease site						
Breast	Reference			—	—	—
Colorectal	1.0	0.6 to 1.8				
NSCLC	0.7	0.4 to 1.3	.465			
Setting						
Palliative	Reference			—	—	—
Adjuvant neoadjuvant	2.3	1.4 to 3.6	.0007			
Control arm						
Active agent	Reference			—	—	—
No active agent	4.7	2.0 to 10.8	.0003			
Primary end point						
Response rate	Reference			Reference		
Time to event	2.9	1.6 to 5.2	.0003	4.1	1.6 to 10.3	.003
Effect size, unit = 0.1	1.3	1.2 to 1.4	< .0001	1.1	1.1 to 1.2	.0004
P for primary end point						
> .05	Reference			Reference		
≤ .05	25.2	13.6 to 46.9	< .0001	19.6	8.9 to 43.1	< .0001
Not known	1.5	0.3 to 7.4		0.7	0.02 to 26.3	
Sponsorship						
Nonprofit	Reference			Reference		
For-profit/mixed	2.3	1.4 to 3.7	.003	3.5	1.6 to 7.5	.004
Not known	1.0	0.4 to 2.1		1.0	0.3 to 3.5	

NOTE. Strong endorsement defined as RCT author score of 6 or 7.
Abbreviations: RCT, randomized controlled trial; NSCLC, non–small-cell lung cancer.

- Randomized controlled trials in the era of molecular oncology: methodology, biomarkers, and end points
  - Kay et al., *Annals of Oncology*

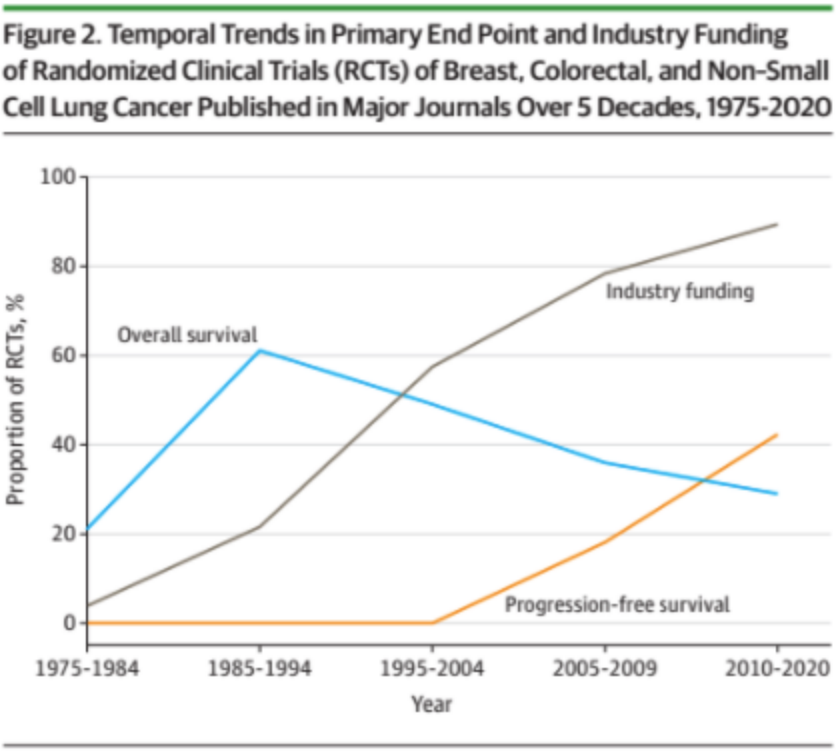
Table 2. Use of time-to-event primary end points among oncology RCTs 2005–2009[a]

	Total RCTs[b] (n = 123)	Breast (n = 59)	CRC (n = 29)	NSCLC (n = 35)
OS	50	7 (5A, 2P)	12 (6A, 6P)	31 (3A, 27P, 1N)
Other time-to-event end points				
DFS	25	21 (21A)	4 (4A)	
RFS	9	9 (8A, 1N)		
TTP	10	7 (7P)	3 (3P)	
PFS	25	11 (11P)	10 (1A, 9P)	4 (4P)
EFS	3	3 (3A)		
DDFS	1	1 (1A)		

[a]Results in parentheses refer to trial setting; A, adjuvant; N, neoadjuvant; P, palliative.
[b]RCTs included in this Table include only those studies with a time-to-event primary end point (i.e. 123/137).
RCT, randomized controlled trial; OS, overall survival; DFS, disease-free survival; RFS, relapse-free survival; TTP, time to progression; PFS, progression-free survival; EFS, event-free survival; DDFS, distant disease-free survival.

