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Adjuvant Therapy of Melanoma

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Abstract

The incidence of melanoma is rapidly increasing, especially in younger female and older male patients. Recent fundamental advances in our knowledge of melanoma tumorigenesis have established roles for inhibitors of the MAPK pathway and regulatory immune checkpoints CTLA-4 and PD-1/PD-L1. However, the majority of patients continue to present with non-metastatic disease—typically managed with surgical resection and adjuvant therapy. High-dose IFN-α2b (HDI) is the main adjuvant therapeutic mainstay in high-risk disease following definitive resection. In this chapter, we review the evidence supporting the use of adjuvant HDI in high-risk melanoma. We also discuss some of the other treatment modalities that have been evaluated including vaccines, chemotherapy, and radiotherapy.

Keywords

Melanoma; Adjuvant; High-dose IFN-α2b; HDI; Pegylated IFN; Vaccines; Chemotherapy; Radiotherapy; PD-1; PD-L1; CTLA-4; Ipilimumab; Nivolumab; Pembrolizumab

1 Introduction

Data from the US Surveillance, Epidemiology, and End Results (SEER) program indicate that melanoma is rapidly increasing in incidence. In 2014 there were 76,100 new cases of melanoma and 9,710 deaths—an incidence that has quadrupled over the past 4 decades, increasing by 2.6 % annually over the last 10 years [1].

Patients with early-stage (T1-2) disease have generally excellent outcomes following surgery. However, patients with thicker (≥T3) or ulcerated tumors, or with regional lymph node involvement, have a higher risk of relapse and death, underscoring the interest in effective adjuvant therapy for resected high-risk disease.

Early studies of interferons demonstrated a broad range of direct antitumor activities as well as immunomodulatory functions in a range of preclinical disease models. Clinical activity in the advanced disease setting was modest and attention turned to evaluating interferons in the adjuvant setting. The pivotal Eastern Cooperative Oncology Group trial (E1684) randomized high-risk patients defined as those with T4 primary lesions or any nodal involvement either at presentation or at regional recurrence to high-dose IFN-α2b (HDI) versus observation and

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demonstrated substantial improvements in relapse-free survival (RFS) and overall survival (OS) and led the first Food and Drug Administration (FDA) approval for an adjuvant therapy of resected high-risk melanoma [2]. HDI and the more recently approved pegylated IFN (pegIFN) remain the only approved adjuvant treatments for resected high-risk melanoma (primary tumor thickness ≥T4 mm and/or regional lymph node metastases) [2].

Although approved in the USA, Australia, and Europe, substantial treatment-related constitutional, hematologic, hepatic, and psychiatric toxicities have impeded the adoption of this regimen in parts of Europe and the USA, as well as in Australia. Subsequent trials have evaluated various dosages, schedules, and routes of administration in an attempt to improve the therapeutic index while assessing which treatment component was most critical to efficacy. These studies have not offered substantial evidence that any alternative schedule or dose has benefits that would rival those observed with HDI. Retrospective studies evaluating a variety of predictive biomarkers have suggested several promising candidates, none of which have been prospectively evaluated.

In this chapter, we first discuss the clinical factors associated with recurrence risk. We outline the development of IFN-α in the adjuvant setting, focusing on the various clinical studies that led HDI to becoming the standard of adjuvant therapy, and discuss emerging options including pegylated IFN, vaccines, CTLA-4 blockade, chemotherapy, and radiotherapy.

2 Indications for Adjuvant Therapy

Adjuvant therapy is typically considered for patients whose risk of recurrence is higher than 30–40 % at 5 years, following the surgical extirpation of detectable disease, for the purposes of preventing the likelihood of recurrence and ultimately toward the goal of improving the overall long-term disease-specific survival.

Of the various clinicopathologic factors important in melanoma, 5 factors with independent predictive value in relation to relapse and mortality have been identified based on relapse and survival data from patients in the American Joint Committee on Cancer (AJCC) Melanoma Staging Database [3]. These factors were included in the revised 2009 classification on the staging and prognosis of cutaneous melanoma copublished by the AJCC and the International Union Against Cancer (UICC):

- Primary tumor depth or Breslow thickness.
  - Measured in millimeters [<1.00 mm (T1), 1.01–2.00 mm (T2), 2.01–4.00 mm (T3), and >4.00 mm (T4)], and this is the most important prognostic factor, with survival decreasing commensurately to increasing thickness.
- Ulceration.
  - Adversely increases the prognosis of melanoma of any thickness—ulcerated melanoma of any T depth is associated with a risk of relapse and/or death of the next higher non-ulcerated T depth.

