Article published online: 2021-05-14

Combining Immunotherapy with Multikinase Inhibitors: A Cautious New Promise

Abstract

Immune check point inhibitors have made a sea change in oncology practice in current times. These drugs have crossed the conventional boundaries of histology and organ of origin. Tumor agnostic approvals for mismatch repair deficient, microsatellite-instability (MSI)-H and recently tumor mutational burden-high solid tumors have been a giant leap. The Oncology community seems poised to embrace the concept of "immunotherapy for all." Recent studies have evaluated the manipulation of tumor-associated macrophages using multi-kinase inhibitors, to make even MSI low tumor responsive to checkpoint inhibitors. With accelerated food and drug administration approvals, the promise of this combo is palpable but definitely merits caution.

Keywords: *Immune checkpoint inhibitors, lenvatinib, regorafenib*

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Immune checkpoint inhibitors (ICIs) have carved a niche for themselves in modern oncology practice. Crossing the barriers of histology and organ of origin, they now have tumor agnostic approval for any metastatic tumor that is mismatch repair (MMR) deficient, microsatellite- instability (MSI) high or has a high tumor mutational burden (TMB). While they work wonders for some patients, the effect is at best modest in others. Indeed, we are yet to find a sure-shot biomarker for these agents. Whenever any metastatic tumor progresses beyond 1–2 lines, and the treating oncologist feels pushed to the wall, running out of options; one explores this option. In reality, this option is scientifically applicable for only a select handful of patients.

For head neck squamous cancers, lung cancers without driver mutations, renal cell cancers, urothelial cancers, hepatocellular cancers, indications are broader and ICIs are applicable for the majority of metastatic cases as initial or subsequent treatment. But for adenocarcinomas of the gastrointestinal (GI) tract and gynecological malignancies, the indications are limited. MSI-H or MMRd tumors were traditionally eligible for ICI in the metastatic setting only after the failure of conventional first or second-line options. Recently, MSI-H colon cancers showed a doubling of progression free survival (PFS) with upfront (first-line) use of Pembrolizumab compared to chemotherapy and targeted therapy and it has received Food and Drug Administration (FDA) approval for the same.[1,2] High TMB tumors, agnostic of its tissue, have also received approval for ICI therapy recently, but the oncology community has taken this approval with a pinch of salt.[3] However, still then, in reality only a small fraction of these cancers; colorectal, gastric, pancreatic, biliary tract, ovarian, endometrial would be eligible for ICI therapy.

What if we can render these microsatellite-stable (MSS) or MMR proficient (MMRp) tumor immunologically hot and eligible for immunotherapy with ICIs? Will it open the Pandora's box and make all these tumors responsive to immune checkpoint inhibition? Definitely, but how's that possible?

Recently investigators have studied a novel strategy of combining multikinase inhibitors with immune-checkpoint inhibitors (such as Nivolumab and Pembrolizumab) to manipulate the tumor microenvironment and render MSS tumors responsive to ICIs. Results of some of these phase-1/2 studies have been recently published, reporting response rates of around 40% in several

How to cite this article: Pramanik R, Sharma A, Kumar A. Combining immunotherapy with multikinase inhibitors: A cautious new promise. Indian J Med Paediatr Oncol 2020;41:901-5.

Submitted: 08-Jul-2020
Revised: 02-Aug-2020
Accepted: 05-Sep-2020
Published: 31-Dec-2020

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Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_326_20

Quick Response Code:

tumor types. These results are exciting and have given hope for the concept of "immunotherapy for all." These studies have given us very important insights into the mechanism of ICI resistance and simultaneously provide the proof of the concept that tumor-associated macrophages (TAMs) can indeed be modulated in favor of an anti-tumor immune response. An accelerated approval by the FDA to the combination of Lenvatinib and Pembrolizumab for metastatic endometrial carcinoma based on these early results, speaks for itself.