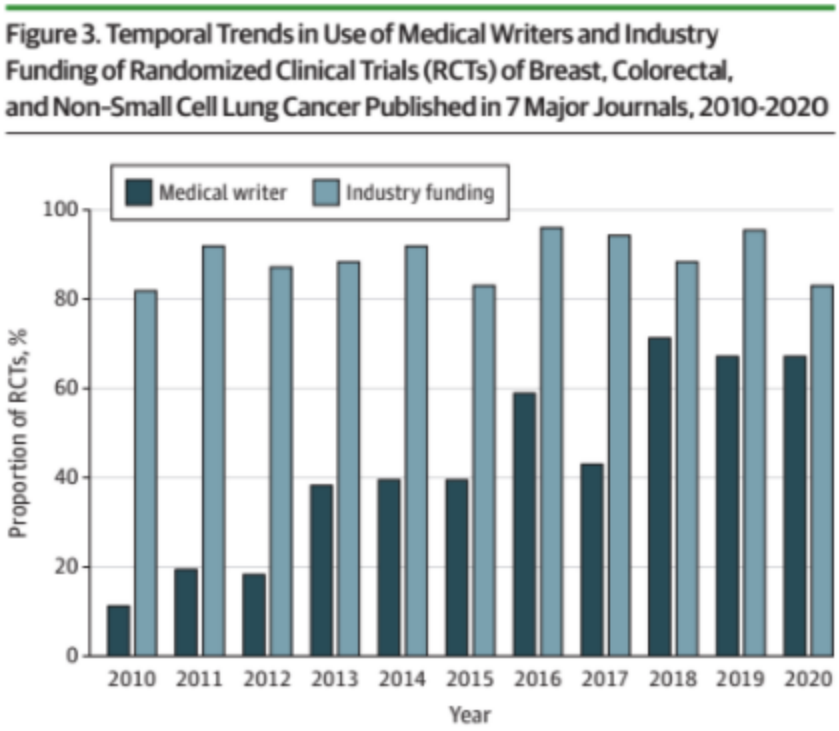
Kay et al.

- Evolution of the Randomized Clinical Trial in the Era of Precision Oncology
  - Del Paggio et al., *JAMA Oncology*



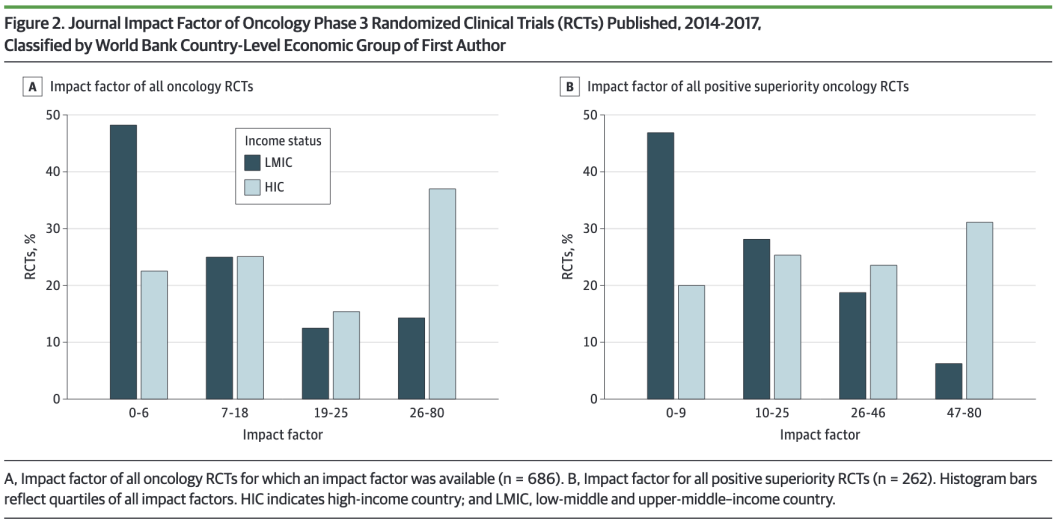
Del Paggio et al.

