CARE™ ADJUVANT MELANOMA UPDATE 2021

With Additional Perspectives on Navigating the New Normal during the COVID-19 Pandemic
Updates and Recommendations for Adjuvant Systemic Therapy

Interferon

No Longer recommended given significant improvement in outcomes with novel targeted and immunotherapy options.

Immunotherapy

The availability of novel immunotherapy options has revolutionized management of adjuvant melanoma in recent years. PD-1 inhibition with pembrolizumab or nivolumab monotherapy is recommended in the adjuvant setting based on the consistent, substantial, and clinically significant improvements in recurrence-free survival (RFS) demonstrated in phase III randomized control trials (RTCs).

Available immunotherapies, notable updates, and additional recommendations are outlined below.

Monotherapy:

Pembrolizumab (PD 1 inhibitor) shows a clinically meaningful, sustained improvement in RFS that is consistent across subgroups (PD-L1 positive, PD-L1 negative, and BRAF-mutated). Choice of regimen may vary based on physician or patient preference. Recent data supports q6w regimen (every 6 weeks), provides more options and flexibility with administration for patients.

Pivotal Phase III RCT: Keynote 054 (European Organisation for Research and Treatment of Cancer [EORTC] 1325); NCT02362594

Nivolumab (PD 1 inhibitor) shows improvement in RFS that is consistent across subgroups (PD-L1 positive, PD-L1 negative, and BRAF-mutated).

Pivotal Phase III RCT: Checkmate 238; NCT02388906

Ipilimumab (CTLA-4 inhibitor) is less effective and more toxic compared to other immunotherapy options (nivolumab and pembrolizumab and should only be considered for patients that recur on adjuvant nivolumab or pembrolizumab.

Combining Immunotherapy:

Several RCTs have compared combination nivolumab and ipilimumab to ipilimumab alone in patients with advanced melanoma. Data demonstrates longer OS and PFS with the immunotherapy combination regime, however, was associated with greater toxicity.

Combination immunotherapy may be considered for patients with stage IV disease regardless of BRAF V600 mutation status, who have high tumour volume or brain metastases, and who are able to tolerate potential toxicity.

Key Immunotherapy Clinical Trial Updates from 2020:

ESMO 2020 Abstract LBA46. Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: final results regarding distant metastasis-free survival from the EORTC 1325-MG/Keynote 054 double-blinded phase 3 trial

AACR CT042. Pembrolizumab 400 mg Q6W dosing: First clinical outcomes data from Keynote-555 cohort B in metastatic melanoma patients
Targeted Therapies

The discovery of oncogenic molecular pathways in melanoma has led to the identification of targetable mutations. Mutations of the BRAF gene is one such target and is found in approximately 40% of melanomas.1

A review of the available targeted therapy, notable updates, and additional recommendations are outlined below.

Dabrafenib plus trametinib (BRAF inhibitor and a MEK inhibitor) results in combined inhibition of the MAPK pathway and has led to practice changing improvements in outcomes for patients with metastatic BRAF mutant melanoma.

Pivotal Phase III RCT: COMBI-AD; NCT01682083

Key Targeted Therapy Clinical Trial Updates from 2020:

ASCO 2020 Abstract 10001. Long-term benefit of adjuvant dabrafenib + trametinib (D+T) in patients (pts) with resected stage III BRAF V600–mutant melanoma: Five-year analysis of COMBI-AD.

ESMO 2020 LBA43. Spartalizumab plus dabrafenib and trametinib (Sparta-DabTram) in patients (pts) with previously untreated BRAF V600–mutant unresectable or metastatic melanoma: results from the randomized part 3 of the Phase III COMBI-i trial

Patient Care During COVID-19

Consult Considerations

Assess whether an in-clinic visit is warranted. The decision between in-clinic vs. virtual consultations should be made on an individual patient basis considering:

- COVID-19 infection rate in the respective community.
- stage of disease
- reason for consult
  - First consult for clinically suspicious lesions should done with in-person and should not be delayed.
  - For patients who are COVID-19 positive, the choice to bring the patient in is based on individual criteria: age and flat or nodular melanoma.
- virtual consult recommended for psychological support visits, or visits between two treatments for patients on immunologic therapies.

In cases that warrant in-person consult, share protocols with patients before coming to clinic (masking of all patients, physical distancing, hand and surface hygiene, and identification of upper respiratory infection symptoms)

- If possible, organize investigative tests and face-to-face consultations so that the patient spends as little time as possible in the hospital.
  - Most centers will have a COVID-19 testing protocol appropriate for their circumstances in place.
  - It is important to maintain documentation standards during a virtual care appointment with a patient.

