Combination Immunotherapiess for Renal cell carcinoma

Subjects: Immunology
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Renal cell carcinoma (RCC) constitutes a considerable burden on public health, with an estimated 81,800 new diagnoses and 14,890 mortality cases predicted for 2023 in the United States alone. Over the recent years, the incidence of RCC has exhibited a consistent upward trend. Among the various subtypes, clear cell renal cell carcinoma (ccRCC) predominates, accounting for approximately 70–80% of RCC cases, with the majority originating from the proximal convoluted tubule. Conversely, the non-clear cell renal cell carcinomas (nccRCCs), encompassing entities such as papillary, chromophobe, translocation, and medullary RCC, as well as collecting duct carcinoma, comprise 20–30% of RCC and harbor distinct histopathological and molecular characteristics.

clear cell renal cell carcinoma | immune checkpoint inhibitors | immunotherapeutic combinations | bispecific antibodies

1. Rationale for Combining Immunotherapies

Checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 have significantly advanced treatment options for metastatic clear cell renal cell carcinoma (ccRCC) [1]. However, many patients exhibit resistance initially or relapse following monotherapy [2][3]. Both preclinical and clinical evidence suggest the potential utility of combination strategies, either pairing checkpoint inhibitors or integrating agents such as VEGF inhibitors or immunomodulators [4][5]. These combinatorial regimens aim to exert a broader anticancer effect, with goals to improve response rates, extend response duration, and overcome resistance mechanisms in immunogenic tumors. The synergy observed in these combinations could markedly alter therapeutic approaches for metastatic ccRCC [4]. (See **Table 1** for a summary of key studies.)

Table 1. Key clinical trials of immune checkpoint inhibitor combinations in ccRCC.

NCT Number	Trial Name	Phase	Therapy Setting	Patients	Description	mOS (Months)	mPFS (Months)	ORR (%)
NCT02231749	CheckMate 214	3	1st line	425 vs. 422	nivolumab + ipilimumab vs. sunitinib	47.0 (95% CI, 35.4–57.4) vs. 26.6 (95% CI,	11.6 (95% CI, 8.7–15.5) vs. 8.4 (95%	42 (95% CI, 37–47) vs. 27

NCT Number	Trial Name	Phase	Therapy Setting	Patients	Description	mOS (Months)	mPFS (Months)	ORR (%)
						22.1–33.5); HR = 0.68 (95% CI, 0.58–0.81), *p* < 0.0001	CI, 7.0–10.8) HR = 0.82 (99.1% CI, 0.64–1.05), *p* = 0.03	(95% CI, 22–31)
NCT01472081	CheckMate 016	1	2nd line	47 vs. 47	3 mg/kg nivolumab + 1 mg/kg ipilimumab vs. 1 mg/kg nivolumab + 3 mg/kg ipilimumab	NR (95% CI, 26.7-NE) vs. 32.6 (95% CI, 26.0-NE)	7.7 (95% CI, 3.7–14.3) vs. 9.4 (95% CI, 5.6–18.6)	40 (95% CI, 26–56) vs. 40 (95% CI, 26–56)
NCT02684006	Javelin Renal 101	3	1st line	442 vs. 444	avelumab + axitinib vs. sunitinib	NE (95% CI, 30-NE) vs. NE (95% CI, 27.4-NE) HR = 0.80 (95% CI, 0.62–1.03), *p* = 0.0392	13.3 (95% CI, 11.1–15.3) vs. 8.0 (95% CI, 6.7–9.8) HR = 0.69 (95% CI, 0.57–0.83), *p* < 0.0001	53 (95% CI, 48–57) vs. 27 (95% CI, 23–32)
NCT02853331	KEYNOTE-426	3	1st line	432 vs. 429	pembrolizumab + axitinib vs. sunitinib	NR vs. 35.7 (95% CI, 33.3-NE) HR = 0.53 (95% CI, 0.38–0.74), *p*	15.4 (95% CI, 12.7–18.9) vs. 11.1 (95% CI, 9.1–12.5) HR = 0.71	59 (95% CI, 55–64) vs. 36 (95% CI, 31–40)

