VIOLA ADVISORY

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Exelixis (EXEL) 4Q19: Threshold Limits to Advance Cabozantinib to Front-Line Setting in Renal Cell Carcinoma (RCC)

TABLE 1: Exelixis (EXEL) – Key Valuation Metrics

Mkt. Cap			Mkt. Price			Viola Advisory		Upside Potential	
(US$)	Symbol	Company	04/01/20	P/S	YTD	Rating	PT	52-Week High	PT
5.0B	EXEL	Exelixis, Inc.	16.46	5.4	-6.8%	Buy	22.00	53%	34%

Source: Yahoo Finance, Ycharts.com, Viola Advisory LLC

Summary: **Since FY2019, Exelixis has seen sales of its single agent drug Cabozantinib decline steadily as several competitors brought to market immuno-oncology (IO) combination treatments for first-line advanced clear cell renal cell carcinoma (RCC). The company is now preparing to show top-line results in 1H20 for its completed Phase III CheckMate-9ER clinical trial which compares the combination of cabozantinib (Cabometyx) and Nivolumab (Opdivo) versus sunitinib (Sutent) in patients with previously untreated advanced or metastatic RCC (mRCC). Favorable results from CheckMate-9ER will help improve sales of cabozantinib. In this report, we estimate what the minimum threshold limits are for both efficacy and safety that CheckMate-9ER needs to show in order to convince clinicians to advance Cabonzantinib up from second- to first-line treatment for patients with advanced RCC.**

Summary of Contents

I. Treatment Landscape and Competitive Dynamics in mRCC

A. Treatment Types in Advanced RCC: Targeted Therapy vs. Immunotherapy

1. Targeted Therapy

Targeted therapy is a treatment with drugs that target a unique feature of cancer cells. These drugs stop the action of molecules that help cancer cells grow. Targeted therapy is used to treat newly diagnosed stage IV (with or without metastases) kidney cancer or cancer that has returned (relapsed). Stage IV kidney cancer is sometimes referred to as advanced RCC. A list of targeted therapy drugs used in treating patients with advanced kidney cancer is listed in Table 2.

TABLE 2: Targeted Therapies for Advanced Kidney Cancer

Generic	Brand	Company	Type	Target	Method	Indication
Axitinib	Inlyta	Pfizer	TKI	VEGF	pill	Advanced RCC with pembro or alone with other treatments
Bevacizumab or biosimilar	Avastin	Roche	mAB	VEGF	infusion	Advanced clear cell and non-clear cell RCC alone or with other treatments
Cabozantinib	Cabometyx	Exelixis	TKI	multi-kinase/ VEGF	pill	Advanced clear cell and non-clear cell RCC
Erlotinib	Tarceva	Roche	TKI	EGFR	pill	Advanced clear cell and non-clear cell RCC
Everollimus	Afinitor	Novartis	mTOR kinase inhibitor	mTOR	pill	Advanced clear cell and non-clear cell RCC
Lenvatinib	Lenvima	Eisai	TKI	multi-kinase/ VEGF	pill	Use with Everolimus for advanced clear cell and non-clear-cell RCC
Pazopanib	Votrient	GlaxoSmith Kline	TKI	multi-kinase/ VEGF	pill	Advanced clear cell and non-clear cell RCC
Sorafenib	Nexavar	Bayer	TKI	multi-kinase/ VEGF	pill	Advanced clear cell and non-clear cell RCC
Sunitinib	Sutent	Pfizer	TKI	multi-kinase/ VEGF	pill	Advanced clear cell and non-clear cell RCC
Temsirolimus	Torisel	Pfizer	mTOR kinase inhibitor	mTOR	infusion	Advanced clear cell and non-clear cell RCC

Note: TKI – tyrosine kinase inhibitor; mAb – monoclonal antibody

Source: NCCN Guidelines, Kidney Cancer 2020

There are two types of targeted therapy: a) those that affect the outside or surface of the cancer cell are called monoclonal antibodies, and b) those that affect the inside of the cancer cell are called kinase inhibitors.

