Advanced/Metastatic Renal Cell Carcinomas

Subjects: Oncology
Contributor: Eun-mi Yu

The use of checkpoint inhibitors in advanced and metastatic renal cell carcinomas (RCCs) has rapidly evolved over the past several years. While immune-oncology (IO) drug therapy has been successful at resulting in improved responses and survival, combination therapies with immune checkpoint inhibitors and vascular endothelial growth factor (VEGF) inhibitors have further improved outcomes. This article reviews the landmark trials that have led to the approval of IO therapies, including the Checkmate 214 trial and combination IO/VEGF TKI therapies with Checkmate 9ER, CLEAR, and Keynote-426, and it includes a discussion on promising therapies moving in the future.

Keywords: renal cell cancer ; checkpoint inhibitors ; immunotherapy ; vascular endothelial growth factors ; renal cell carcinoma

1. Introduction

Cancers of the kidney and renal pelvis are the sixth most common cancers among men and the ninth most common cancers in women. There will be an estimated number of 76,080 new cases of and 13,780 deaths from these cancers in 2021 [1]. Although there is a wide array of histology in these cancer types, the vast majority of kidney cancers are of clear cell histology [2][3]. The work of the Cancer Genome Atlas Project [4] resulted in the discovery that clear cell renal cell carcinomas (ccRCCs) are defined primarily by mutations in the von-Hippel Lindau/hypoxia-inducible factor (VHL/HIF) pathway, which is directly involved in angiogenesis [3]. Inhibition of the mammalian target of rapamycin (mTOR) pathway is one of several other known mechanisms of carcinogenesis.

Early-stage disease is primarily treated with surgical resection via a partial or radical nephrectomy [5]. Adjuvant therapy with sunitinib can be offered in high-risk cases based on the results of the S-TRAC study [6], though not widely used in clinical practice due to perceived toxicity. While previously there were few effective systemic treatment options available for advanced RCC, we have observed improved outcomes over the past two decades with the development of new anti-VEGF targeted agents and immune checkpoint inhibitors (ICIs). The insights we have gained regarding RCC pathogenesis from the TCGA study have been vital to the development of effective treatment regimens in this disease that has been historically challenging to manage in its advanced stages.

There are several prognostic models that have been proposed for the risk classification of metastatic ccRCC. The most commonly used classification systems in contemporary trials are the Memorial Sloan Kettering Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC) models. The MSKCC model established serum lactate dehydrogenase level (LDH), hemoglobin, Karnofsky performance status, corrected serum calcium level, and time from diagnosis to treatment as predictors of outcome based on retrospective data [7]. The IMDC model, initially validated in 2009 and again in 2013, includes the same variables as the MSKCC model, with the exception that neutrophil count and platelet count are used in lieu of serum LDH [8][9]. In both risk models, patients with no negative prognostic factors are considered low or favorable risk. Patients with one or two prognostic factors are placed in the intermediate-risk group, and those with three or more prognostic factors are considered poor risk. Most contemporary interventional trials include subgroup analyses of outcomes based on the prognostic risk group. However, it should be noted that the MSKCC and IMDC models were created and validated prior to the widespread use of ICIs in the treatment of metastatic ccRCC.

2. Immune Checkpoint Inhibitors as First-Line Therapy

The KEYNOTE-426 trial also compared the combination of an ICI (pembrolizumab) with a VEGFR TKI (axitinib) with sunitinib in patients with advanced ccRCC in the first-line setting. After a median follow-up of 12.8 months, the median PFS was 15.1 months in the axitinib plus pembrolizumab group and 11.1 months in the sunitinib group. The 12-month OS rate was nearly 90% in the combination treatment arm versus 78.3% in the sunitinib arm. There was also a significant improvement in ORR, 59.3% versus 35.7%, in the investigational and sunitinib arms, respectively. Treatment with axitinib

plus pembrolizumab was favored in patients across all International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups. Moreover, the combination regimen proved to be beneficial over sunitinib irrespective of tumor PD-L1 expression [10].

