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International Journal of Molecular and Immuno Oncology

Conference Review

6th Molecular Oncology Society Conference: Improving patient survival by molecularly targeted therapies

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Received : 26 August 2021
Accepted : 30 August 2021
Published : 27 September 2021

DOI
10.25259/IJMIO_20_2021

Quick Response Code:

Molecular oncology has facilitated the identification of many genes that are responsible for cancer occurrence. The advent of molecular oncolytic therapies, including immunotherapy and gene therapy, has revolutionized cancer treatment in the past few decades. The continuum of molecular oncology is constantly evolving, thanks to the cutting edge technology, and will help us do a better job in personalized medicine over the years to come.

With this motive to enlighten the oncology community in this modern setting, the 6th Medical Oncology Society Conference (MOSCON) was conducted from March 4 to 7, 2021. The meeting facilitated the congregation of many esteemed and accomplished oncologists across India and several molecular diagnostic and pharmaceutical companies on a single dais where the key opinion leaders could discuss, brainstorm, and debate existing challenges and their mitigation strategies as well as enlighten the community with new happenings in medical oncology.

Since the start of COVID-19 pandemic, all health care workers have strived hard to optimize patient care in respective specialties, especially with the help of virtual platforms. This was the first virtual MOSCON. Its positive impact was minimizing travel and reducing contact in view of the COVID-19 pandemic. It was easy to manage time schedules of meetings virtually as it could be accessed from anywhere. Virtual meetings also have some disadvantages in general. There is less of personal networking or team building – as compared with face-to-face meetings.

Dr. Manoj Mahajan, the program director, began the conference with a theme of "everything is theoretically impossible until it is done." Dr. Vineet Talwar spoke about the updates in the maintenance management of newly diagnosed ovarian cancer in the first session of the conference. He highlighted that patients' survival can be prolonged with maintenance olaparib, a strategy that doubled the 5-year disease-free survival (DFS) in newly diagnosed advanced ovarian cancer patients with BRCA mutations (long-term results of the pivotal SOLO-1 trial).[1] In the PAOLA-1 trial, the addition of olaparib to bevacizumab significantly improved progression-free survival (PFS) versus placebo and bevacizumab combination.[2]

The next brainstorming session heralded the evolving trends in the treatment landscape of hormone receptor (HR)+ and human epidermal growth factor receptor 2 (HER2)– advanced breast cancer (ABC) by Dr. Lalit Mohan Sharma. The speaker shared data on how alpelisib is a new standard of care for PIK3CA-mutant HR+ metastatic breast cancer (MBC) post-cyclin-dependent kinase (CDK) 4/6 inhibitor therapy. In CDK4/6 inhibitor-resistant patients (in the SOLAR-1 study), treatment with abemaciclib in combination with fulvestrant demonstrated

continued benefits in PIK3CA-mutated HR+/HER2-negative advanced or MBC.[3] Dr. Partha Basu talked about risk stratification in cancer screening including sonomammography and clinical breast examination, and laid down the approaches and resources required for cancer screening programs in developing countries such as India.

The sessions on "early breast cancer (EBC)" were chaired by Dr. Sudeep Gupta and Dr. Garima Yadav. In this session, Dr. Chintan Shah showcased the first results of the phase III SWOG S1007 (RxPonder) study, demonstrating a strong invasive DFS (IDFS) benefit for chemoendocrine therapy in premenopausal patients, with an early indication of an overall survival (OS) improvement.[4] Furthermore, it is likely safe to forgo adjuvant chemotherapy without compromising IDFS in postmenopausal women involving 1–3 lymph nodes and a oncotype recurrence score of <25.[5]

