4.26: Recent Kidney Cancer Trials, Unethical Cancer Clinical Trial, & CASSIOPEIA

Season	4
Type	Plenary Session

We Discuss:

- Systematic Review [1:08]
- Lymphoma [7:00]
- CASSIOPEIA [24:00]

Plenary Session 4.26 Show Notes

Overview

Monologue

- **Systematic Review [1:08]**
  - Use of Second-line Immunotherapy in Control Arms of Randomized Clinical Trials in Kidney Cancer
    - Sharp et al., JAMA Network Open
  - We are all aware that, until recently, the gold standard of therapy for RCC was a TKI frontline regimen (e.g., Sunitinib or Pazopanib)
    - Immunotherapy is often used to treat second line upon progression
  - The trials

Table. Postprotocol Immunotherapy Administration Characteristics in Trials of Combination Immunotherapy Regimens vs TKI for First-line Advanced Kidney Cell Carcinoma

Trial	Intervention arm	Control arm	Total patients assigned to control arm	Patients in the control arm, No. (%)				
				Discontinued TKI	Receiving any postprotocol therapy	Receiving postprotocol immunotherapy	Receiving immunotherapy as percentage of those who discontinued TKI	Receiving immunotherapy as percentage of those who received any postprotocol therapy
CLEAR (NCT02811861)[10,a]	Pembrolizumab + lenvatinib	Sunitinib	357	290 (81.2)	206 (57.7)	154 (43.1)	154/290 (53.1)	154/206 (74.8)
CheckMate 9ER (NCT03141177)[12]	Nivolumab + cabozantinib	Sunitinib	328	236 (72.0)	108 (32.9)	67 (20.4)	67/236 (28.4)	67/108 (62.0)
IMmotion151 (NCT02420821)[8]	Atezolizumab + bevacizumab	Sunitinib	461	323 (70.1)	238 (51.6)	144 (31.2)	144/323 (44.6)	144/238 (60.5)
KEYNOTE-426 (NCT02853331)[11,b]	Pembrolizumab + axitinib	Sunitinib	429	353 (82.3)	242 (56.4)	169 (39.4)	169/353 (47.9)	169/242 (69.8)
JAVELIN Renal 101 (NCT02684006)[9,b]	Avelumab + axitinib	Sunitinib	444	336 (75.7)	227 (51.1)	159 (35.8)	159/336 (47.3)	159/227 (70.0)
CheckMate 214 (NCT02231749)[17,b]	Nivolumab + ipilimumab	Sunitinib	546	531 (97.3)	382 (56.4)	239 (43.8)	239/531 (45.0)	239/382 (62.6)
Total	Combination immunotherapy	Sunitinib	2565	2069 (80.7)	1403 (54.7)	932 (36.3)	932/2069 (45.0)	932/1403 (66.4)

Abbreviation: TKI, tyrosine kinase inhibitor.

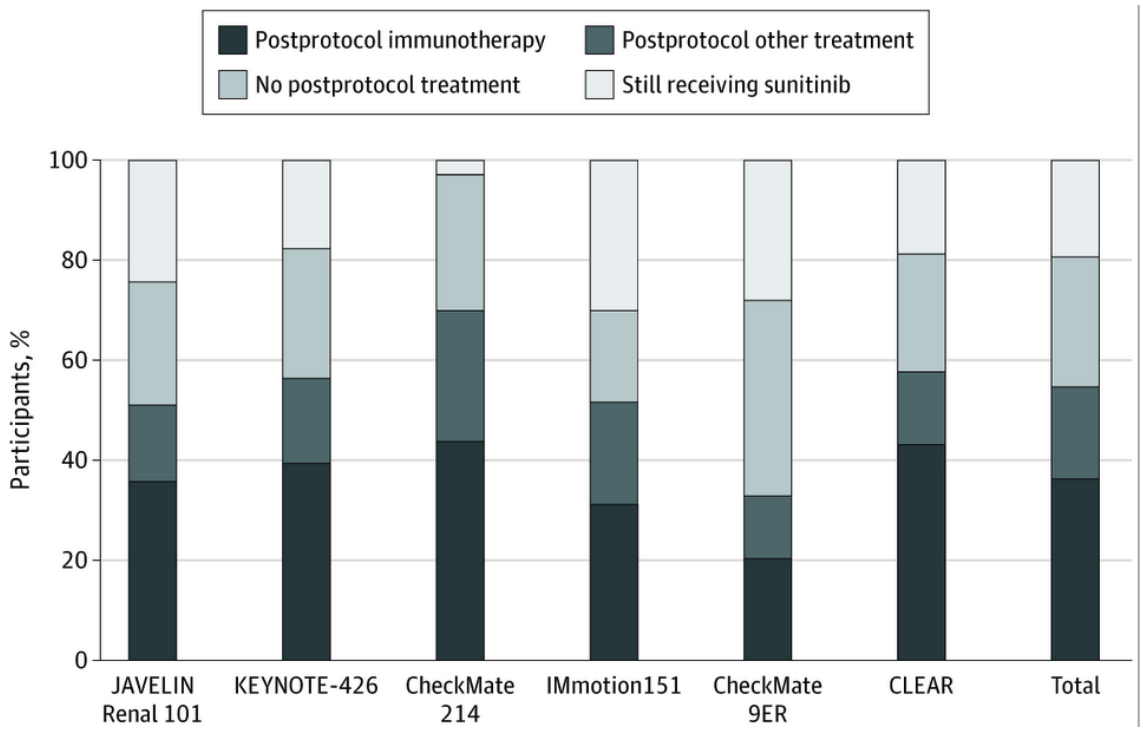
[a] An additional intervention arm of lenvatinib or everolimus was not included in our analysis because it did not include an immunotherapy component.