Furthermore, there are 3 main targets of targeted therapy used in treating kidney cancer:

- **Angiogenesis inhibitors** target blood vessel growth by blocking vascular endothelial growth factor (VEGF)
- **Mammalian target of rapamycin (mTOR) kinase inhibitors** target cancer cell growth
- **Epidermal growth factor receptor (EGFR) inhibitors** target cancer cell growth

2. Immunotherapy

Immunotherapy is a type of systemic treatment that increases the activity of the immune system. In so doing, it improves the body's ability to find and destroy cancer cells. Immunotherapy can be given alone or with other types of treatment. It is used in stage IV kidney cancer or cancer that has relapsed. Table 3 lists the immunotherapy drugs used in advanced kidney cancer treatment.

TABLE 3: Immunotherapies for Advanced Kidney Cancer

Generic	Brand	Company	Type	Target	Method	Indication
Aldesleukin or IL-2	Proleukin	Clinigen	Cytokine	Immune system boost	infusion	Only used in some cases
Avelumab	Bavencio	Pfizer	mAb	PD-L1 blocking	infusion	Used with Axitinib for advanced clear cell RCC
Ipilimumab	Yervoy	Bristol-Myers Squibb	mAb	CTLA-4 blocking	infusion	Used with Nivolumab for advanced clear cell RCC
Nivolumab	Opdivo	Bristol-Myers Squibb	mAb	PD-1 blocking	infusion	Used with Ipilimumab or alone for advanced RCC after one prior angiogenesis inhibitor
Pembrolizumab	Keytruda	Merck	mAb	PD-1 blocking	infusion	Used with axitinib for advanced RCC

Source: NCCN Guidelines, Kidney Cancer 2020

There are two types of immunotherapy used to treat kidney cancer: Cytokine therapy and monoclonal antibody therapy.

- **Cytokine therapy** – cytokines are proteins made by the immune system to either stimulate or slow down the immune system. Interleukin (IL) is a type of cytokine therapy that stimulates the immune system. Interleukin-2 (IL-2) is a drug used under certain circumstances to treat relapsed or advanced clear cell RCC. Due to its serious risks, high-dose IL-2 is only used for patients who are healthy enough to handle the side effects (i.e., those in the favorable risk group – good overall health and good organ function).

- **Monoclonal antibody (mAb)** is a type of protein that attacks cancer cells. There are 4 types of immuno-therapy mAbs approved to treat kidney cancer:
  1. Pembrolizumab – also called "pembro" for short. Pembro blocks the action of PD-1 which allows the immune system to attack and stop or slow down the growth of cancer
  2. Nivolumab – also blocks the action of PD-1
  3. Ipilimumab – also called "Ipi" for short. Ipilimumab targets and blocks the CTLA-4 protein which allows the immune system to attack cancer cells
  4. Avelumab – blocks PD-L1 (programmed death-ligand 1), a protein found on some cancer cells which allows the immune system to attack cancer cells