- Mitotic rate.
  - Defined as the number of mitoses per square millimeter (mm^2) in the primary tumor, and this discriminates between aggressive lesions (>1 mitoses/mm^2) and less aggressive lesions (<1 mitoses/mm^2) especially in T1 melanomas. Besides ulceration, the mitotic index separates T1a from T1b lesions.
- Regional metastatic burden.
  - Absolute risk of lymph node involvement increases proportionally to tumor thickness—2–5 % for T1 and up to 34 % for T4 lesions [4]. Both macroscopic tumor burden (1, 2–3 and ≥4) and microscopic tumor burden have prognostic implications—latter subdividing N1 and N2 classifications into N1a/N2a (micro-metastatic) and N1b/N2b (macro-metastases). Survival decreases with increasing lymph node involvement—5-year survival ranges from 78 % (stage IIIA) to 59 % (stage IIIB) down to 40 % (stage IIIC). Prognostic implication of sub-micro-metastases (<0.1 mm) is contentious: Some authors deem sentinel lymph node (SLN) involvement of any degree significant, while others argue that patients with melanoma micro-metastases have similar rates of relapse and/or death as patients with SLN-negative disease [4, 5].
- Location and extent of distant metastatic disease.
  - Location and extent of distant metastases and serum lactate dehydrogenase (LDH) enzyme level predict survival. Of the former, distant skin, subcutaneous, and/or lymph node metastases (M1a) have the best prognosis, while non-lung visceral metastases and tumors with LDH elevation (M1c) have the worst. Pulmonary metastases (M1b) have an intermediate prognosis. The extent of tumor, and particularly whether the disease is solitary or not, has been shown to be important both in the regional lymph node and in the distant visceral sites including the brain [6].

Several authors have developed prediction tools that use proprietary nomograms to estimate the risk of nodal metastases (Memorial Sloan Kettering Sentinel Node Metastasis prediction tool) and 5-/10-year survival (AJCC Individualized Melanoma Patient Outcome Prediction Tool) [7, 8].

Current practice standards advocate either clinical trial enrollment or adjuvant therapy with interferon [either high-dose interferon for 1 year or pegylated interferon (pegIFN) for 2 years] in patients with high-risk resected melanoma whose estimated risk of recurrence exceeds 30 %, i.e., high-risk node-negative disease (T3b or T4 a/b) and node-positive melanoma.

3 Evolution of HDI and PegIFN in Adjuvant Therapy of High-Risk Resected Melanoma

Melanoma is an immunogenic solid tumor, as first suggested by reports of spontaneous regressions in advanced disease; and by the subsequent documentation of melanoma-specific immune responses to cancer germ line antigens (MAGE and NY-ESO-1), melanoma differentiation antigens, and presence of tumor-infiltrating lymphocytes (TILs). These observations paralleled our early forays into understanding the cellular and humoral basis of immunity.

Evidence of the antineoplastic effects of a variety of cytokines including IFN-α, IL-2, IL-7, and IL-21 heralded the dawn of cancer immunotherapy. These early results yielded in a series of trials in an array of preclinical disease models and in human melanoma. Early studies of IFN-α in metastatic melanoma were promising, with several durable responses and occasional complete responses, although overall response rates were low (~15 %)—a response pattern that came to characterize the antitumor efficacy of early immunomodulatory agents in this setting. Encouraged by observed activity in the setting of advanced disease, investigators turned to evaluating IFN-α in the adjuvant postoperative high-risk setting. Following initial dose-finding trials, US, European, and Australian investigators conducted multiple adjuvant phase III trials evaluating different subtypes (IFN-α2a, IFN-α2b, and IFN-α2c), dosages (low dose, ≤ 3 MU/dose; intermediate dose, 5–10 MU/dose; and high dose ≥10 MU/dose), routes [intravenous (IV), intra-muscular (IM), subcutaneous (SC)], and schedules (induction, maintenance, combination) to refine the therapeutic index. These trials are summarized in Table 1 [9-28].