NCT Number	Trial Name	Phase	Therapy Setting	Patients	Description	mOS (Months)	mPFS (Months)	ORR (%)
						< 0.0001	(99.8% CI, 0.60–0.84), *p* < 0.0001	
NCT03141177	CheckMate 9ER	3	1st line	323 vs. 328	carbozantinib + nivolumab vs. sunitinib	NR vs. NR HR = 0.60 (98.9% CI, 0.40–0.89), *p* = 0.001	16.6 (95% CI, 12.5–24.9) vs. 8.3 (95% CI, 7.0–9.7) HR = 0.51 (95% CI, 0.41–0.64), *p* < 0.0001	56 (95% CI, 50–61) vs. 27 (95% CI, 22–32)
NCT02811861	Clear	3	1st line	355 vs. 357	lenvatinib + pembrolizumab vs. sunitinib	NR vs. NR HR = 0.66 (95% CI, 0.49–0.88), *p* = 0.005	23.9 (95% CI, 20.8–27.7) vs. 9.2 (95% CI, 6.0–11.0) HR = 0.39 (95% CI, 0.32–0.49), *p* < 0.001	71 (95% CI, 66–76) vs. 36 (95% CI, 48–59)
NCT02420821	Immotion 151	3	1st line	454 vs. 461	atezolizumab + bevacizumab vs. sunitinib	36.1 (95% CI, 31.5–42.3) vs. 35.3 (95% CI, 28.6–42.1)	9.6 (95% CI, 8.3–11.5) vs. 8.3 (95% CI, 7.0–9.7)	37 (95% CI, 32–41) vs. 33 (95% CI,

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(11.6 vs. 8.4 months with sunitinib). These pivotal findings have underpinned guidelines endorsing nivolumab/ipilimumab as a first-line therapy for intermediate/poor-risk metastatic ccRCC [6].

NCT Number	Trial Name	Phase	Therapy Setting	Patients	Description	mOS (Months)	mPFS (Months)	ORR (%)
						HR = 0.0.91 (95% CI, 0.76–1.08), p = 0.27	HR = 0.88 (95% CI, 0.74–1.04), p = 0.12	29–38)
[8] NCT02501096	KEYNOTE-146	1b/2	2nd line	145	lenvatinib + pembrolizumab	32.2 (95% CI, 29.8–55.8)	14.1 (95% CI, 11.6–18.4)	63 (95% CI, 55–71)

Abbreviations: CI: confidence interval; HR: hazard ratio; mOS: median overall survival; mPFS: median progression-free survival; NCT: National Clinical Trial; NE: not estimable; NR: not reached; ORR: objective response rate.

3. Checkpoint Inhibitors + Vascular Endothelial Growth Factor Inhibitors

A promising therapeutic strategy in oncology entails the combination of immune checkpoint inhibitors with VEGF inhibitors, such as cabozantinib and axitinib [9]. VEGF inhibitors target the VEGF signaling cascade, a crucial mechanism in tumor angiogenesis [10]. By suppressing VEGF, angiogenesis may be hindered, thereby potentially restricting tumor growth. The combination of VEGF inhibitors with a checkpoint blockade could enhance antitumor immune responses and mitigate tumor-induced immunosuppression.

3.1. Avelumab + Axitinib

The JAVELIN Renal 101 phase III trial evaluated the efficacy of first-line avelumab plus axitinib compared to sunitinib in patients with advanced ccRCC [11]. This research demonstrated pronounced improvements in PFS and ORR with combination therapy compared to sunitinib monotherapy for untreated metastatic ccRCC. Among 886 randomized participants, the subgroup with PD-L1-positive tumors exhibited a superior median PFS of 13.8 months with avelumab-axitinib versus 7.0 months with sunitinib. This PFS benefit persisted in the overall population, with medians of 13.3 and 8.0 months for the combination and sunitinib arms, respectively. The combination therapy also yielded a higher ORR of 53% compared to 27% for sunitinib [11]. An extended follow-up analysis demonstrated sustained improvements in survival, response rates, and DOR with the combination of avelumab and axitinib compared to sunitinib. The median OS was not reached for the combination of avelumab and axitinib, compared to 37.8 months for sunitinib. The median PFS was 13.9 months for avelumab and axitinib, versus 8.5 months for sunitinib [12]. In summary, avelumab-axitinib demonstrated enhanced efficacy and acceptable safety compared to sunitinib, although researchers await more comprehensive data.