Dr. Bhuvan Chugh, while presenting the evidence for neoadjuvant immunotherapy in patients with early stage (ES) triple-negative breast cancer (TNBC) from the global Phase III IMpassion 031 trial, showed that atezolizumab neoadjuvant chemotherapy led to improved pathological complete response rates compared to placebo, regardless of programmed death ligand 1 (PD-L1) expression.[6] Dr. Mangesh P. Kamath indicated that Ki-67 biomarker as per the Phase III monarchE trial could be used together with clinicopathological features of nodal involvement, tumor size, and grade, to identify patients with HR+, HER2−, and EBC at high risk of recurrence. In patients with high Ki-67 (≥20%), abemaciclib in combination with standard adjuvant endocrine therapy significantly decreased the risk of breast cancer recurrence by 30.9% compared to patients receiving endocrine therapy alone.[7] The session on molecular drivers of Oncotype DX, Prosigna, EndoPredict (EP), and the Breast Cancer Index (BCI) from the TransATAC study[8] by Dr. Shruti Kate concluded that in contrast to common understanding, recurrence scores are determined more strongly by estrogen-related features and only weakly by proliferation markers. However, EP, BCI and particularly risk of recurrence scores are determined largely by proliferative measures. It is important that the oncologist interpreting and applying the scores for patient management have an understanding of the biologic features the tests reflect, particularly when trying to understand the difference among their readouts. In this context, data from CanAssist Breast are especially applicable to Indian context – because it has been studied in large number of our patients and has a clear-cut division into two groups irrespective of age or menopausal status (limitations with Oncotype DX). This session was followed by an intense panel discussion on the management of HR+ and HER2− EBC, moderated by Dr. Seema Gulia. The panel concluded that the decision to withhold chemotherapy (CT) in the HR+ EBC is based on the combination of clinicopathological factors and genomic factors. The patients at high risk may need adjuvant CD4/6 inhibitors, but the data are immature on the definition of "high risk," the ideal duration of CD4/6 treatment, and also on the impact of late recurrence.

Subsequent sessions on "ABC" were chaired by Dr. Poonam Patil and Dr. D. C. Doval. The circulating tumor DNA (ctDNA) analysis provides an accurate, rapid genotyping evaluation that facilitates identification of mutation-directed therapies in breast cancer patients according to the plasmaMATCH study.[9] The ctDNA also enables the identification of the target mutations for breast cancer treatment. The potential role of novel liquid biopsy platform to screen for rare oncogenic mutations in breast cancer can transform clinical trial approaches as stated by the speaker Dr. Rajeev Vijaykumar. Looking beyond the conventional treatments in HER2+ MBC, Dr. M. V. Chandrakanth opined that new therapeutic compounds in the form of drug conjugates may be effective for HER2− low disease. Apart from the established first- and second-line therapies including trastuzumab, pertuzumab, and T-DM1, the new oral tyrosine kinase inhibitors (TKIs) (tucatinib, neratinib, and pyrotinib), antibody drug conjugates (trastuzumab deruxtecan and trastuzumab duocarmazine), and Fc engineered antibodies (margetuximab) have demonstrated promising activity in the management of HER2+ MBC patients. Following this session, a panel discussion provided insights into the management of HER2+ BC with brain metastasis (BM), which was moderated by Dr. Chirag Desai. As per the current American Society of Clinical Oncology (ASCO) guidelines for managing HER2+ BM, routine surveillance with imaging in the absence of symptoms is not recommended and there is a low threshold for performing diagnostic brain magnetic resonance imaging for any neurologic symptoms suggestive of BM.[10] This session also listed the novel drugs and their combinations used for HER2+ central nervous system (CNS) metastasis. Dr. Raghunadharao Digumarti and Dr. Ajay Rao chaired the final session on day 1, which was a panel discussion on personalized therapy for advanced sarcoma, moderated by Dr. Jyoti Bajpai. It was emphasized that as sarcoma is a rare disease, cases from across the country can be pooled to generate interesting data on disease management and prognosis, which may provide more practical approaches to the treating doctors.