B. Survival and Efficacy Trends in RCC and Recommended Treatment Guidelines

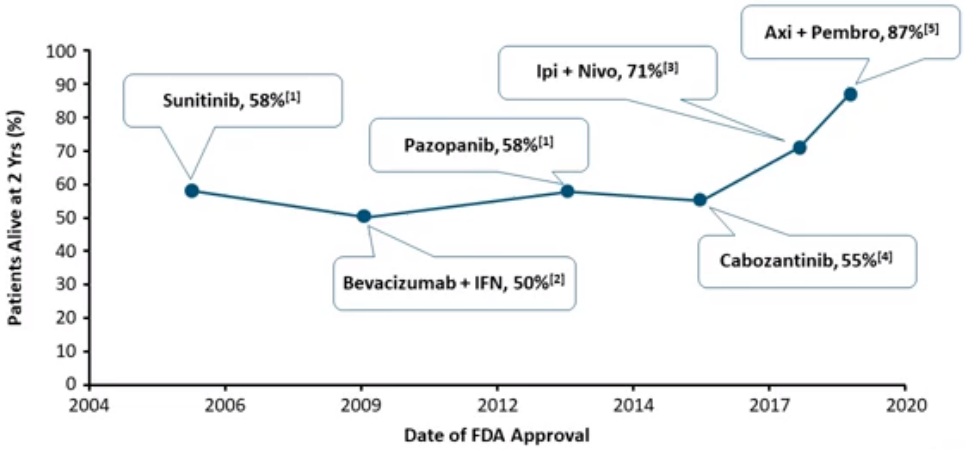
When doctors make treatment decisions on advanced RCC patients, they base it on real world evidence which is primarily survival and efficacy data collected on clinical trials of various single-agent therapies or combination therapies. Currently, there are two trends observed in clinical trial studies for therapies in advanced RCC.

<u>Trend #1: Vast Improvements in 2-Year Overall Survival in 1L RCC especially for IO Combos</u>

Historically, monotherapies dominated the metastatic renal cell carcinoma (mRCC) treatment landscape with FDA approval of several angiogenesis inhibitors, such as sunitinib (Sutent), pazopanib (Votrient), cabozantinib (Cabometyx), axitinib (Inlyta), sorafenib (Nexavar), and bevacizumab (Avastin); mTOR inhibitors, such as everolimus (Afinitor) and temsirolimus (Torisel); and single-agent immunotherapies, such as high-dose interleukin-2 (HD IL-2) and nivolumab (Opdivo).

However, in recent years, a shift from the use of single agents to combination approaches has occurred. This is due to the great improvement in survival data produced by immuno-oncology combination therapies over single agent therapies. Figure 1 below shows how the 2-year overall survival rates have vastly improved from 2006 to 2018.

FIGURE 1: Improved 2-Year Overall Survival in First-line RCC



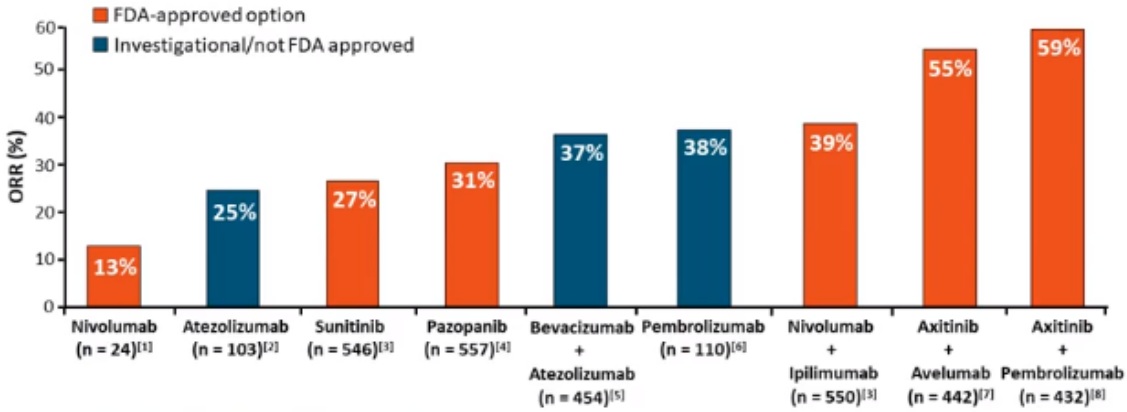
Source: Practical Application of IO in Renal Cell Carcinoma webinar (ClinicalOptions.com)

Sunitinib, first approved in January 2006 produced a 2-year OS rate of 58%. That means that after tracking the treatment group for an average 24 months, 58% of the patients in the group saw their advanced RCC disease under control. In 2009, a study of bevacizumab + interferon alfa-2a also produced an OS rate of 50%. Pazopanib, approved in October 2009 also showed an OS rate of 58% while cabozantinib in April 2016 produced a 2-year OS rate of 55% (see Figure 1).

