Renal Cell Carcinoma Clinical Decision Making

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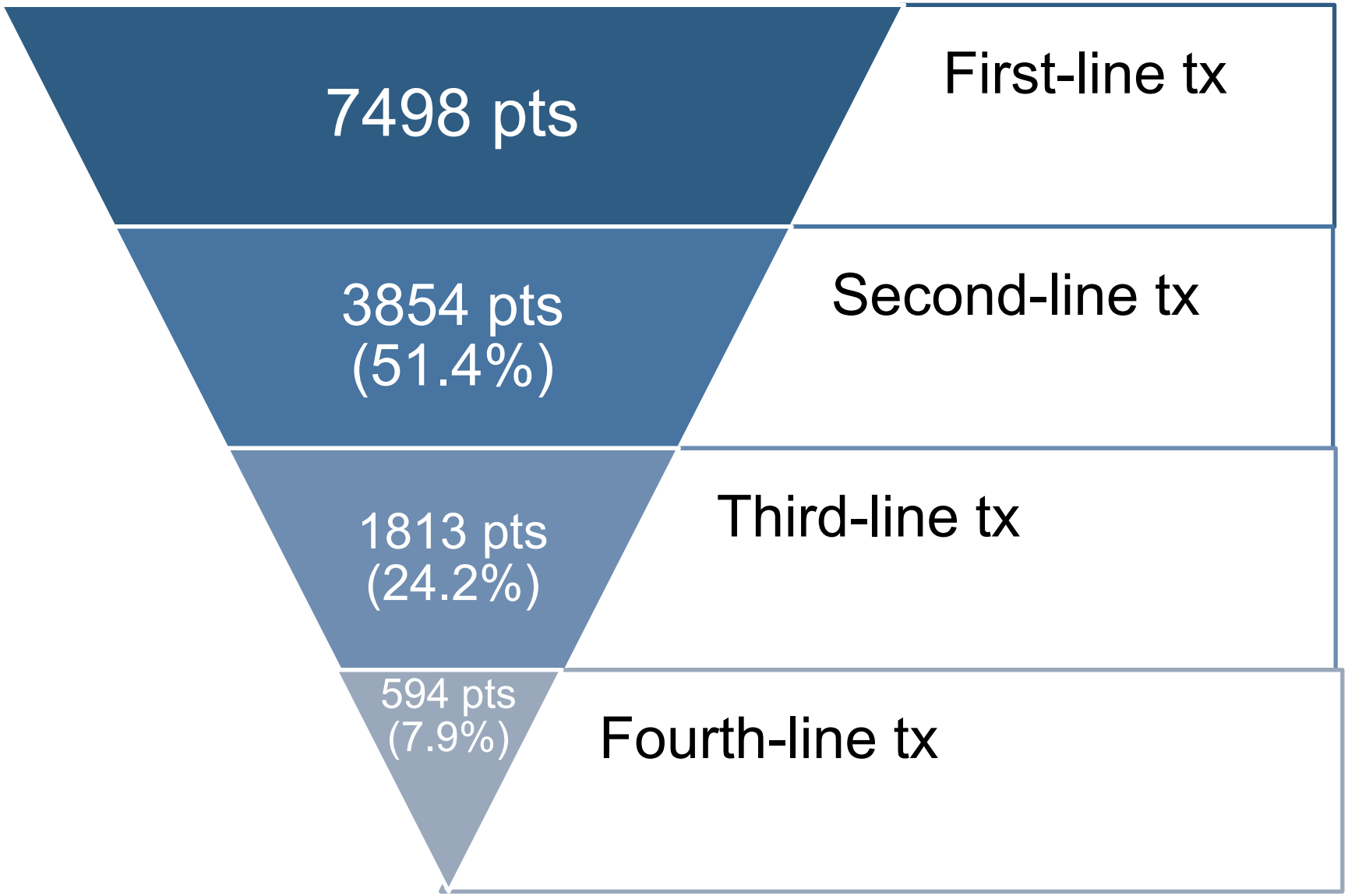
Cytoreductive Nephrectomy

- In pre-TKI era, RCTs showed improved OS with cytoreductive Nx
- In TKI era, role of Nx is not established
  - CARMENA study: sunitinib non-inferior to sunitinib plus Nx
    - High proportion of poor risk
    - Post-hoc analysis: OS improved in patients with 1 risk factor
- **No prospective data with CPIs**
- Consider in patients with good PS and $\leq$ 1 risk factor after major response to 8-12 weeks of systemic therapy
- Several ongoing studies in ICI era: NORDIC-SUN, CYTOSHRINK, PROBE

Méjean A, et al. *N Engl J Med*. 2018;379(5):417-427. Méjean A, et al. *Eur Urol*. 2021;80(4):417-424.