3.2. Pembrolizumab + Axitinib

The KEYNOTE-426 phase III trial evaluated the efficacy of combined pembrolizumab plus axitinib compared to sunitinib monotherapy in patients with previously untreated advanced or metastatic ccRCC [13]. Across 861 randomized participants, the treatment arms consisted of pembrolizumab-axitinib combination therapy versus sunitinib alone, with primary endpoints of OS, PFS, and ORR. After a median follow-up of 42.8 months, results demonstrated superior efficacy for the combination regimen. The median OS was not reached with pembrolizumab-axitinib, showing marked improvement compared to 35.7 months for sunitinib. The combination yielded a higher ORR of 59.3% versus 35.7% for sunitinib, alongside complete response rates of 5.8% and 1.9%, respectively. Combination therapy also conferred a superior median PFS of 15.4 months compared to 11.1 months with sunitinib [13]. These findings underlie the FDA approval of pembrolizumab-axitinib as a first-line therapy for advanced ccRCC.

After 67.2 months of extended follow-up (five-year analysis), pembrolizumab-axitinib maintained improved outcomes versus sunitinib for advanced ccRCC [14]. At 60 months, OS rates were 41.9% for pembrolizumab-axitinib and 37.1% for sunitinib, while PFS rates were 18.3% and 7.3%, respectively. The median DOR was longer with pembrolizumab-axitinib. Accounting for more subsequent therapies in the sunitinib arm, the OS advantage of pembrolizumab-axitinib remained significant [14]. Collectively, these data from KEYNOTE-426 demonstrate enhanced efficacy for pembrolizumab-axitinib combination therapy in advanced RCC [15].

3.3. Nivolumab + Cabozantinib

The phase III CheckMate 9ER trial evaluated the nivolumab plus cabozantinib combination therapy compared to sunitinib monotherapy in untreated patients with advanced or metastatic ccRCC [16]. This international, open-label, randomized study of 651 patients set PFS as the primary endpoint, assessed by an independent blinded review. After a median follow-up of 18.1 months, the nivolumab-cabozantinib combination demonstrated a superior median PFS of 16.6 months versus 8.3 months with sunitinib. Additionally, the combination conferred a markedly higher ORR of 55.7% compared to 27.1% for sunitinib. At one year, OS rates were 85.7% for the combination versus 75.6% with sunitinib. These compelling data endorse nivolumab-cabozantinib as a notable first-line strategy integrating immunotherapy and targeted therapy for metastatic ccRCC [16].

Extended three-year follow-up data showed durable advantages for nivolumab-cabozantinib over sunitinib, including a median PFS of 16.6 versus 8.4 months and median OS of 49.5 versus 35.5 months [17]. The combination therapy also maintained a higher ORR (56% vs. 28%) and complete response rate (13% vs. 5%). While adverse events were slightly increased with nivolumab-cabozantinib, no new safety signals emerged. These sustained benefits further endorse nivolumab-cabozantinib as a first-line therapy for advanced ccRCC [17].

3.4. Pembrolizumab + Lenvatinib

The phase III CLEAR trial assessed the combination therapy of lenvatinib and pembrolizumab compared to sunitinib monotherapy in untreated patients with advanced or metastatic ccRCC [18]. Across 1,069 randomized

participants, the treatment arms consisted of lenvatinib-pembrolizumab, lenvatinib-everolimus, or sunitinib, with PFS as the primary endpoint. The lenvatinib-pembrolizumab combination demonstrated a superior median PFS of 23.9 months versus 9.2 months for sunitinib, alongside a higher ORR (71.0% vs. 36.1%) and complete response rates (16.1% vs. 4.2%). This combination also showed a pronounced OS advantage over sunitinib. Meanwhile, lenvatinib-everolimus conferred an improved median PFS of 14.7 months compared to 9.2 months with sunitinib [18].

In the extended follow-up from the CLEAR trial, lenvatinib-pembrolizumab maintained a superior PFS of 23.3 months versus 9.2 months for sunitinib after a median follow-up of 27.8 months [19]. Lenvatinib-pembrolizumab also exhibited prolonged OS (median not reached) compared to 33.7 months for sunitinib. Hazard ratios confirmed the significant benefits of the combination over sunitinib [19]. These durable efficacy data underscore the potential of lenvatinib-pembrolizumab as a first-line therapy for advanced ccRCC.