Combining a kinase inhibitor to immunotherapy is not new to oncology, for example, the ICI + tyrosine kinase inhibitors (TKI) combinations are the current standards of care in intermediate/poor-risk advanced renal cell carcinoma.[4,5] The novelty, however, is evident in the mechanism of action. Sunitinib and Pembrolizumab tackle the two different active hallmark pathways (vascular endothelial growth factor [VEGF] pathway and immune synapses) each of which is known to provide a survival advantage to renal cell carcinoma. In contrast, the proposed mechanism of action of the combination of regorafenib with nivolumab is based on the theory that regorafenib would reduce T-regulatory cells and TAMs through suppression of VEGF receptor 2 and colony-stimulating factor 1 receptor.[6] These are important immune-suppressive pathways that dampen the response to PD1/PDL1 axis inhibition. Lenvatinib has been shown to increase the anti-tumor activity of DD-1 by decreasing TAMs and enhancing the activation of the interferon signaling pathway in an *in-vivo* model.[7] Thus, this dual combination can reverse the PD1/PDL1 axis inhibition converting an ICI resistant tumor into an ICI sensitive one, like a "magic wand."

Let us now focus on the three published studies in the last few months [Table 1]. Results of the REGONIVO, EPOC1603 study by Fukuoka *et al*. was published in the Journal of Clinical Oncology.[6] They treated 50 patients (25 each with gastric and colorectal cancer) with regorafenib and nivolumab in this phase Ib dose-expansion study, and all of them had progressed on least 2 lines of chemotherapy. They reported an objective tumor response in 20 patients (40%), gastric cancer (44%), and colorectal cancer (36%). Median PFS was 5.6 months for gastric cancers and 7.9 months in patients with colorectal cancers, respectively. Rash (12%), proteinuria (12%), and palmar-plantar erythrodysesthesia (10%) were reported as major side-effects. Fukuoka *et al*. concluded that the combination of Nivolumab and Regorafenib 80 mg was safe and had encouraging antitumor activity, which merits further investigations in larger cohorts.

In another Japanese phase II trial, the EPOC1706 published in The Lancet Oncology, Kawazoe *et al*. administered the combination of lenvatinib and pembrolizumab as first-or second-line treatment for 29 patients of advanced gastric cancers.[8] An objective response was observed in 20 (69%) patients, with similar responses in first line or second line settings (71% and 67%, respectively). At a median follow-up of 12.6 months, while median overall survival (OS) was not reached, the median PFS was 7.1 months. Interestingly, for the 19 patients who had a PD-L1 combined positive score (CPS) of ≥1, the objective response rate (ORR) was 84% and PFS was 9.1 months. In contrast, ORR was 40% in 10 patients with CPS <1 with a PFS of 5.9 months. Patients with high TMB score (above the median of 10) had better ORR (82% versus 60%) than a low TMB score. Hypertension (38%) and proteinuria (17%) were reported as the main Grade-3 adverse events.

These two studies are important because they both report the first results of a potentially path-breaking dual combination regimen in an extremely challenging clinical situation for two common cancers. Treating metastatic colon and gastric cancers after 2 lines are extremely depressing in contemporary times. Most of us would either re-challenge a previous therapy or hunt for a targetable mutation by sequencing the tumor in this scenario, hoping against hope. A vast majority of these tumors are MMR proficient and hence not eligible for immune-oncology (IO) drugs. Thus, this scenario presents a real unmet need. Current standards of care in metastatic colorectal cancer (mCRC) include, FOLFOX ± targeted therapy (Bevacizumab/epidermal growth factor receptor inhibitor) followed by FOLFIRI ± targeted drugs as first- and second-line or vice-versa. Regorafenib and Trifluridine/Tipiracil are the FDA approved subsequent lines of therapy. IO drugs are indicated in approximately 2%–4% of metastatic cases.[9] Similarly, for metastatic stomach cancer, first-line 5FU + platins± (trastuzumab if human epidermal growth factor receptor 2 amplified) is followed by taxanes ± ramucirumab in the second line. Nivolumab is approved in Japan as 2nd/more line therapy based on the ATTRACTION 2 trial but is not yet FDA or European Medicines Agency approved.[10] Pembrolizumab is FDA approved in the 3rd line in those with CPS ≥ 1.[11] Again, around 10%–22% of all gastric tumors are MSI-H.[12] Thus, for both these advanced cancers, this combination may apply to a huge proportion of hitherto ineligible patients. Although cross-trial comparisons are not encouraged, yet a glimpse of the synergistic effect of these combinations is evident from Table 2, which compares the single agent activities of these agents with the combination strategies. We can appreciate that for relapsed metastatic gastric cancers, single agent nivolumab or pembrolizumab has a meager 11% ORR, and regorafenib as a single agent has an ORR of < 1%. However, the combination of nivolumab and regorafenib was able to produce an ORR of 44% and it reached 69% with Lenvatinib and pembrolizumab combination. Similarly, for mCRCs, ORR for regorafenib and nivolumab combination was 36% in MSS tumors, while regorafenib alone could produce 1%–4% ORR. Notably, in MSI-H mCRC the ORR for nivolumab was 31%.