Attrition From One Line to Next Line of Therapy: IMDC Data



Stukalin. *Kidney Cancer* 2018;2:31.

First-line IO Combination Trials in mRCC

	CheckMate 214 (Ipi/Nivo)[1] (n=550 vs n=546)	KEYNOTE-426 (Axi/Pembro)[2] (n=432 vs n=429)	CheckMate 9ER (Cabo/Nivo)[3,4] (n=323 vs n=328)	CLEAR (Len/Pembro)[5] (N=355 vs n=357)
HR mOS, months	**0.72** 55.7 vs 38.4	**0.73** 45.7 vs 40.1	**0.70** 49.5 vs 35.5	**0.72** NR vs NR
Landmark OS 12 mo Landmark OS 24 mo	**83%** vs. 78% **71%** vs. 61%	**90%** vs. 79% **74%** vs. 66%	**86%** vs. 76% **70%** vs 60%	**90%** vs 79% (est.) **79%** vs. 70%
HR mPFS, months	**0.86** 12.3 vs 12.3	**0.68** 15.7 vs 11.1	**0.58** 16.6 vs 8.4	**0.39** 23.9 vs 9.2
ORR, %	**39** vs 32	**60** vs 40	**56** vs 28	**71** vs 36
CR, %	**12** vs 3	**10** vs 4	**12** vs 5	**16** vs 4
Med f/u, months	**67.7**	**42.8**	**44.0**	**33.7**
Primary PD, %	**18**	**11**	**6**	**5**
Landmark PFS	30% (5 years)	29% (3 years)	39% (2 years)	

[1] Motzer et al. *Cancer*. 2022;128(11):2085-2097.[2] Rini et al. ASCO 2021. [3] Motzer et al. *Lancet Oncol*. 2022;23(7):888-898.. [4] Burroto, et al. J Clin Oncol. 2023;41:6_suppl, 603.
[5]Motzer et al. *N Engl J Med*. 2021;384(14):1289-1300.