If a choice of virtual consultation is made:

- Patient education material “how to access/use” should be provided.
- Obtain informed consent prior to the initiation of virtual care /telehealth.
- Clear, consistent, and simple language is used with patients.
- Ensure the availability of other ancillary services in the virtual care setting (i.e. interpreter services if a language barrier has been identified)
Considerations for Melanoma Therapy during COVID-19

The aim of melanoma patient care during the COVID-19 pandemic is to continue to deliver all appropriate treatments to patients who require them as safely as possible for the care team and the patient.

- It is imperative that clinics ensure open and proactive communication with patients about COVID-19 protocols in place at clinic, how to maintain access to value clinic and support services, therapeutic options being considered, and any potential risks associated with their care during COVID-19.
- Regimens that limit time in hospital should be adopted where possible.
  - For patients starting immunotherapy, the majority should start single agent PD-1 inhibitor. Consideration should be given to choosing 6-weekly pembrolizumab with a telephone call at 2–3 weeks.
  - Where possible, choose a treatment that minimizes the risk of admission to hospital due to risk of treatment-related toxicity.
    - Significant immune toxicity is common with combination immunotherapy, frequently leading to hospital admission. The same toxicities are seen for single agent PD-1 inhibitors, although much less frequently.
    - Targeted therapy with dabrafenib and trametinib is associated with a high risk of fever and malaise, which mimic COVID-19 symptoms. Although the majority of patients do not require hospitalisation, the possibility of COVID-19 infection must now be considered.
- Treatment frequency and supervision considerations:
  - Immunotherapy: a one cycle break is acceptable in patients on treatment for >3 months. Patients require blood tests at the missed cycle timepoint and a telephone review.
  - Targeted therapy: aim for continuous treatment; patients stable on treatment beyond 4 months can safely be dispensed 8 weeks of drug without blood tests in between.
- In regions where there are high rates of COVID-19 infection, prioritizing patients coming in for therapy may be required. Select recommendations on patient groups that may be considered higher priority from the National Institute for Health and Care Excellence (NICE) and NHS England are summarized below:
  - **First-line metastatic disease** is considered the highest priority given the major impact on long-term survival, with a median expected 5-year survival of about 50%.
  - **Adjuvant therapy** has a major impact on risk of recurrence so should also be considered high priority (but lower than first-line treatment for metastatic disease).
  - **Second-line metastatic disease for patients with a BRAF mutation** have effective second-line treatments available (targeted therapy or immunotherapy), although outcomes not as good as for first line.
- The following table outlines recommendations for management of patients who have a positive COVID-19 diagnosis.

### Table. Recommendations for COVID-19 Positive Patients

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Surgery (sentinel lymph node biopsy)</td>
<td>Surgery is scheduled according to the availability of operating rooms suitable for COVID-19 positive</td>
</tr>
<tr>
<td>Radiotherapy (palliative)</td>
<td>Consider medication approach in case of pain or dedicated COVID-19 positive radiotherapy pathways</td>
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<tr>
<td>Systemic adjuvant therapy</td>
<td>No treatment</td>
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<tr>
<td>Systemic therapy (metastatic setting)</td>
<td>Delay treatment</td>
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Moving Forward

Regarding Clinical Updates - Clinical trials comparing front-line systemic targeted therapy and checkpoint inhibitors are ongoing and will help refine optimal approaches.

Regarding Patient Management during COVID-19 - All patients, regardless of ongoing treatment, should receive SC2 vaccination unless they have documented, severe allergic reactions to one or more vaccine constituents. As more patients begin to go back into clinic, it will also be important to anticipate and plan for challenges with coordinating patient load and testing.

The CARE™ Oncology Faculty will be connecting next around the ASCO 2021 Annual Meeting to review data, consider clinician needs across various malignancies (including melanoma and other skin cancers), and discuss COVID-vaccines and approaches /considerations with cancer therapy.

Stay tuned for CARE™ Faculty coverage of the conference and updated guidance/recommendations on the COVID pandemic, COVID vaccines, and treatment of melanoma!

References and Resources Consulted


Additional COVID-19 Resources consulted:


ASCO Coronavirus Resources. Available at: https://www.asco.org/asco-coronavirus-information


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