Day 2 started with a session on the role of immunotherapy in metastatic TNBC (mTNBC). Dr. Ajay Bapna suggested that atezolizumab is recommended for patients with PDL-1 immune cells (IC)+ mTNBC as per the National Comprehensive Cancer Network (NCCN) guidelines. Atezolizumab along with nab-paclitaxel has shown prolonged PFS in mTNBC patients, specifically in PDL-1-positive patients, in the Impassion130 trial.[11]

The sessions on "non-small cell lung cancer (NSCLC)" were chaired by Dr. Nalini Kilara. On maximizing the utility of

immunotherapy in metastatic NSCLC (mNSCLC), Dr. Suman Karanth presented that comutations in DNA damage repair pathways are significantly associated with a higher response to atezolizumab, improving survival in NSCLC patients, and may help in identifying patients who could benefit from immune checkpoint inhibitor (ICI) therapy.

Thinking beyond epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS mutations in mNSCLC, Dr. Rakesh Pinninti showed that tepotinib resulted in partial response (PR) in ~50% of patients with advanced NSCLC with confirmed MET exon 14 skipping mutation.[12] Dr. Deepak Shukla discussed the results of the Phase II CodeBreak 100 trial, which showed that sotorasib provided durable clinical benefit with a favorable safety profile in pre-treated NSCLC patients with KRAS p.G12C mutations.[13] In the LIBRETTO-001 study, selpercatinib resulted in 64% objective response rate in RET fusion-positive NSCLC patients previously treated with platinum-based chemotherapy as presented by Dr. Pushpak Chirmade.[14] In the ARROW study, pralsetinib produced robust clinical responses in RET fusion-positive NSCLC patients.[15]

A panel discussion on the "treatment of Stage IV NSCLC with actionable mutation" was moderated by Dr. G. S. Bhattacharyya. There are two aspects of care in these patients: (1) patient centric care and (2) evidence-based medicine. The advanced stage lung cancer with adenocarcinoma component should undergo genomic analysis irrespective of the age, gender, smoking history, or ethnicity, but the ES testing is always an institutional policy decision. The molecular testing guidelines for NSCLC were discussed, and the targeted therapies for different genetic mutations were elaborated.

Dr. Ankit Agarwal discussed the personalized therapies to further improve outcomes in BRAF-mutated NSCLC. More than 60% of patients with BRAF V600E mutant metastatic NSCLC responded to dabrafenib and trametinib combination in a pivotal study.[16] The topic on the "VALUE of comprehensive genomic profiling (CGP) in modern lung cancer practice" was taken by Dr. Natasha Leighl who suggested that patients with actionable genomic targets identified in liquid biopsy should proceed to targeted therapy without waiting for confirmation from tissue testing. Dr. Naresh Somani was the speaker for the session on "alectinib in first-line new standard of care in ALK+ NSCLC patients." Alectinib provides the longest duration of disease control along with a defined treatment sequence, improving the prognosis for patients with advanced ALK+ NSCLC.[17]

Topics on "Genitourinary Cancer" were chaired by Dr. Maheboob Basade and Dr. Shailesh Talati. The roles of rucaparib in metastatic castration-resistant prostate cancer (mCRPC) with HRR gene alterations were discussed by Dr. Chaitanya Krishna. Two poly-ADP ribose polymerase (PARP) inhibitors (PARPi), rucaparib and olaparib, have been approved by the Food and Drug administration (FDA) for the treatment of mCRPC. While both agents are approved for tumors with BRCA1/2 alterations, olaparib is also indicated in patients with 12 other homologous recombination deficiency gene alterations including ATM and PALB2.[18] Dr. Amit Sehrawat pointed to the FDA approval of relugolix for advanced prostate cancer based on the HERO study[19] Dr. Pradip Mondal elaborated on whether immunotherapy is changing survival in metastatic renal cell carcinoma (mRCC) and concluded that first-line pembrolizumab plus axitinib extended survival among patients with advanced RCC, as per the Phase III KEYNOTE-426 study.[20] The panel discussion on "CRPC with novel mutations" was moderated by Dr. Shyam Aggarwal. The panel stated that beyond chemotherapy and hormonal therapy in metastatic prostate cancer, emerging treatments for mCRPC include immunotherapy, PARPi, and prostate-specific membrane antigen-targeted approaches. In addition, genomically targeted agents may also become relevant for a subset of patients with mCRPC.