CheckMate 9ER is a phase 3, randomized, open-label trial that evaluated the use of cabozantinib, an oral multi-kinase inhibitor with multiple targets (VEGFR2, c-MET, AXL, and RET), in combination with nivolumab in untreated advanced ccRCC patients. Outcomes were compared to the control group who received standard-of-care sunitinib monotherapy, and the findings from this trial were published in March 2021. At a median follow-up of 18.1 months, the median PFS was 16.6 months for the cabozantinib plus nivolumab treatment arm versus 8.3 months in the sunitinib arm. Combination therapy with cabozantinib plus nivolumab appeared to result in a statistically significant improvement in PFS (hazard ratio for disease progression or death, 0.51, with 95% confidence interval ranging from 0.41 to 0.64; $p < 0.001$), and the 12-month OS probability was 85.7% in the combination treatment arm versus 75.6% in the sunitinib arm. ORR was significantly improved with combination therapy, 55.7% versus 27.1% in those who were treated with sunitinib [11]. Based on these results, cabozantinib in combination with nivolumab was FDA-approved for use in the first-line setting for advanced ccRCC patients in January 2021.

The use of immune checkpoint inhibitors in RCC is generally safe, and while autoimmune toxicities are common, they are manageable when identified early. Milder grade 1 or 2 adverse reactions can be managed by supportive measures (i.e., topical steroid for skin toxicity, thyroid replacement therapy for hypothyroidism), temporary holding of ICI therapy, or low-dose systemic corticosteroid administration. Grade 3 or 4 usually requires higher-dose systemic corticosteroids in addition to holding or permanently discontinuing ICI. Often, toxicity profiles can overlap between ICI and TKI agents. For example, both nivolumab and cabozantinib can cause diarrhea via different mechanisms, making this particular side effect challenging to manage in a patient who is on this combination treatment regimen. **Table 1** provides a summary of the toxicity profiles for the first-line immunotherapy regimens that have been discussed.

Table 1. mRCC first-line immunotherapy trials: toxicity profiles.

	Checkmate 214: N+I		**Checkmate 9ER: N+C**		**CLEAR: L+P**		**Keynote 426: P+Axitinib**		**Javelin Renal 101: Avelumab+Axitinib**	
All TRAEs, %	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**	**All grades**	**Grade 3–4**
Fatigue	**37.8%**	**4.4%**	**32.2%**	**3.4%**	**40.1%**	**4.3%**	**38.5%**	**2.8%**	**36%**	**3 (0)**
Increased ALT	**6.0%**	**4.0%**	**28.1%**	**5.3%**	**NR**	**NR**	**26.8%**	**13.3%**	**13%**	**4 (1)**
Hand-foot syndrome	**<1%**	**<1%**	**40.0%**	**7.5%**	**28.7%**	**4.0%**	**28.0%**	**5.1%**	**33%**	**6 (0)**
Nausea	**20.1%**	**1.5%**	**26.6%**	**0.6%**	**25.8%**	**2.6%**	**27.7%**	**0.9%**	**25%**	**1 (0)**
Diarrhea	**24.0%**	**4.0%**	**63.8%**	**6.9%**	**61.4%**	**9.7%**	**54.3%**	**9.1%**	**54%**	**5 (0)**
Decreased appetite	**13.9%**	**1.3%**	**13.9%**	**1.3%**	**40.3%**	**4.0%**	**29.6%**	**2.8%**	**20%**	**2 (0)**
TRAEs leading to d/c of Rx	**22%**		**19.7% d/c: 6.6% N only; 7.5% C only; 5.6% d/c N+C**		**37.2% (L: 25.6%; P: 28.7%; 13.4%: both)**		**D/c of either drug = 30.5%; d/c both drugs = 10.7%; dose reduction of axitinib in 20.3% 4.8%; 18.9%: both)**		**4.0%**	
TRAEs leading to death	**1%**		**<1%**		***n* = 15**		**2.6%**		**1.0%**	

mRCC = metastatic renal cell carcinoma, TRAE = treatment related adverse event, ALT = alanine transaminase, D/C = discontinuation, N = nivolumab, C = cabozantinib, L = lenvatinib, P = pembrolizumab.