Separately, the phase Ib/II KEYNOTE-146 trial evaluated lenvatinib-pembrolizumab as a second-line therapy [20]. After initial dose-finding across multiple tumor types, the study focused on ccCC, with 65% of patients having received prior ICI and/or tyrosine kinase inhibitor (TKI) therapy. Early results indicated positive effects on PFS and response rates, supporting further research on lenvatinib-pembrolizumab in this setting [21].

4. Ongoing Clinical Trials of Combination Immunotherapies

Numerous clinical trials are currently in progress with the aim of advancing therapeutic approaches for ccRCC by harnessing synergistic combination immunotherapies [4]. These studies are exploring diverse regimens encompassing checkpoint inhibitors, VEGF inhibitors, and innovative agents. As summarized in **Table 2**, notable investigations include the assessment of a personalized vaccine (NCT05269381), the enzymatic inhibitor valemetostat (NCT04388852), the IL-8 inhibitor (NCT04572451), and aldesleukin (NCT03260504). There is also increasing interest in the monoclonal antibody SRF388 (NCT04374877) and the integration of radiation therapy (NCT05327686). Additional trials are evaluating neoadjuvant checkpoint inhibitor combinations, including NCT04393350 and NCT05319015.

Table 2. Key ongoing clinical trials of combination immunotherapies in advanced or metastatic RCC.

NCT Number	Trial Name	Phase	Estimated Patients	Description	Sponsor
NCT05269381	PNeoVCA	1	36	pembrolizumab + personalized neoantigen peptide vaccine	Mayo Clinic
NCT04388852	NA	1	80	ipilimumab + valemetostat	M.D. Anderson Cancer Center
NCT04572451	NA	1	50	nivolumab + anti IL-8 + SBRT	University of Pittsburgh

NCT Number	Trial Name	Phase	Estimated Patients	Description	Sponsor
NCT03260504	NA	1	15	pembrolizumab + aldesleukin	University of Washington
NCT04374877	KEYNOTE-C16	1	220	pembrolizumab + anti IL-27	Surface Oncology
NCT05327686	SAMURAI	2	240	nivolumab or pembrolizumab + axitinib + cabozantinib + SBRT	NRG Oncology
NCT04393350	NA	2	22	pembrolizumab + perioperative lenvatinib	Emory University
NCT05319015	NA	2	30	pembrolizumab + neoadjuvant lenvatinib	UTSW
NCT02811861	KEYNOTE-581	3	1069	levatinib + everolimus or pembrolizumab	Eisai Inc.
NCT05361720	OPTIC	2	54	ipilimumab + nivolumab + cabozantinib	Vanderbilt-Ingram Cancer Center
NCT03288532	RAMPART	3	1750	durvalumab + tremelimumab	University College, London
NCT05148546	NESCIO	2	69	neoadjuvant nivolumab+ ipilimumab + relatlimab	The Netherlands Cancer Institute
NCT04322955	Cyto-KIK	2	48	nivolumab + cabozantinib + cytoreductive nephrectomy	Columbia University
NCT05188118	NA	1	20	ipilimumab + nivolumab + cabozantinib	Icahn School of Medicine at Mount Sinai
NCT05363631	NA	1/2	55	pembrolizumab + axitinib + selenomethionine	University of Iowa
NCT04981509	NA	2	65	bevacizumab + erlotinib + atezolizumab	National Cancer Institute
NCT04090710	CYTOSHRINK	2	78	ipilimumab + nivolumab + SBRT	Ontario Clinical Oncology Group
NCT05411081	PAPMET2	2	200	atezolizumab + cabozantinib	National Cancer Institute

Examining select examples illustrates the intricate details and objectives. The phase I trial NCT03260504 is evaluating aldesleukin plus pembrolizumab for metastatic ccRCC, based on the premise that aldesleukin can potentiate anti-cancer immune responses which pembrolizumab may enhance by blocking immune evasion [22]. The phase I/Ib study NCT04374877 is pioneering SRF388, a monoclonal antibody targeting IL-27, first as a monotherapy in advanced solid tumors, and then in combination with pembrolizumab in specific malignancies like ccRCC to assess potential synergistic benefits [23]. Another phase II trial, NCT05319015, is investigating

Abbreviations: IL: interleukin; NA: not available; NCT: National Clinical Trial; NRG: non-profit research organization; SBRT: stereotactic body radiotherapy; UTSW: University of Texas Southwestern Medical Center.

neoadjuvant lenvatinib-pembrolizumab prior to surgical resection in ccRCC with inferior vena cava invasion, with the goal of optimizing pre-surgical anti-tumor effects.