IO/TKI vs IO/IO

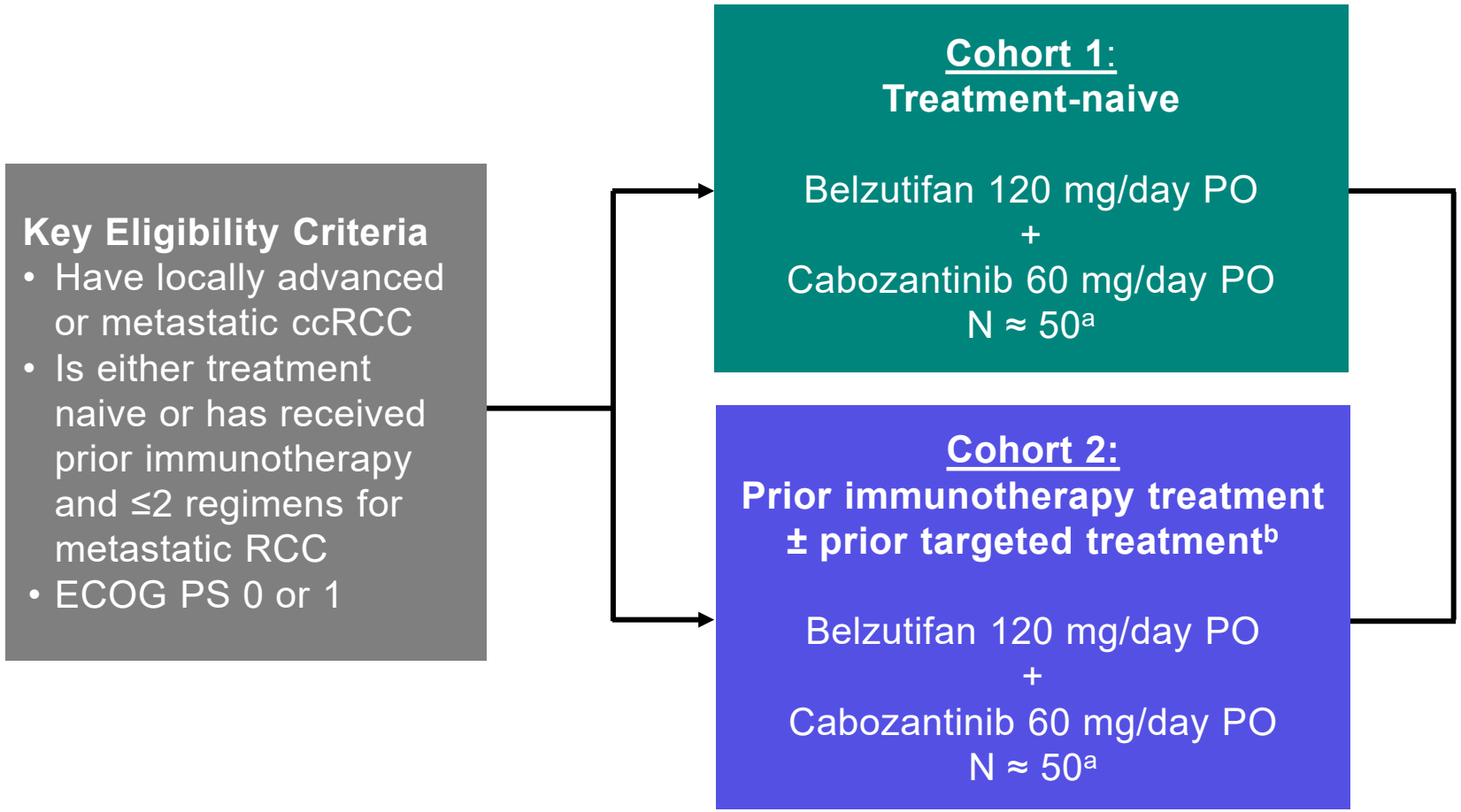
	Pros	Cons
IO/TKI	• Consistent effects on OS, PFS and ORR across IMDC risk groups • Significant tumor burden reduction reflected in high ORR and long PFS • Manageable toxicity • QoL maintained vs TKI	• Long-term durability of response yet to be demonstrated • Potential for acute and chronic TKI toxicity
IO/IO	• OS and ORR advantages over TKI monotherapy • Durability of response / disease-control • Treatment-free interval possible • QoL improved vs TKI	• Sometimes significant initial toxicity • Lower ORR and shorter PFS compared with IO/TKI regimens • Less effect in favorable risk patients

Phase 2 LITESPARK-003 Study of Belzutifan in Combination With Cabozantinib for Advanced Clear Cell Renal Cell Carcinoma

Toni K. Choueiri[1]; Todd Bauer[2]; Jaime Merchan[3]; David McDermott[4]; Robert Figlin[5]; Edward Arrowsmith[6]; Marc Dror Michaelson[7]; Elisabeth I. Heath[8]; Anishka D'Souza[9]; Song Zhao[10]; Leila Mhamdi[11]; Rodolfo Perini[11]; Donna Vickery[11]; Scott S. Tykodi[12]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [3]University of Miami Health System, Miami, FL, USA; [4]Beth Israel Deaconess Medical Center, Boston, MA, US; [5]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [6]Tennessee Oncology, Chattanooga, TN, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]Karmanos Cancer Institute, Detroit, MI, USA; [9]University of Southern California, Los Angeles, CA, USA; [10]Swedish Medical Center, Seattle, WA, USA; [11]Merck & Co., Inc., Rahway, NJ, USA; [12]University of Washington and Fred Hutchinson Cancer Center, Seattle, WA, USA

Study Design of LITESPARK-003 (NCT03634540)