The real-world treatment of advanced RCC has become complicated given the compelling data reported across all of the aforementioned first-line trials in the past three years. That said, it is a good problem to have several treatment regimens to choose from. It is unlikely we will have data comparing these first-line regimens head-to-head in a single prospective trial to determine which regimen is truly superior; therefore, it is reasonable to offer any of these regimens to an advanced ccRCC patient in the clinical setting. In addition, these different trials set different primary endpoints. Some primarily evaluated progression-free survival as the primary endpoint (for Checkmate 9ER and CLEAR) , others used dual primary

endpoints such as Keynote 426 or, specifically, the PD-L1 population of patients, in Javelin Renal 101. The choice of therapy, in our opinion, is contingent upon a number of factors including the presence of comorbid conditions (autoimmune disease, cardiovascular disease such as poorly controlled hypertension, pre-existing organ dysfunction) and patient preference as it relates to the treatment schedule and potential toxicities. The management of toxicities can be complicated as there is an overlap of the potential side effects that can occur in TKIs and ICI, for example, diarrhea. When a patient develops diarrhea while on a combination ICI+TKI regimen, it is often difficult to ascertain whether or not it is an immune-mediated toxicity that requires systemic steroids versus simply holding or discontinuing either one or both drugs. Therefore, one could justify a preference for offering nivolumab plus ipilimumab (dual ICI regimen) in the first-line setting based on the CheckMate 214 trial in the appropriate patient as the management of immune-mediated side-effects is more straightforward. On the other hand, adequate resources for education of patients and clinicians, who may not often see such oncology patients who develop autoimmune side-effects but interact with them in various settings (for instance, in the emergency room), is imperative since early recognition of autoimmune toxicity would lead to appropriate treatment and, ultimately, better outcomes. Familiarity with management of autoimmune toxicity as well as drug availability are important considerations as well, along with changes in quality of life parameters that are seen in each of these trials.

3. Second-Line Therapy

In spite of the advancements that have been made in the first-line treatment of advanced ccRCC, the majority of patients inevitably require subsequent lines of therapy due to development of disease progression. Several studies have evaluated various systemic single-agent and combination treatment regimens that have changed the landscape of ccRCC management in the second-line setting and beyond. These studies are outlined in **Table 2** .

Table 2. Landmark second-line mRCC trials.

Trial Name	Date Published	MOA of Investigational Arms	Patient Population	Primary Endpoint	Results to Date
RECORD-1	**August 2008**	**mTOR inhibitor**	**Pretreated with sunitinib and/or sorafenib**	**PFS**	**E vs. Placebo Median PFS: 4.9 vs. 1.9 months**
AXIS	**December 2011**	**TKI**	**Pretreated with sunitinib, bevacizumab plus IFN-gamma, temsirolimus or cytokine**	**PFS**	**Axitinib vs. Sorafenib Median PFS: 6.7 vs. 4.7 months**
CheckMate 025	**November 2015**	**PD-1 inhibitor**	**Pretreated with 1–2 regimens of antiangiogenic therapy**	**OS**	**Nivo vs. E Median OS: 25 vs. 19.6 months**
METEOR	**July 2016**	**TKI**	**Pretreated with at least one previous VEGFR-TKI**	**PFS**	**Cabo vs. E Median OS: 21.4 vs. 16.5 months ORR: 17% vs. 3%**
STUDY 205	**November 2015**	**VEGFR-TKI ± mTOR inhibitor**	**One prior line of VEGFR-TKI**	**PFS**	**E+L vs. L vs. E Median PFS: 14.6 vs. 7.4 vs. 5.5 months**

mTOR = mammalian target of rapamycin, PFS = progression free survival, E = everolimus, TKI = tyrosine kinase inhibitor, PD-1 = programmed cell death protein 1, OS = overall survival, Nivo = nivolumab, VEGFR = vascular endothelial growth factor receptor, Cabo = cabozantinib, ORR = objective response rate, L = lenvatinib.