The treatment landscape for advanced RCC changed dramatically in early 2018 with the approval of nivolumab and ipilimumab in April 2018 and the IO combo producing a 71% OS rate. This was followed up by axi/pembro in April 2019 with the IO combo hitting a 2-year OS rate of 87% (see Figure 1). The FDA also approved the IO combo treatment of axitinib/avelumab in May 2019 with the OS rate hitting 64% after an 18-month follow-up.

Trend #2: Higher Response Rates especially for IO Combination Therapies

FIGURE 2: Response Rates in Frontline Metastatic Clear Cell RCC (All Risk Groups)



Source: Practical Application of IO in Renal Cell Carcinoma webinar (ClinicalOptions.com)

Trend #2 also shows higher overall response rates of IO combo therapies, particularly VEGF + immune checkpoint blockade therapies over single-agent TKI or immunotherapy therapies. For example, axi/pembro and axitinib/avelumab, both considered VEGF/immune checkpoint blockade combos, produced the highest response rates in clinical trial studies at 59% and 55% respectively (see Figure 2).

Treatment Guidelines for 1L and 2L Clear Cell RCC

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines provide guidelines to clinicians in recommending treatment plans to their patients. The NCCN guidelines is also used by health insurance companies and other 3rd party payers like pharmacy benefit managers (PBMs) in determining whether certain drugs are covered under various treatments or indications. Table 4 shows the drugs that are approved for treating advanced RCC patients (either newly diagnosed or relapsed) in the front-line setting.

TABLE 4: NCCN Treatment Guideline for First-line (1L) Advanced or Relapsed Clear Cell Kidney Cancer

Risk Group	Preferred	Other	Useful in Some Cases
Favorable	Axitinib + pembrolizumab	Ipilimumab + nivolumab	Active surveillance
	Pazopanib	**Cabozantinib**	Axitinib
	Sunitinib	Axitinib + avelumab	High-dose IL-2
Poor/Intermediate	Ipilimumab + nivolumab	Pazopanib	Axitinib
	Axitinib + pembrolizumab	Sunitinib	High-dose IL-2
	Cabozantinib	Axitinib + avelumab	Temsirolimus

Source: NCCN Guidelines, Kidney Cancer 2020

When discussing treatment plans with their patients, doctors recommend therapies with the best survival and response outcome (i.e., real-world evidence). Treatment plans are also based on the risk categories of the individual patients. For patients in the favorable risk group, axi/pembro is the No. 1 recommended treatment (see Table 4). However, not all patients prefer a doublet therapy. In that case, Pazopanib and Sunitinib are the recommended No. 2 and No. 3 single-agent therapies. Cabozantinib currently ranks No. 5 in the front-line setting.

If the patient's disease shows no response to first-line therapy (i.e., disease is refractory) or if it begins to progress after having been previously under control (i.e., disease has relapsed), then the treatment plan moves to second line setting. Table 5 shows the NCCN treatment guideline for advanced RCC patients whose disease was either refractory or progressed after first-line treatment.

TABLE 5: NCCN Treatment Guideline for Subsequent (2L) Advanced or Relapsed Clear Cell Kidney Cancer

Preferred	Other	Useful in Some Cases
Cabozantinib	Axitinib	Bevacizumab or similar
Nivolumab	Lenvatinib + everolimus	Sorafenib
Ipilimumab + nivolumab	Axitinib + pembrolizumab	High-dose IL-2
	Everolimus	Temsirolimus
	Pazopanib	
	Sunitinib	

In the second-line setting, Cabozantinib is the No. 1 recommended treatment followed by nivolumab and ipilimumab/nivolumab.