Table 1: Three recent publications of the combination of multi-kinase inhibitors with Immune checkpoint inhibitors

Study name, author, journal	Combination	Tumour type	Type of study	*n*	ORR	PFS (months)	OS	Comments
REGONIVO/ EPOCH 1603; Fukuoka *et al*., JCO, March 2020[6]	Regorafenib + nivolumab	CRC + gastric Ca ≥2 lines	Phase 1b	50 25 (CRC) 25 (gastric)	36% (CRC) 44% (gastric)	7.9 (CRC) 5.6 (gastric)	-	80 mg RP2D for regorafenib Nivolumab=3 mg/kg/ 2 weeks
EPOC1706; Kawazoe *et al*., The Lancet Oncology, June 2020[8]	Lenvatinib (20 mg/day) + pembrolizumab (200 mg q 3 weekly)	Gastric cancer and GEJ adeno Ca	Phase II	29 14 (1st line) 15 (2nd line)	69%	7.1 months	Not reached	12.6 months follow up PDL-1 CPS ≥1% (ORR=84%) TMB high (ORR=82%)
Study 111/ KEYNOTE-146 trial (NCT02501096); Makker *et al*., JCO, Jan 2020[17]	Lenvatinib (20 mg/day) + pembrolizumab (20 0mg q 3 weekly)	Metastatic endometrial cancers	Phase -Ib/II	108 58 patients in interim analysis	ORR 24 weeks=38.3% CR=10.6%	7.4	16.7	18.7 months follow up

JCO –Journal of clinical oncology; CRC –Colorectal cancer; Ca –Cancer; GEJ – Gastro-oesophageal cancers; ORR – Overall response rate; PFS – Progression free survival; OS – Overall survival; RP2D – Recommended phase 2 dose; TMB – Tumour mutation burden; PDL1 – Programmed death ligand-1; CPS – Combined positive score

Table 2: Comparision of the efficacy data on single agents (immune-oncology and tyrosine kinase inhibitors) and the immune-oncology - tyrosine kinase inhibitors combination strategies in metastatic colorectal and gastric cancers

Study name	Drug used	Type of study	*n*	ORR (CR + PR)	DCR	PFS (median months); HR	OS (median months); HR	Comments
Metastatic colorectal cancer (mCRC)								
CONCUR[13]	Regorafenib (R) versus placebo (P)	RCT	R=136 P=68	R=4% P=0%	R=51% P=7%	R=3.2m P=1.7m HR=0.31*	R=8.8m P=6.3m HR=0.55*	Asian population
CORRECT[14]	Regorafenib (R) versus placebo (P)	RCT	R=505 P=255	R=1% P=0.4%	R=41% P=15%	R=1.9m P=1.7m HR=0.49*	R=6.4m P=5.0 m HR=0.77*	Western population
CheckMate 142[15]	Nivolumab	Ph-II	74	23/74=31%	51/74=69%			dMMR/MSI-H only
REGONIVO/ EPOCH 1603[6]	Regorafenib + nivolumab	Ph-Ib	25	36%		7.9m		MSS tumours
Metastatic Gastric cancer (mGC)								
ATTRACTION-2[10]	Nivolumab (N) Versus placebo (P)	RCT	N=493	N=11% P=0%	N=40% P=25%	--	N=5.26m P=4.14m; HR=0.63*	mGC ≥2 lines
KEYNOTE 059[11]	Pembrolizumab	Ph-II	N=259	11.6% 15.5% (PDL1+) 6.4% (PDL1-)				mGC + GEJ
INTEGRATE[16]	Regorafenib (R) versus placebo (P)	Ph-II RCT	R=97 P=50	R=3/97 P=1/50		R=2.6m P=0.9m HR=0.40*	R=5.8m P=4.5m HR=0.74#	multinational
REGONIVO/ EPOCH 1603[6]	Regorafenib + nivolumab	Ph-Ib	N=25	44%		5.6 m		Gastric Ca ≥2 lines
EPOC1706[8]	Lenvatinib + pembrolizumab	Ph-II	29 14 (1st line) 15 (2nd line)	69%		7.1m	NR	