The RECORD-1 trial, the results of which were reported in 2008, was the first study that led to the FDA approval of an mTOR inhibitor for second-line use in metastatic ccRCC. In this multi-centered, open-label, randomized controlled trial, prolongation of PFS was observed with those who received everolimus compared to placebo (4.9 months vs. 1.9 months; $p < 0.0001$) after progression during or within 9 months of treatment with a VEGF-targeted therapy (sunitinib, sorafenib, or both). The ORR for everolimus, however, was only 1.8% [12]. The RECORD-3 trial evaluated alternate sequencing of everolimus and sunitinib. At final analysis, reported in 2017, the median combined PFS was 21.7 months with everolimus followed by sunitinib and 22.2 months with sunitinib followed by everolimus. Median OS was 22.4 months for everolimus followed by sunitinib and 29.5 months for sunitinib followed by everolimus [13]. Results from this final analysis support the use of everolimus in the second-line setting after disease progression on first-line sunitinib.

It became clear that mTOR inhibition alone is not highly effective in the treatment of metastatic ccRCC, based on the low response rate reported in the RECORD-1 trial with everolimus monotherapy. mTOR inhibitors have subsequently been studied both compared to and in combination with TKI agents as alternative second-line therapies in ccRCC. In 2015, a significant PFS benefit was reported with the use of everolimus in combination with lenvatinib (a multi-kinase inhibitor) in previously treated advanced ccRCC patients compared to those who received everolimus alone (14.6 vs. 5.5 months; p = 0.005) [14]. Similarly, the METEOR trial demonstrated improvements in both PFS and OS with the of use of another multi-kinase inhibitor, cabozantinib, compared to everolimus, which was reported in 2016 [15], leading to the FDA approval of both cabozantinib monotherapy and everolimus in combination with lenvatinib in the second-line setting for advanced ccRCC in 2016. The reported ORR of cabozantinib in the METEOR study was relatively low at 17%. The combination of everolimus and lenvatinib seemed to benefit a greater proportion of patients based on the reported ORR of 43% (22 of 51 patients), but the small sample size was a limitation of this study.

4. Immune Checkpoint Inhibitors as Second-Line Therapy

As a result of the positive first-line ccRCC ICI studies, including CheckMate 214, JAVELIN Renal 101, and Keynote 426, there has been an increasing proportion of advanced ccRCC patients previously treated with an ICI by the time second- or third-line therapy is being considered. Conversely, the use of TKI monotherapy is generally limited to those with favorable risk disease or for patients with contraindications to ICI therapy. Given the paucity of data relating to the continuation of immune checkpoint inhibition post-progression on an ICI, patients who have received and progressed on an ICI-based regimen typically move on to receive TKI monotherapy in the second-line setting.

Although limited, there are studies currently re-exploring the use of single-agent ICI, or ICI in combination with other ICIs or TKIs, in patients with ccRCC who have progressed on or after ICI monotherapy, or ICI combination therapy, in the first-line setting. A multicentered, retrospective, cohort study of 69 metastatic RCC patients between 2012 and 2019 assessed the outcomes of rechallenging with an ICI in patients who had previously received an ICI agent. Twenty-nine (42%) patients received first-line ICI in combination with targeted therapy, and 27 (39%) received ICI monotherapy. This study showed an ORR of 23% at ICI rechallenge, compared to an ORR of 37% with ICI exposure in the first-line setting. There were patients who responded to ICI rechallenge regardless of their response to initial ICI therapy, but the likelihood of response to rechallenge was higher among patients who had previously responded to ICI (ORR of 29%) [16]. A similar retrospective analysis published in 2020 looked at the role of salvage ipilimumab and nivolumab in patients with metastatic RCC who had previous exposure to an anti-PD-1 or anti-PD-L1 agent. Ipilimumab and nivolumab combination therapy led to objective responses in a subset of patients with metastatic RCC who had prior exposure to PD-1/PD-L1 inhibitors but were naïve to anti-CTLA-4 antibody [17].