- The industry is both good and bad:
    1. The good thing about the industry is we have more putative cancer compounds than we've ever had in history
    2. The bad is we are increasingly measuring endpoints that do not themselves matter to patients
- Use of medical writers



Del Paggio et al.

- **Time toxicity [33:00]**
  - Has the Current Oncology Value Paradigm Forgotten Patients' Time?
    - Fundytus et al., *JAMA Oncology*
- **Global oncology [35:00]**
  - An Analysis of Contemporary Oncology Randomized Clinical Trials From Low/Middle-Income vs High-Income Countries
    - Wells et al., *JAMA Oncology*



Wells et al.

- This show that a positive trial from an LMIC is still published in a much lower impact journal than a negative trial from an HIC

- **Moonshots [42:00]**
  - Cancer groundshot: going global before going to the moon
    - Gyawali et al., *Lancet Oncology*
  - Access to cancer medicines deemed essential by oncologists in 82 countries: an international, cross-sectional survey
    - Fundytus et al., *Lancet Oncology*

	Overall		Low-income and lower-middle-income countries		Upper-middle-income countries		High-income countries	
	Top 20 drugs	Number of respondents (%)	Top 20 drugs	Number of respondents (%)	Top 20 drugs	Number of respondents (%)	Top 20 drugs	Number of respondents (%)
1	Doxorubicin	499 (53%)	Doxorubicin	105 (64%)	Doxorubicin	94 (57%)	Pembrolizumab*	311 (50%)
2	Cisplatin	470 (50%)	Cisplatin	91 (55%)	Pembrolizumab*	86 (52%)	Doxorubicin	300 (49%)
3	Paclitaxel	423 (45%)	Cyclophosphamide	90 (55%)	Trastuzumab	84 (51%)	Cisplatin	300 (49%)
4	Pembrolizumab	414 (44%)	Carboplatin	84 (51%)	Cisplatin	79 (48%)	5-fluorouracil	277 (45%)
5	Trastuzumab	402 (42%)	Capecitabine	80 (48%)	Carboplatin	72 (44%)	Paclitaxel	276 (45%)
6	Carboplatin	390 (41%)	Paclitaxel	79 (48%)	Paclitaxel	68 (41%)	Trastuzumab	275 (44%)
7	5-fluorouracil	386 (41%)	Docetaxel	56 (34%)	Tamoxifen	67 (41%)	Carboplatin	234 (38%)
8	Tamoxifen	345 (36%)	Tamoxifen	50 (30%)	Capecitabine	64 (39%)	Tamoxifen	228 (37%)
9	Capecitabine	329 (35%)	5-fluorouracil	49 (30%)	5-fluorouracil	60 (36%)	Capecitabine	185 (30%)
10	Cyclophosphamide	318 (34%)	Imatinib	45 (27%)	Docetaxel	57 (35%)	Oxaliplatin	184 (30%)
11	Docetaxel	296 (31%)	Gemcitabine	45 (27%)	Cyclophosphamide	51 (31%)	Docetaxel	183 (30%)
12	Oxaliplatin	269 (28%)	Trastuzumab	43 (26%)	Oxaliplatin	48 (29%)	Dexamethasone	182 (29%)
13	Dexamethasone	248 (26%)	Dexamethasone	41 (25%)	Abiraterone	41 (25%)	Cyclophosphamide	177 (29%)
14	Nivolumab	205 (22%)	Methotrexate	40 (24%)	Anastrozole	31 (19%)	Nivolumab	173 (28%)
15	Rituximab	203 (21%)	Vincristine	40 (24%)	Osimertinib†	29 (18%)	Rituximab	146 (24%)
16	Imatinib	184 (19%)	Oxaliplatin	37 (22%)	Imatinib	28 (17%)	Osimertinib†	112 (18%)
17	Gemcitabine	180 (19%)	Etoposide	36 (22%)	Goserelin	27 (16%)	Imatinib	111 (18%)
18	Etoposide	170 (18%)	Rituximab	35 (21%)	Gemcitabine	26 (16%)	Letrozole*	111 (18%)
19	Osimertinib†	157 (17%)	Bortezomib	28 (17%)	Dexamethasone	25 (15%)	Gemcitabine	109 (18%)
20	Letrozole*	143 (15%)	Gefitinib	25 (15%)	Etoposide	25 (15%)	Etoposide	109 (18%)