Day 3 started with a session on recent updates on durvalumab in Stage III NSCLC and ES-squamous cell lung cancer (SCLC). Dr. Amit Rauthan presented the Phase III PACIFIC study results in patients with Stage III NSCLC with a PD-L1 status ≥1% treated with durvalumab, an ICI, which showed a significantly longer PFS, OS, and long-term clinical benefits versus placebo.[21] Dr. Deepak Gupta concluded that osimertinib, the only EGFR-TKI and the first-line standard of care, has significantly improved OS in EGFR-mutated NSCLC patients.

The sessions on "Gastrointestinal Tumors" were chaired by Dr. Narendra Singh Rathore. Immunotherapy has led to improved survival in Stage III lung cancer. Dr. Bharat Vaswani showed that in the Phase III KEYNOTE 177 study, pembrolizumab led to significantly longer PFS versus chemotherapy when received as first-line therapy for microsatellite instability high/deficient mismatch repair (MSI-H/dMMR) metastatic colorectal cancer (mCRC).[22] The new markers for immunotherapy in mCRC including tissue or plasma tumor mutational burden (TMB) were elaborated by Dr. Gaurav Mantri. The CCTG CO.26 trial evaluated dual inhibition of PD-L1 and cytotoxic T-lymphocyte-associated protein 4 through durvalumab plus tremelimumab and best supportive care (BSC) versus BSC alone on patient survival in rmCRC, where plasma TMB appeared prognostic in the BSC arm. Durvalumab plus tremelimumab significantly prolonged OS. High TMB may select a group of microsatellite stable patients who benefit from durvalumab plus tremelimumab.[23] The new target fibroblast growth factor receptors (FGFRs) in advanced gastric/gastroesophageal junction adenocarcinoma were discussed by Dr. N. Aditya Murali. Targeting FGFR2b

with bemarituzumab plus chemotherapy led to clinically meaningful and statistically significant improvements in PFS, OS, and response rates in the Phase II FIGHT trial in advanced gastric/GE junction adenocarcinoma.[24] The panel discussion on the management of mCRC for MSI-H/dMMR was moderated by Dr. Senthil Rajappa. The molecular characteristics facilitate choosing the appropriate drugs in these patients. Several points were discussed that favored the use of ICI as first-line management. The panel was hopeful that Keynote-177 trial will further show survival advantages with ICIs.

The sessions on "pancreatobiliary cancers" were chaired by Dr. B. N. Kapur and Dr. Sadashivudu Gundeti. Expanding the horizons of Paribs in metastatic pancreatic cancer BRCA/PALB2 mutation, Dr. A. P. Dubey discussed the Phase III POLO trial, which has established proof of principle for the use of olaparib as maintenance therapy with prolonged survival for germline BRCA-mutated metastatic pancreatic cancer.[25] In patients with pancreatic ductal adenocarcinoma and a germline BRCA/PALB2 mutation, first-line therapy with cisplatin plus gemcitabine has yielded high response rates and encouraging survival outcomes, however, concurrent veliparib did not result in improved response[26] as presented by Dr. Nirmal Raut. A transcriptomic signature to predict adjuvant gemcitabine sensitivity in pancreatic adenocarcinoma was discussed by Dr. Kshitij Joshi who concluded that the RNA-based GemPred stratification predicts the benefits of adjuvant gemcitabine in these patients. The panel discussion on the "management of metastatic pancreatic cancers with actionable mutations" was led by Dr. Ghanashyam Biswas. Deliberations were made regarding the factors influencing the selection of first-line chemotherapy regimens in advanced pancreatic cancer, which could include the Eastern Cooperative Oncology Network Performance Status, age, comorbidities, risk of endobiliary stent complications, convenience, patient preference, cost, and the predictive biomarkers. Germline testing is recommended for any patient with confirmed pancreatic cancer using the comprehensive gene panel for hereditary cancer syndromes.