Tumor Assessments

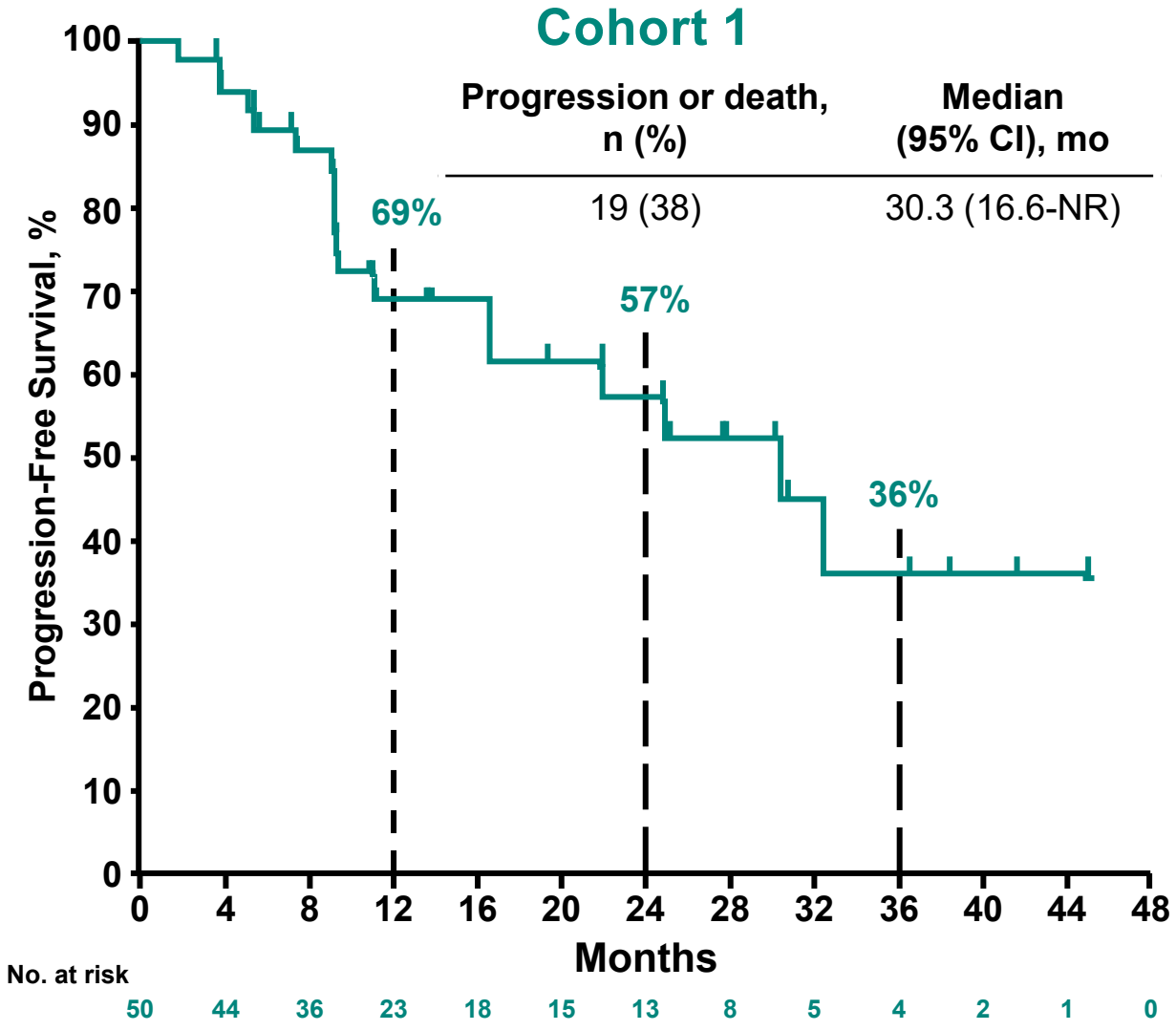
- Week 9, then Q8W for 12 months and Q12W thereafter