Collectively, these clinical initiatives highlight promising progress in ccRCC therapeutic development and the vast potential of combination immunotherapy. Beyond advancing treatment modalities, these studies embody resilience and the commitment to transforming renal cancer care through pioneering research and cross-disciplinary collaboration. The breadth of strategies under exploration indicates a steadfast momentum to reshape the future landscape of ccRCC therapy.

References

1. Hah, Y.-S.; Koo, K.-C. Immunology and immunotherapeutic approaches for advanced renal cell carcinoma: A comprehensive review. Int. J. Mol. Sci. 2021, 22, 4452.
2. Jian, Y.; Yang, K.; Sun, X.; Zhao, J.; Huang, K.; Aldanakh, A.; Xu, Z.; Wu, H.; Xu, Q.; Zhang, L. Current advance of immune evasion mechanisms and emerging immunotherapies in renal cell carcinoma. Front. Immunol. 2021, 12, 639636.
3. Au, L.; Hatipoglu, E.; de Massy, M.R.; Litchfield, K.; Beattie, G.; Rowan, A.; Schnidrig, D.; Thompson, R.; Byrne, F.; Horswell, S. Determinants of anti-PD-1 response and resistance in clear cell renal cell carcinoma. Cancer Cell 2021, 39, 1497–1518.e11.
4. Jonasch, E.; Atkins, M.B.; Chowdhury, S.; Mainwaring, P. Combination of anti-angiogenics and checkpoint inhibitors for renal cell carcinoma: Is the whole greater than the sum of its parts? Cancers 2022, 14, 644.
5. Navani, V.; Heng, D.Y. Treatment selection in first-line metastatic renal cell carcinoma—The contemporary treatment paradigm in the age of combination therapy: A review. JAMA Oncol. 2022, 8, 292–299.
6. Motzer, R.J.; Tannir, N.M.; McDermott, D.F.; Arén Frontera, O.; Melichar, B.; Choueiri, T.K.; Plimack, E.R.; Barthélémy, P.; Porta, C.; George, S. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N. Engl. J. Med. 2018, 378, 1277–1290.
7. Motzer, R.J.; McDermott, D.F.; Escudier, B.; Burotto, M.; Choueiri, T.K.; Hammers, H.J.; Barthélémy, P.; Plimack, E.R.; Porta, C.; George, S. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. Cancer 2022, 128, 2085–2097.
8. Hammers, H.J.; Plimack, E.R.; Infante, J.R.; Rini, B.I.; McDermott, D.F.; Lewis, L.D.; Voss, M.H.; Sharma, P.; Pal, S.K.; Razak, A.R.A. Safety and efficacy of nivolumab in combination with

ipilimumab in metastatic renal cell carcinoma: The CheckMate 016 study. J. Clin. Oncol. 2017, 35, 3851–3858.