The sessions on "gynecological cancers" were chaired by Dr. Lalit Kumar. The role of immunotherapy in endometrial/ovarian cancer was elaborated by Dr. Priya Nayak with results from the Phase II KEYNOTE-158 study having clinical benefit of anti-programmed death-1 therapy with pembrolizumab among patients with previously treated unresectable or metastatic MSI-H/dMMR non-CRC,[27] and by Dr. Prashant Mehta who highlighted KEYNOTE 100 study, where pembrolizumab monotherapy demonstrated modest anticancer activity in recurrent advanced ovarian cancer, with increasing response rates with higher PD-L1 expression.[28] Results from the Phase III ENGOT-OV16/NOVA trial demonstrated the long-term safety profile of niraparib in patients with recurrent ovarian cancer.[29] The panel discussion on the "management of endometrial cancer" was moderated by Dr. Ashish Singh. The molecular classification of endometrial cancer, and the best evidence-based adjuvant treatment strategies for low-, intermediate-, and high-risk patients, the role of surgery and radiotherapy in advanced or recurrent endometrial cancer, the optimal systemic therapies, and promising targeted agents were discussed. Day 3 ended with the last session "From clinical trials to clinical practice: Navigating management of ER+ HER2− MBC with CDK 4/6 inhibitors" by Dr. Ajay Bapna who concluded that the use of CDK4/6 inhibitors in the first-line setting significantly increases overall response rate and consistently improves the PFS as compared with endocrine therapy alone based on the PALOMA-2,[30] MONALEESA-2,[31] and MONARCH-3[32] trials.

On day 4, the management aspects of the hematological malignancies including lymphoma, multiple myeloma (MM), and leukemia were discussed. The sessions on lymphoma/leukemia were chaired by Dr. Tapan Saikia. The speaker for the first session on follicular lymphoma, Dr. Nilesh Wasekar, presented that activating mutations of enhancer of Zeste homolog 2 (EZH2) are present in ~20% of patients with follicular lymphoma. Tazemetostat, a first-in-class, oral EZH2 inhibitor, showed clinically meaningful, durable responses and was generally well-tolerated in heavily pretreated patients with relapsed or refractory follicular lymphoma.[33] Dr. Irom Anil Singh highlighted that newer BTK inhibitors are better in the management of chronic lymphocytic leukemia (CLL). Therapeutic targeting of BTK has dramatically improved survival outcomes for patients with CLL. Acalabrutinib, an oral highly selective BTK inhibitor, demonstrated efficacy (response rate: 94%), durability of response, and long-term safety in patients with previously treated CLL.[34] Dr. H. S. Darling presented the 5-year data from the MURANO study and reported that fixed duration venetoclax/rituximab in patients with relapsed/refractory CLL had time-to-next treatment benefits, improved time to second PFS event, and showed high response rates to subsequent therapies including re-exposure or cross-over to venetoclax-based regimens.[35] A panel discussion on "diffuse large β-cell lymphoma (DLBCL)" was moderated by Dr. Pankaj Malhotra. The CNS risk stratification and therapy were elaborated. Information on germinal center β-cell, activated β-cell, Ki-67, CD30, Myc, and β-cell lymphoma (BCL)2/BCL6 are required before initiating DLBCL treatment. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone is the standard of care for DLBCL and avoided in some patients such as those with cardiac compromise, the elderly, and with the use of targeted drugs such as ibrutinib and lenalidomide.

Dr. K. Pavithran and Dr. Ajay Sharma chaired the sessions on MM. The chimeric antigen receptor (CAR)-T therapy