Data are n (%). Medicines listed are those selected by oncologists in response to the primary study question. Overall results are shown for all respondents in addition to rank order lists for three different World Bank economic classifications based on respondents' country of practice. *Valid substitution for a listed WHO Essential Medicines List (EML) medication based on identical drug class or mechanism. †Not included on the current WHO EML.

***Table 2:* 20 most commonly selected cancer medicines by 948 oncologists**

Fundytus et al.

- When considering financial toxicity

	Overall number of responses*	Universally available†	Substantial OOP expenses‡	Risk of catastrophic expenditure§	Not available
Top 20 medications in low-income and lower-middle-income countries					
Doxorubicin	102	37 (36%)	33 (32%)	27 (27%)	5 (5%)
Cisplatin	77	42 (48%)	25 (28%)	18 (21%)	3 (3%)
Cyclophosphamide	88	37 (42%)	27 (31%)	20 (23%)	4 (5%)
Carboplatin	86	26 (33%)	27 (34%)	26 (33%)	0
Capecitabine	74	18 (24%)	27 (37%)	26 (35%)	3 (4%)
Paclitaxel	73	18 (25%)	31 (43%)	21 (29%)	3 (4%)
Docetaxel	55	13 (24%)	21 (38%)	19 (35%)	2 (4%)
Tamoxifen	47	17 (36%)	18 (38%)	9 (19%)	3 (6%)
5-fluorouracil	47	21 (45%)	10 (21%)	12 (26%)	4 (8%)
Imatinib	42	15 (36%)	21 (50%)	6 (14%)	0
Gemcitabine	42	8 (19%)	16 (38%)	16 (38%)	2 (5%)
Trastuzumab	41	6 (15%)	6 (15%)	28 (68%)	1 (2%)
Dexamethasone	41	22 (54%)	12 (29%)	6 (15%)	1 (2%)
Methotrexate	37	16 (43%)	12 (32%)	6 (16%)	3 (8%)
Vincristine	39	19 (49%)	7 (18%)	9 (23%)	4 (10%)
Oxaliplatin	35	8 (23%)	12 (34%)	14 (40%)	1 (3%)
Etoposide	34	13 (38%)	9 (27%)	9 (27%)	3 (9%)
Rituximab	35	3 (9%)	9 (26%)	22 (63%)	1 (3%)
Bortezomib	28	6 (21%)	12 (43%)	7 (25%)	3 (11%)
Gefitinib	24	8 (33%)	12 (50%)	3 (13%)	1 (4%)
Top 20 medications in upper-middle-income countries					
Doxorubicin	88	77 (88%)	5 (6%)	2 (2%)	4 (4%)
Pembrolizumab	80	10 (13%)	22 (28%)	32 (40%)	16 (20%)
Trastuzumab	79	50 (63%)	18 (23%)	7 (9%)	4 (6%)
Cisplatin	74	65 (88%)	6 (8%)	2 (3%)	1 (1%)
Carboplatin	66	55 (83%)	6 (9%)	2 (3%)	3 (5%)
Paclitaxel	64	55 (86%)	6 (9%)	2 (3%)	1 (2%)
Tamoxifen	63	54 (86%)	7 (11%)	0	2 (4%)

(Table 3 continues on next page)

Fundytus et al.

- **Moving forward [50:00]**
  - Cancer patients need better care, not just more technology
    - Sullivan et al., *Nature*

> "I remain hopeful that current conversations and in fact, the next generation of physicians, but also our patients,

> who serve as the inspiration for much of what we do will drive change so that we can move towards a system that prioritizes, high value cancer care.” - Dr. Booth

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