In this article, we summarise a paper by **Agop Y. Bedikian**, published in the **OncoDaily Medical Journal**, tracing how care for metastatic cutaneous melanoma moved from cytotoxic agents to precision targets and immune checkpoint blockade, and what still limits durable control.

Title: *Evolution of the Treatment of Metastatic Cutaneous Melanoma over the Past 5 Decades*
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Full article

Metastatic cutaneous melanoma has undergone one of oncology's most dramatic transformations. For much of the 1960s–80s, **dacarbazine (DTIC)**, alone or in multi-drug regimens, offered modest responses without clear survival benefit. **High-dose interleukin-2 (IL-2)** delivered durable complete responses for a minority but demanded intensive inpatient monitoring. "Biochemotherapy" (IL-2/interferon plus CVD) improved response rates and long-term survival in institutional series, yet meta-analyses failed to show an overall survival advantage versus chemotherapy, setting the stage for a new therapeutic era.

That inflection point came with **targeted therapy**. About half of melanomas harbor **BRAF V600** mutations; paired **BRAF/MEK inhibition**, **dabrafenib+trametinib**, **vemurafenib+cobimetinib**, **encorafenib+binimetinib**, consistently beat single-agent therapy on response and survival, and rapidly debulk disease. Still, **acquired resistance** is common via MAPK reactivation and alternative pathways, leading to relapse even after complete responses. KIT-altered acral/mucosal melanoma remains a smaller, mixed-response niche.

In parallel, **immune checkpoint inhibitors** reshaped outcomes. **Ipilimumab (anti-CTLA-4)** improved overall survival over historical controls; **anti-PD-1 agents** (**nivolumab**, **pembrolizumab**) outperformed chemotherapy. Combinations, **nivolumab+ipilimumab** and **relatlimab (anti-LAG-3)+nivolumab**, raise response rates and durability, at the expense of higher immune-related toxicity. For **BRAF-mutant** disease, the **DREAMseq** strategy supports **immunotherapy first**, reserving targeted therapy for patients with rapidly progressive disease who need immediate tumor control.

Management of **brain metastases** has also advanced. **Dabrafenib+trametinib** achieves meaningful intracranial responses in BRAF-mutant disease; **nivolumab+ipilimumab** shows robust activity in asymptomatic brain metastases regardless of BRAF status, whereas single-agent anti-PD-1 is less effective in symptomatic or previously treated CNS disease.

Cellular therapies are expanding options. **Tumor-infiltrating lymphocyte (TIL) therapy (lifileucel)** recently gained FDA approval for previously treated melanoma, offering durable benefit for a subset despite significant logistical and cost barriers. **CAR-T** approaches remain investigational without a validated melanoma target.

Where next?
The dominant challenge is therapeutic resistance to both targeted and immune approaches. Active studies are probing next-generation checkpoints, rational **targeted-immunotherapy combinations**, and strategies to prevent or overcome resistance, alongside efforts to broaden molecular testing and access to advanced drugs.

Bottom line: In five decades, metastatic melanoma care has shifted from modest, inpatient cytotoxics to mainly outpatient **precision and immune** therapies, with multi-year survivals now common. The field's next leap will depend on cracking resistance and ensuring equitable access.