in refractory myeloma was presented by Dr. Swami Padmanabhan Iyer. CAR-T uses a patient's own T cells, which are removed and then engineered to identify and kill malignant MM cells. Dr. Iyer showed that CAR-T cell therapy effectively treated refractory myeloma.[36] Several clinical trials have demonstrated enhanced efficacy and tolerability of daratumumab-based combinations in both transplant ineligible and eligible MM patients, without compromising transplant ability. Daratumumab as first-line treatment of transplant eligible MM was elaborated by Dr. Nishad Dhakate. The Phase III CASSIOPEIA trial showed that daratumumab with bortezomib, thalidomide, and dexamethasone (VTd) decreased the risk (by 53%) of progression or death compared with VTd alone in newly diagnosed patients with MM who were candidates for autologous stem cell transplant.[37] The session concluded with a panel discussion on the "current management of relapse refractory MM," which was moderated by Dr. Abhay Bhave. The panel members debated on the recommendations of the International Myeloma Working Group on the management of relapsed MM. The panel members opined that venetoclax addition to bortezomib plus dexamethasone significantly improves the PFS, especially in patients with t(11;14) or BCL2 high gene expression where venetoclax shows a favorable benefit–risk profile.

The sessions on leukemia were started by Dr. Sameer Tulpule. The current treatment mainstays for acute myeloid leukemia (AML) include chemotherapy or mutation-specific targeting molecules including FLT3 inhibitors, IDH inhibitors, and monoclonal antibodies. Dr. Sameer Tulpule showed that post-transplantation maintenance therapy with sorafenib is effective in reducing the relapse in FLT3-ITD AML patients undergoing allogeneic HSCT.[38] Dr. Abhishek Dudhatra discussed the inhibition of PI3K as an alternative therapeutic strategy in CLL.[39] The PI3K inhibitors have an important role in patients progressing after BTKi and BCL2 antagonist and in patients with comorbidities such as cardiac or renal dysfunctions. Dr. Varun Bafna highlighted the IDH mutation, which occurs in ~20% of AML patients. Targeted therapies for patients with AML and IDH mutations are now approved both in the newly diagnosed and relapsed/refractory settings. The therapeutic efficacy in IDH mutant AML can be maximized through the concurrent inhibition of IDH and methyltransferase.[40] The panel discussion on the "management of AML" was moderated by Dr. Hemant Malhotra. The panel members discussed the front-line treatment for patients' who are ineligible for intensive therapy, for younger patients fit and eligible for intensive therapy, and the mutations that impact the addition of venetoclax to hypomethylating agents. Venetoclax plus azacitidine has shown survival improvement in newly diagnosed AML. The cytogenetics affect the durability of the venetoclax/azacitidine response in AML patients. Gilteritinib, quizartinib, and crenolanib are the front-line FLT3 inhibitors in the treatment of AML. The minimal residual disease assessment should become the standard of care in AML treatment.

The session on "optimize CML management in new decade" was taken by Dr. Vishnu Sharma. The overall CML therapeutic landscape has dramatically changed with TKI development, which allows a near-normal life expectancy. Treatment-free remission, through the achievement of a stable deep molecular response, is increasingly regarded as a feasible treatment goal. On the question of "Do I need single test to assess all mutations in mNSCLC?", Dr. Aparna Dhar indicated that CGP using liquid biopsy of a blood sample is feasible in patients where traditional testing methods are contraindicated due to insufficient tissues samples.[41] In NSCLC, available tumor tissue is a practical concern for some patients, and in addition, a liquid test is desirable at the time of disease progression as it avoids a repeat biopsy.[42] Dr. Manoj Mahajan delivered the concluding remarks for MOSCON 2021 and highlighted how the journey from organ of origin based conventional chemotherapy has transformed to personalized therapy with druggable molecular targets in cancer management. Clearly, the conference had shown that OS in cancer patients is improving meaningfully and significantly, thanks to the use of molecularly targeted therapies.

Our experience of organizing and conducting an international virtual conference was unique in many ways. It taught us how to optimize experience sharing and continuing medical education while facing unprecedented challenges thrown up by the ongoing COVID-19 pandemic. We thank all the faculty and participants in cooperating with us and making 6th MOSCON a grand success.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Mahajan M, Mandawade N, Singh R, Parikh P, Sharma S. 6th Molecular Oncology Society Conference: Improving patient survival by molecularly targeted therapies. Int J Mol Immuno Oncol 2021;6(3):111-7.