[b] Published updates of results for these trials were used for calculations.

Sharp et al.

- All of these studies went up against sunitinib which was the standard of care and they all have found some PFS benefit
    - When you combine active anti-cancer drugs, there will be a deeper response rate and a PFS benefit
        - However, you will exhaust some tools in your toolbox and what do you have left when the patient progresses?
            - Keeping this in mind, the relevant question is do you improve PFS-2 or do you improve PFS-3? And of course most importantly, do you improve overall survival or global health related quality of life?
                - That's the question that these trials have to answer

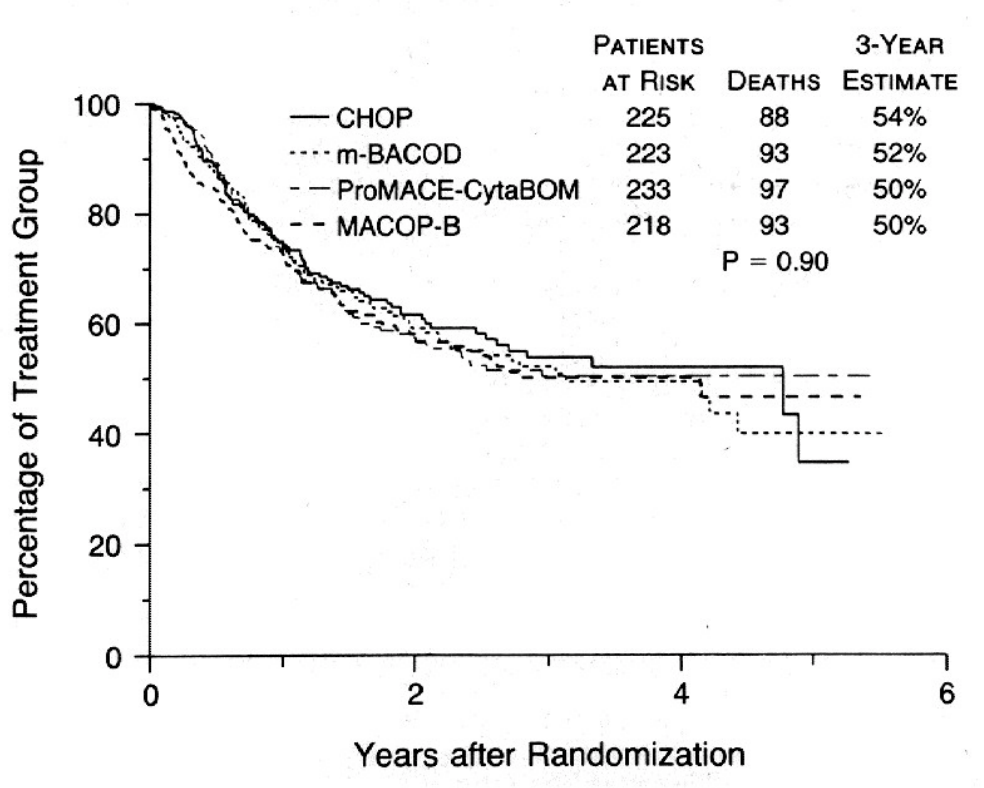
- The story



Sharp et al.

- The dark bar should be much higher
  - A counterpoint is that patients are not fit enough for further trials, but this is ignorant because these patients are of a highly select group participating in a regimented RCT
- Why does this happen?
  - This has become the common of nature of modern randomized control trials
    - The likely answer is that trialists are going to places where post protocol immunotherapy is essentially untenable (i.e., the patients can't afford it)

- **Lymphoma [7:00]**
  - Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma
    - Fisher et al., NEJM 1993



Fisher et al.