These retrospective data prompted further study of salvage ipilimumab and nivolumab therapy after single-agent nivolumab in subsequent clinical trials. For example, HCRN GU16-260 (NCT03117309) and OMNIVORE (NCT03203473) are evaluating the clinical outcomes of the addition of ipilimumab in patients with metastatic RCC who do not achieve an objective response to nivolumab monotherapy. The phase 2 TITAN-RCC (Tailored immunotherapy approach with nivolumab in advanced renal cell carcinoma) trial studied the use of nivolumab plus ipilimumab as an “immunotherapeutic boost” in 86 intermediate-/poor-risk or metastatic ccRCC patients who experienced progressive disease or stable disease after four doses of nivolumab monotherapy. This study included two independent patient cohorts: those who had no prior therapy (receiving nivolumab first-line) and those previously treated with a TKI agent (receiving nivolumab second-line). The primary endpoint of this study was ORR. Secondary outcomes included remission rate (RR), PFS, and OS. Preliminary results of the study showed that in patients treated in the first-line setting, the ORR to nivolumab alone was 28.7% compared to 37.0% in patients receiving nivolumab followed by the nivolumab/ipilimumab boost. In the second-line setting the ORR was 18.2% among patients receiving nivolumab alone and 28.3% in those receiving nivolumab followed by the nivolumab/ipilimumab boost [18]. The preliminary results of this study support the addition of ipilimumab to nivolumab after initial treatment with nivolumab alone in advanced ccRCC.

PDIGREE (Alliance A031704) is an adaptive phase III trial currently enrolling intermediate-/poor-risk advanced ccRCC patients which will investigate the use of nivolumab and/or cabozantinib after first-line induction with nivolumab and ipilimumab. Treatment of these patients beyond the initial induction phase consisting of four cycles of nivolumab and ipilimumab, as per the CheckMate 214 protocol, will depend on their response to induction therapy. Those who experience a CR with initial induction therapy will continue with nivolumab maintenance. Those patients who have non-CR or non-PD (partial response or stable disease) will receive cabozantinib in addition to nivolumab. Patients who experience

progressive disease with induction nivolumab and ipilimumab will subsequently be treated with cabozantinib monotherapy. The primary endpoint for this study will be 3-year OS, and this study will also investigate the use of IL-6 as a potential biomarker [19].