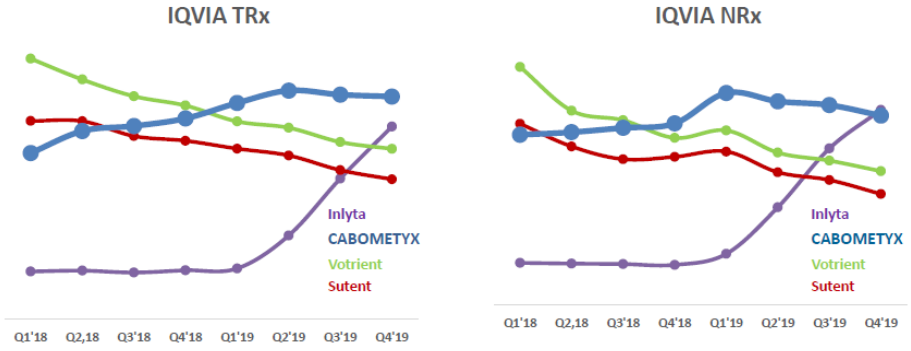
Source: NCCN Guidelines, Kidney Cancer 2020

II. Gradual Sales Decline and Threshold Limits to Advance Cabozantinib to Front-line Setting

A. Prescription Trends for Cabometyx in Advanced RCC

Figure 3 shows cabometyx (brand name for cabozantinib) prescription trend line stabilizing in FY2019. Most noteworthy is the trend in new prescriptions (see Figure 3 right chart), which seems to have peaked in early 2019 and has gradually declined over the rest of the year. This was due to the surge in sales of Inlyta (brand name for Axitinib) beginning in 2Q19, after its IO combination treatment with pembrolizumab and avelumab received FDA approval in April 2019 and May 2019, respectively.

FIGURE 3: Cabometyx Prescription Trends: Total Scripts (TRx, left) vs. New Scripts (NRx, right)



Source: Exelixis 4Q19 and FY2019 earnings results

Management at Exelixis has stated that the 1L new patient share of the two new IO combinations has begun to stabilize at the 70% to 75% share in the 1L RCC market. Furthermore, new patient share in the 2L setting continues to grow as cabometyx continues to capture the majority of 1L IO combination progressors in the 2L setting. Management has stated that cabometyx's growth potential continues to remain in 2L setting as more 1L IO combination patients progress into 2L setting.

Clearly, Figure 3 shows the possibility of additional market share losses for cabometyx going forward as the advanced RCC treatment landscape continues to shift towards IO combinations and Sutent (brand name for sunitinib) continues to be the preferred single agent treatment of patients with non-clear cell RCC.

B. CheckMate-9ER Trial: Minimum Threshold Results to Advance Cabozantinib to 1L Setting

1. Benchmark Outcomes for Approved Phase III Trials in First-line Advanced RCC

At this time, Exelixis seems to be in a defensive posture. The company's randomized Phase III CheckMate-9ER trial is completed and is set to report results in 1H20. CheckMate-9ER compares the combination of cabozantinib and Nivolumab (Opdivo) versus sunitinib (Sutent) in patients with previously untreated advanced or metastatic RCC. The study addresses the important question of safety and efficacy of VEGF in combination with immune checkpoint blockade in the frontline setting of RCC.

In order to move up the treatment line in the frontline setting and to help stem market share losses, CheckMate-9ER has to report impressive safety and efficacy data similar to top-line results produced by axi/pembro in the Keynote-426 trial, by Nivolumab/Ipilimumab in the CheckMate 214 trial and by axitinib/avelumab in the Javelin Renal 101 study. All three studies compared their respective treatment arms

to sunitinib. Table 6 shows the Phase III clinical trial results for select outcomes of the three IO combination therapies for advanced RCC in the frontline setting.