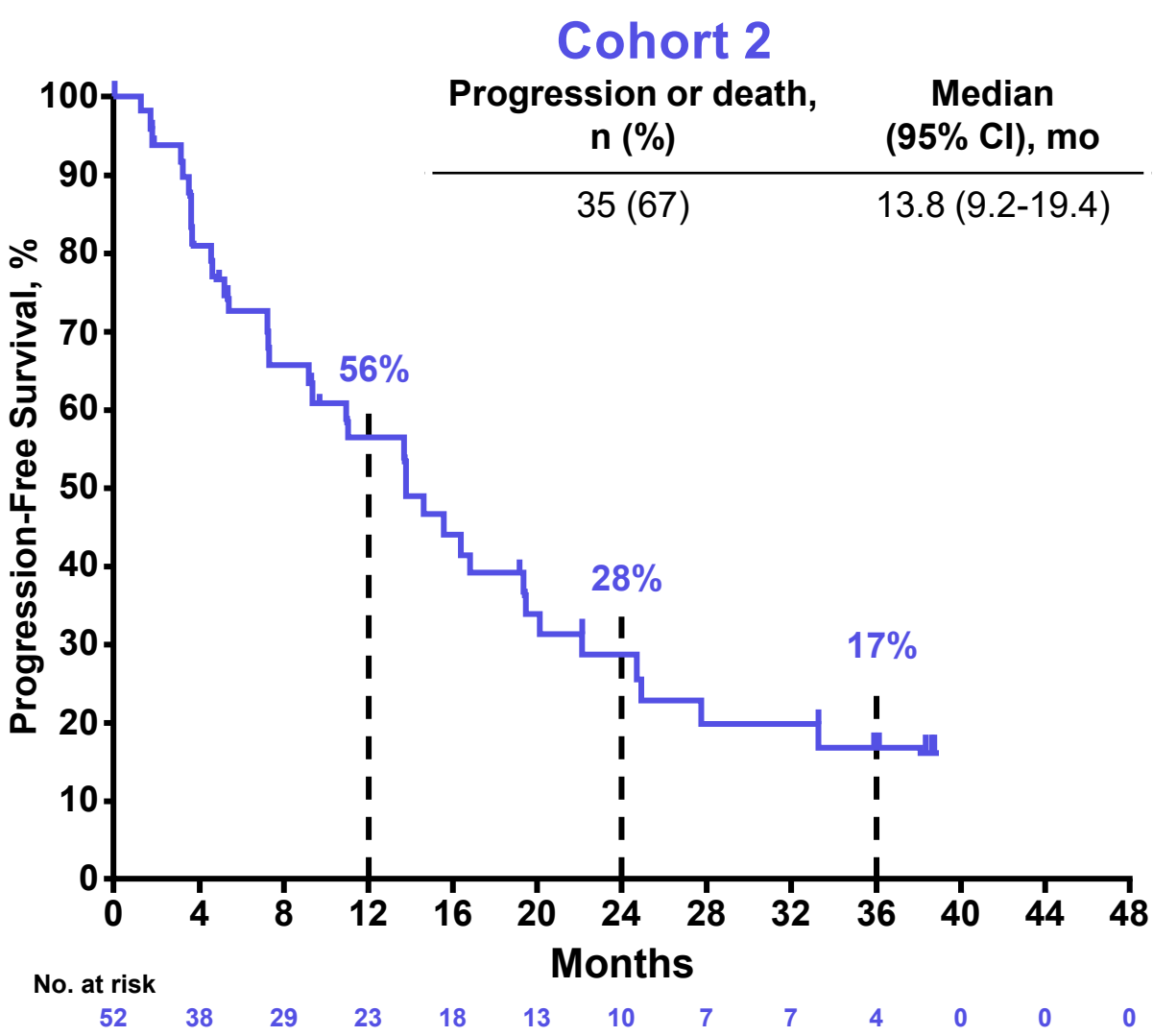
End Points

- Primary: ORR per RECIST v1.1 by investigator
- Secondary: PFS, DOR, and TTR per RECIST v1.1 by investigator, OS, safety/tolerability

[a]Planned enrollment.
[b]No more than 2 prior immunotherapy regimens for locally advanced or metastatic RCC. Combination regimens with a PD-1/L1 inhibitor and CTLA-4 inhibitor or VEGF/VEGFR inhibitor were counted as 1 regimen.

Progression-Free Survival by Investigator





Data cutoff date: May 15, 2023.