References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. CA Cancer J. Clin. 2021, 71, 7–33.
2. Cohen, H.T.; McGovern, F.J. Renal-Cell Carcinoma. N. Engl. J. Med. 2005, 353, 2477–2490.
3. Jonasch, E.; Gao, J.; Rathmell, W.K. Renal Cell Carcinoma. BMJ 2014, 349, g4797.
4. Cancer Genome Atlas Research Network. Comprehensive Molecular Characterization of Clear Cell Renal Cell Carcinoma. Nature 2013, 499, 43–49.
5. Rini, B.I.; Campbell, S.C.; Escudier, B. Renal Cell Carcinoma. Lancet 2009, 373, 1119–1132.
6. Ravaud, A.; Motzer, R.J.; Pandha, H.S.; George, D.J.; Pantuck, A.J.; Patel, A.; Chang, Y.-H.; Escudier, B.; Donskov, F.; Magheli, A.; et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N. Engl. J. Med. 2016, 375, 2246–2254.
7. Motzer, R.J.; Bacik, J.; Murphy, B.A.; Russo, P.; Mazumdar, M. Interferon-Alfa as a Comparative Treatment for Clinical Trials of New Therapies against Advanced Renal Cell Carcinoma. J. Clin. Oncol. 2002, 20, 289–296.
8. Heng, D.Y.C.; Xie, W.; Regan, M.M.; Warren, M.A.; Golshayan, A.R.; Sahi, C.; Eigl, B.J.; Ruether, J.D.; Cheng, T.; North, S.; et al. Prognostic Factors for Overall Survival in Patients with Metastatic Renal Cell Carcinoma Treated with Vascular Endothelial Growth Factor-Targeted Agents: Results from a Large, Multicenter Study. J. Clin. Oncol. 2009, 27, 5794–5799.
9. Heng, D.Y.C.; Xie, W.; Regan, M.M.; Harshman, L.C.; Bjarnason, G.A.; Vaishampayan, U.N.; Mackenzie, M.; Wood, L.; Donskov, F.; Tan, M.-H.; et al. External Validation and Comparison with Other Models of the Inter-national Metastatic Renal-Cell Carcinoma Database Consortium Prognostic Model: A Population-Based Study. Lancet Oncol. 2013, 14, 141–148.
10. Rini, B.I.; Plimack, E.R.; Stus, V.; Gafanov, R.; Hawkins, R.; Nosov, D.; Pouliot, F.; Alekseev, B.; Soulières, D.; Melichar, B.; et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N. Engl. J. Med. 2019, 380, 1116–1127.
11. 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.; et al. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carci-noma. N. Engl. J. Med. 2021, 384, 829–841.
12. Motzer, R.J.; Escudier, B.; Oudard, S.; Hutson, T.E.; Porta, C.; Bracarda, S.; Grünwald, V.; Thompson, J.A.; Figlin, R.A.; Hollaender, N.; et al. Efficacy of Everolimus in Advanced Renal Cell Carcinoma: A Double-Blind, Ran-domised, Placebo-Controlled Phase III Trial. Lancet 2008, 372, 449–456.
13. Knox, J.J.; Barrios, C.H.; Kim, T.M.; Cosgriff, T.; Srimuninnimit, V.; Pittman, K.; Sabbatini, R.; Rha, S.Y.; Flaig, T.W.; Page, R.D.; et al. Final Overall Survival Analysis for the Phase II RECORD-3 Study of First-Line Everoli-mus Followed by Sunitinib versus First-Line Sunitinib Followed by Everolimus in Metastatic RCC. Ann. Oncol. 2017, 28, 1339–1345.
14. Motzer, R.J.; Hutson, T.E.; Glen, H.; Michaelson, M.D.; Molina, A.; Eisen, T.; Jassem, J.; Zolnierek, J.; Maroto, J.P.; Mellado, B.; et al. Lenvatinib, Everolimus, and the Combination in Patients with Metastatic Renal Cell Carcinoma: A Randomised, Phase 2, Open-Label, Multicentre Trial. Lancet Oncol. 2015, 16, 1473–1482.
15. Choueiri, T.K.; Escudier, B.; Powles, T.; Tannir, N.M.; Mainwaring, P.N.; Rini, B.I.; Hammers, H.J.; Donskov, F.; Roth, B.J.; Peltola, K.; et al. Cabozantinib versus Everolimus in Advanced Renal Cell Carcinoma (METEOR): Final Results from a Randomised, Open-Label, Phase 3 Trial. Lancet Oncol. 2016, 17, 917–927.
16. Ravi, P.; Mantia, C.; Su, C.; Sorenson, K.; Elhag, D.; Rathi, N.; Bakouny, Z.; Agarwal, N.; Zakharia, Y.; Costello, B.A.; et al. Evaluation of the Safety and Efficacy of Immunotherapy Rechallenge in Patients With Renal Cell Carcinoma. JAMA Oncol. 2020, 6, 1606.
17. Gul, A.; Stewart, T.F.; Mantia, C.M.; Shah, N.J.; Gatof, E.S.; Long, Y.; Allman, K.D.; Ornstein, M.C.; Hammers, H.J.; McDermott, D.F.; et al. Salvage Ipilimumab and Nivolumab in Patients with Metastatic Renal Cell Car-cinoma After Prior Immune Checkpoint Inhibitors. J. Clin. Oncol. 2020, 38, 3088–3094.
18. Grimm, M.-O.; Schmitz-Dräger, B.; Zimmermann, U.; Grün, B.; Baretton, G.B.; Schmitz, M.; Foller, S.; Schostak, M.; Zengerling, F.; Schumacher, U.; et al. Tailored Immunotherapy Approach with Nivolumab in Advanced Transitional Cell Carcinoma (TITAN-TCC). J. Clin. Oncol. 2021, 39, 446.

19. Zhang, T.; Ballman, K.V.; Choudhury, A.D.; Chen, R.C.; Watt, C.; Wen, Y.; Shergill, A.; Zemla, T.J.; Emamekhoo, H.; Vaishampayan, U.N.; et al. PDIGREE: An Adaptive Phase III Trial of PD-Inhibitor Nivolumab and Ipili-mumab (IPI-NIVO) with VEGF TKI Cabozantinib (CABO) in Metastatic Untreated Renal Cell Cancer (Alli-ance A031704). J. Clin. Oncol. 2021, 39, TPS366.