- Dose adjusted R-EPOCH
  - Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303
    - Bartlett et al., JCO
- Was this Cancer Clinical trial Unethical?
  - YouTube
    - Watch this monologue
  - Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer (POLO)
    - Golan et al., NEJM

- **CASSIOPEIA [24:00]**

- Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial
  - Moreau et al., The Lancet Oncology
- YouTube
  - Watch this monologue
- Results

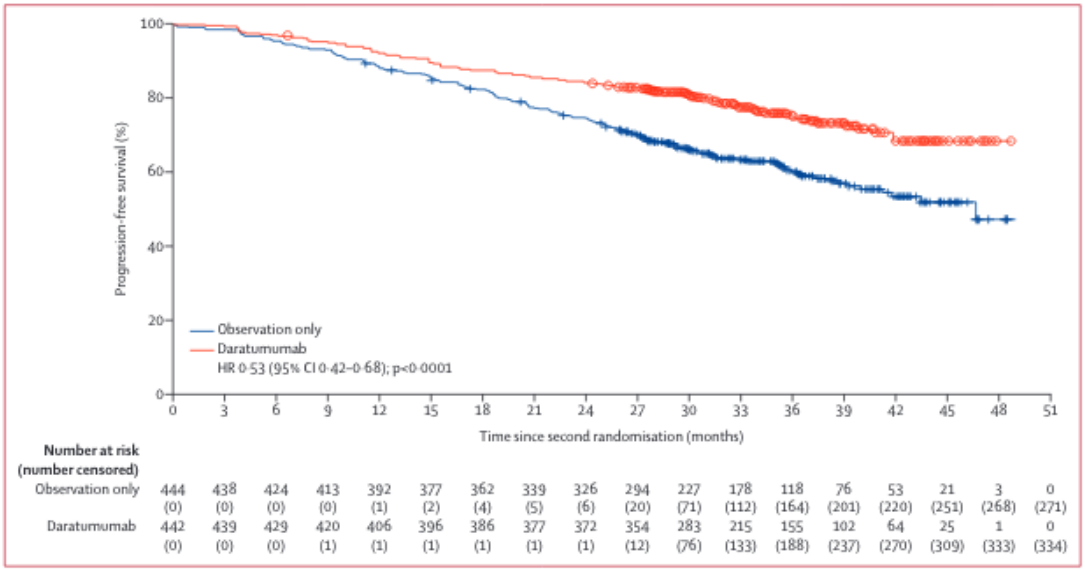


Figure 2: **Kaplan-Meier estimates of progression-free survival in patients in the maintenance-specific intention-to-treat population**
HR=hazard ratio.

Moreau et al.

- Problems
  1. When you take a fixed course of therapy and make it indefinite, the endpoint you want to show is that you improve overall survival
     a. Combining drugs and extending treatment — a PFS end point is not sufficient
        i. Gyawali & Prasad; Nature Reviews Clinical Oncology
  2. When ASCO 2016 rolled out, and McCarthy and colleagues published their meta analysis showing that lenalidomide was the standard of care maintenance therapy in this setting

a. These findings were made public mere days after the trial began

i. It's difficult to imagine the trialists were unaware of the direction of the wind at this moment

1. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis

a. McCarthy et al., JCO

3. VTD

a. Obviously, that's an acceptable regimen in Europe at the time of this study

i. But it wasn't really the US standard of care where we use VRD

4. Do you need to give maintenance DARA or can you just give it relapse and achieve the same outcome?

a. The trial doesn't really answer that question

- Open questions
  - Could you get the same results by using fewer drugs but ensuring that post-procedure care was adequate?
  - Cost
    - Trials need to be ran to answer whether or not:
      1. You need to give all these drugs upfront indefinitely or whether
      2. Or you can actually have a set of standardized sets of drugs for different lines of therapy and achieve the same overall survival

- **Other papers mentioned:**
  - Phase I trials and therapeutic intent in the age of precision oncology: What is a patient's chance of response?
    - Tao et al., EJC
  - Analysis of Control Arm Quality in Randomized Clinical Trials Leading to Anticancer Drug Approval by the US Food and Drug Administration
    - Hilal et al., JAMA Oncology

    - Quality of control groups in randomised trials of multiple myeloma enrolling in the USA: a systematic review
        - Mohyuddin et al., Lancet Haematology
    - Patient Experience Captured by Quality-of-Life Measurement in Oncology Clinical Trials
        - Haslam et al., JAMA Network Open
- **Other people mentioned:**
    - Jack Sharp
    - Ali Khaki

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