*P<0.05, #P>0.05. M – Months; Ph – Phase; ORR – Overall response rate (CR + PR); DCR – Disease control rate (CR + PR + SD ≥12 weeks); CR – Complete response; PR – Partial response; PFS – Progression free survival; OS – Overall survival; NR – Not reported; HR – Hazard ratio; GEJ – Gastroesophageal junction; Ca –Cancer

Many combinations of multikinase TKI and IO drugs are being evaluated for other MSS tumors as well. Lenvatinib + pembrolizumab has recently shown efficacy in advanced MSS endometrial cancers and has received an accelerated approval from the FDA for advanced endometrial cancers that is not MSI-high (MSI-H) or MMR deficient (dMMR). Notably, the doublet was simultaneously approved in the USA, Canada, and Australia after a collaborative review by FDA, Australian Therapeutic Goods Administration, and Health Canada.[18] This review was done under FDA's Real-Time Oncology Review program, which has been developed to review application submissions more efficiently.

The approval was given on the basis of a multi-center, open-label, single arm, multi-cohort phase Ib/II Study 111/KEYNOTE-146 trial (NCT02501096).[17] In this study, 108 patients with previously treated metastatic endometrial cancer received 20 mg lenvatinib orally once daily plus 200 mg pembrolizumab given intravenously every 3 weeks. Of these patients, 87% of patients had non-MSI-H/dMMR tumors. The ORR at 24 weeks, was 38%. At data cut off, around 7.4% patients had a complete response while the partial response rate was 31%. Notably, 69% of responders had duration of response of at least 6 months. The most common grade 3 TRAEs were hypertension (34%) and diarrhea (8%).

While we do see these studies as light at the end of a dark tunnel, we must be extremely realistic in our expectations from these early-phase data. The response rates and survivals drop down in many regulatory phase-III studies when compared to their phase II data. Hence, these combinations should not be viewed as a panacea yet. It is noteworthy to mention the case of an IDO inhibiotor here. Although initial phase 1 and 2 studies of combined anti-PD-1/IDO (epacadostat) inhibitors (NCT02318277) were promising, surprisingly a phase III trial studying an epacodostat-pembrolizumab combination was abandoned as it failed to show a significant improvement in both PFS and OS.[19]

Nevertheless, while we palpate the potential of the above three combinations, we also identify some concerns and suggest ideas to these investigators when they plan their larger regulatory studies with these combinations. In the REGONIVO study, 98% of the patients were ECOG-PS 0, which is difficult to find in the real-world scenario in a 2nd/3rd line setting. The most common grade 3 or more dose-limiting toxicities reported in this study were skin rash and all these responded to steroids. This likely means that they may also be nivolumab related. The 3 + 3 design was planned for regorafenib dose determination only, keeping the nivolumab partner constant. There is no dose-response relationship in IO drugs. Recent studies suggest similar efficacy with lower doses or decreased frequency of nivolumab.[20-22] We, therefore, suggest the use of lower nivolumab dosage also as an arm of any future planned study. This will also increase the reach and usage of this combo in the community practice. Given the case that generic regorafenib and lenvatinib is now available at an affordable price in many countries, these combos seem to have a future. It would also be interesting to see how this combo compares to single-agent Regorafenib in the 3rd line setting in mCRC and how well this combo or the lenvatinib/pembrolizumab combo compare to single-agent IO drugs in advanced gastric cancer. The authors do acknowledge the limitations of small sample size and rightly plan for larger studies. They must consider these issues while designing the comparator arms of future studies. Future studies must also be multicentric to improve the generalizability of the results.

Several ongoing trials are evaluating one of the multikinase inhibitors with ICI for the treatment of different tumors and we should expect interesting results in this field. Nivolumab in combination with cabozantinib is being studied in breast cancer, melanoma, carcinoids, nonclear cell renal cell cancers.[23] The combination of regorafenib and pembrolizumab is being studied in colon cancers and hepatocellular cancers.[24] Preclinical studies have established the pro-immunogenic effect of radiotherapy and its synergistic role with IO drugs.[25,26] Radiotherapy is also being tried to augment the response to IO drugs (nivolumab and ipilimumab) in colon and pancreatic cancers, by converting "immunologically cold" tumors into "immunologically hot" ones.[27]

Immunotherapy seems poised to reach all tumors irrespective of the MSI boundaries. The oncology community must approach this "magic-wand" with utmost wisdom and caution. With the FDA accelerated approval, the combo is already in the prescriptions for endometrial cancers but for other GI tumors, it is at present best regarded as a "Cautious promise."

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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