TABLE 6: Select Outcomes for FDA Approved First-line Phase III Clinical Trials

Clinical Trial:	**CheckMate 214 trial**	**Keynote-426 trial**	**Javelin Renal 101 trial**
Combination Therapy:	Nivolumab/Ipilimumab	Pembrolizumab/Axitinib	Avelumab/Axitinib
Treatment Period:	Oct. 2014 – Feb. 2016	Oct. 2016 – Jan. 2018	Mar. 2016 – Dec. 2017
Number of Patients:	546	429	444
Outcome:			
- OS:	75%	**87%**	64% (after 18-mos. f/u)
- mPFS:	11.6 mos.	11.1 mos.	**13.8 mos.**
- ORR:	39%	**59.3%**	55%
- mDOR:	NR, but 72% still responding at 25 mos. follow-up	NR	n/a
- Hazard Ratio:	66%	**53%**	61%

Note: NR – not yet reached; n/a – not available

Source: Savard, Wells, Graham, et. al., "Real World Assessment of Clinical Outcomes Among First-Line Sunitinib Patients with clear cell mRCC, The Oncologist, Jan. 23, 2020; and Practical Application of IO in Renal Cell Carcinoma webinar (ClinicalOptions.com)

2. Minimum Threshold Results for CheckMate-9ER to Advance Cabozantinib in 1L RCC

In order to move up the frontline setting in advanced RCC, CheckMate-9ER has to show comparable or better efficacy and survival data than the 3 recently approved IO combination treatments of axi/pembro, nivo/ipi and axi/avelumab. Table 7 shows our estimates on what the CheckMate-9ER topline data needs to show in order for cabozantinib/nivolumab to advance up the 1L setting for advanced RCC.

TABLE 7: Projected CheckMate 9-ER Results to Advance Cabozanitinib to 1L Advanced RCC Setting

CheckMate-9ER Minimum Threshold Metrics			
OS (%)	**mPFS (months)**	**ORR (%)**	**HR (%)**
70% - 75%	11 - 14 months	50% - 60%	55% - 60%

Source: Viola Advisory LLC estimates

Overall Survival (OS). Survival data is critical in determining the clinician's treatment plan. The higher the chance of survival, the more likely the treatment will be recommended. At a minimum, the CheckMate-9ER study has to show cabozantinib/nivolumab's 2-year overall survival (OS) rate at a range of 70% to 75%. Axi/pembro has a 2-year OS rate of 87% while Nivo/Ipi's OS rate is at 75%. Both Pazopanib and Sunitinib have a 2-year OS rate of 58%. So, in order to convince clinicians that cabozantinib can extend patient lives, the OS rate has to be in the range of 70% to 75%.

Median Progression Free Survival (mPFS). CheckMate 9-ER has to produce mPFS result in the range of 11 to 14 months. Axi/avelumab has a mPFS of 13.8 mos. while axi/pembro has 11.1 mos. and nivo/ipi has 11.6 mos. Sunitinib has a PFS of 16 mos. in the favorable risk group and 9.7 mos. in the intermediate and poor risk group. Pazopanib has a PFS of 9.2 mos.

Objective Response Rate (ORR). In terms of efficacy, the cabozantinib/nivolumab combo has to show an ORR within the range of 50% to 60%. Nivo/ipi has an ORR of 39% while axi/pembro has an ORR of 59%. Both nivo/ipi and axi/pembro are ahead of cabozantinib in the NCCN Treatment Guideline for 1L advanced RCC.

Hazard Ratio (HR). The hazard ratio tells the percentage by which the drug can reduce the risk of death or disease progression. It is calculated by subtracting the number 1 from the hazard ratio. The lower the hazard ratio, the higher the chances are that the drug can reduce the risk of patient death or the risk that the patient's disease will progress.

If CheckMate-9ER can produce a hazard ratio within the range of 55% to 60%, then it can show good survival data. That means that the cabozantinib/nivolumab combo can reduce the risk of death and disease progression by 40% to 45%. That is comparable to the axi/pembro combo which could reduce the risk of death or disease progression by 47% and much better than the nivo/ipi combo whose treatment could reduce the risk of death or disease progression by 34%.

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