9. Michaelis, J.; Grabbert, M.; Sigle, A.; Yilmaz, M.; Schlager, D.; Gratzke, C.; Miernik, A.; Schoeb, D.S. Tyrosine Kinase Inhibitors in the Treatment of Metastasised Renal Cell Carcinoma—Future or the Past? Cancers 2022, 14, 3777.
10. Oh, H.; Takagi, H.; Otani, A.; Koyama, S.; Kemmochi, S.; Uemura, A.; Honda, Y. Selective induction of neuropilin-1 by vascular endothelial growth factor (VEGF): A mechanism contributing to VEGF-induced angiogenesis. Proc. Natl. Acad. Sci. USA 2002, 99, 383–388.
11. Motzer, R.J.; Penkov, K.; Haanen, J.; Rini, B.; Albiges, L.; Campbell, M.T.; Venugopal, B.; Kollmannsberger, C.; Negrier, S.; Uemura, M. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N. Engl. J. Med. 2019, 380, 1103–1115.
12. Haanen, J.; Larkin, J.; Choueiri, T.; Albiges, L.; Rini, B.; Atkins, M.; Schmidinger, M.; Penkov, K.; Michelon, E.; Wang, J. Extended follow-up from JAVELIN Renal 101: Subgroup analysis of avelumab plus axitinib versus sunitinib by the International Metastatic Renal Cell Carcinoma Database Consortium risk group in patients with advanced renal cell carcinoma. ESMO Open 2023, 8, 101210.
13. Rini, B.I.; Plimack, E.R.; Stus, V.; Gafanov, R.; Hawkins, R.; Nosov, D.; Pouliot, F.; Alekseev, B.; Soulières, D.; Melichar, B. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N. Engl. J. Med. 2019, 380, 1116–1127.
14. Rini, B.I.; Plimack, E.R.; Stus, V.; Gafanov, R.; Waddell, T.; Nosov, D.; Pouliot, F.; Alekseev, B.; Soulieres, D.; Melichar, B. Pembrolizumab Plus Axitinib versus Sunitinib as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma: 5-Year Analysis of KEYNOTE-426; American Society of Clinical Oncology: Alexandria, VA, USA, 2023.
15. Rini, B.I.; Plimack, E.R.; Stus, V.; Waddell, T.; Gafanov, R.; Pouliot, F.; Nosov, D.; Melichar, B.; Soulieres, D.; Borchiellini, D. Pembrolizumab (Pembro) Plus Axitinib (Axi) versus Sunitinib as First-Line Therapy for Advanced Clear Cell Renal Cell Carcinoma (ccRCC): Results from 42-Month Follow-Up of KEYNOTE-426; Wolters Kluwer Health: Philadelphia, PA, USA, 2021.
16. Choueiri, T.K.; Powles, T.; Burotto, M.; Escudier, B.; Bourlon, M.T.; Zurawski, B.; Oyervides Juárez, V.M.; Hsieh, J.J.; Basso, U.; Shah, A.Y. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N. Engl. J. Med. 2021, 384, 829–841.
17. Burotto, M.; Powles, T.; Escudier, B.; Apolo, A.B.; Bourlon, M.T.; Shah, A.Y.; Suárez, C.; Porta, C.; Barrios, C.H.; Richardet, M. Nivolumab Plus Cabozantinib vs. Sunitinib for First-Line Treatment of Advanced Renal Cell Carcinoma (aRCC): 3-Year Follow-Up from the Phase 3 CheckMate 9ER Trial; American Society of Clinical Oncology: Alexandria, VA, USA, 2023.

18. Motzer, R.; Alekseev, B.; Rha, S.-Y.; Porta, C.; Eto, M.; Powles, T.; Grünwald, V.; Hutson, T.E.; Kopyltsov, E.; Méndez-Vidal, M.J. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N. Engl. J. Med. 2021, 384, 1289–1300.
19. Choueiri, T.K.; Eto, M.; Motzer, R.; De Giorgi, U.; Buchler, T.; Basappa, N.S.; Méndez-Vidal, M.J.; Tjulandin, S.; Park, S.H.; Melichar, B. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): Extended follow-up from the phase 3, randomised, open-label study. Lancet Oncol. 2023, 24, 228–238.
20. Lee, C.-H.; Shah, A.Y.; Rasco, D.; Rao, A.; Taylor, M.H.; Di Simone, C.; Hsieh, J.J.; Pinto, A.; Shaffer, D.R.; Sarrio, R.G. Lenvatinib plus pembrolizumab in patients with either treatment-naive or previously treated metastatic renal cell carcinoma (Study 111/KEYNOTE-146): A phase 1b/2 study. Lancet Oncol. 2021, 22, 946–958.
21. Makker, V.; Aghajanian, C.; Cohn, A.L.; Romeo, M.; Bratos, R.; Brose, M.S.; Messing, M.; Dutta, L.; Dutcus, C.E.; Huang, J. A phase ib/II study of lenvatinib and pembrolizumab in advanced endometrial carcinoma (study 111/KEYNOTE-146): Long-term efficacy and safety update. J. Clin. Oncol. 2023, 41, 974–979.
22. Amaria, R.N.; Reuben, A.; Cooper, Z.A.; Wargo, J.A. Update on use of aldesleukin for treatment of high-risk metastatic melanoma. ImmunoTargets Ther. 2015, 4, 79–89.
23. Patnaik, A.; Morgensztern, D.; Mantia, C.; Tannir, N.M.; Harshman, L.C.; Hill, J.; White, K.; Chung, J.-K.; Bowers, B.; Sciaranghella, G. Results of a phase 1 study of SRF388, a first-in-human, first-in-class, high-affinity anti-IL-27 antibody in advanced solid tumors. J. Clin. Oncol. 2021, 39, 2551.