The first two prospective randomized phase III trials of high-dose IFN-α2b (HDI) in stage II/III melanoma were the North Central Cancer Treatment Group (NCCTG) 83-0752 and the Eastern Cooperative Group (ECOG) E1684 trials. NCCTG 83-0752 randomized 262 patients (61 % lymph node positive) to either IFN-α2a (20 MU/m^2 thrice weekly IM for 12 weeks) or observation and reported non-significant trends towards reduced recurrence and improved survival with IFN-α2a [9, 10]. ECOG E1684 utilized IFN-α2b and tested a longer regimen comprising induction (IV 20 MU/m^2 daily for 5 days for 4 weeks) and maintenance (SC 10 MU/m^2 thrice weekly for 48 weeks) phases in 287 stage II/III patients, 89 % of whom had regional lymph node metastases. When initially reported at 6.9 years median follow-up, HDI significantly improved both disease-free survival (DFS) and OS compared to observation. Subset analysis suggested that node-positive patients benefited disproportionately though node-negative patients only represented 11 % of the cohort. Toxicity consisted of near-universal constitutional and flu-like symptoms that were readily supported by properly trained allied health professional teams, and hematologic, and hepatic laboratory findings which were the basis of dose-modification along with the constitutional toxicities, and psychiatric and depressive symptoms that were encountered in <10%. In overview, the toxicities of this therapy resulted in treatment delay and/or dose reduction in * 50 % of patients although the toxicities were nearly all reversible. Based on these statistically significant RFS and OS results at nearly 7 years of median follow-up, the FDA approved HDI for the indication of adjuvant therapy in 1995. When the 7 year survival

data were re-analyzed at 12.6 years median follow-up, RFS improvement favored treatment although at this horizon, the originally noted significant benefit in terms of OS were no longer nominally statistically significant. This may have reflected competing causes of death in an elderly cohort.

Subsequent trials seeking to develop less difficult regimens that might show efficacy have evaluated lower doses of IFN-α in an attempt to extend the OS/RFS benefits [11-27]. Alternative regimens have evaluated *very low-dose regimens* (1 MU SC every other day) in the European Organization for Research and Treatment of Cancer (EORTC) 18871; *low-dose regimen* (3 MU SC thrice weekly) tested in WHO Melanoma Program Trials 16, ECOG E1690 (T4N1), UKCCCR AIM-High trial, Scottish trial, German DeCOG 2008, and DeCOG 2010 studies; and *intermediate-dose regimen* tested in EORTC 18952/18991 and Nordic Melanoma Cooperative Group's Nordic IFN trial. Although several of these reported improvements in RFS, only the German DeCOG 2008 study reported an OS benefit although this trial was only powered to assess the combined regimen of low-dose IFN-α (LDI) with dacarbazine (DTIC), rather than LDI alone, and has never been replicated.

Efforts to add chemotherapeutic agents to HDI to augment the benefits seen with HDI have been generally disappointing with high toxicity rates given the relative duration and toxicity of the HDI regimen itself. Southwest Oncology Group's (SWOG) S0008 was an attempt to evaluate how a shorter (but more intensive) biochemotherapy regimen consisting of IL-2, IFN, cisplatin, vinblastine, and dacarbazine would compare to standard HDI [28]. 402 patients with stage III (24 % IIIC) cutaneous melanoma were randomized to either HDI or biochemotherapy. At a median follow-up of 7.2 years, biochemotherapy was associated with fewer relapse events and improved overall survival; albeit with 40 % incidence of grade 4 toxicity (7 % for HDI) though grade 3/4 toxicity rates and treatment discontinuation rates were similar in both cohorts. Further evaluation of this regimen is not planned with future use being restricted to highly selected patients at experienced centers.

Nineteen phase III trials have evaluated the role of IFN-α2b in reducing risk of relapse and improving overall survival in high-risk melanoma. Two systematic reviews [29, 30], a pooled individual patient data analysis [31], and two meta-analyses of the literature [32, 33] have analyzed the collective data with the singular conclusion that IFN-α-based adjuvant therapy reliably improves RFS by 17 % (HR 0.83, 95 % confidence interval 0.78–0.87, *p* value significant), with a lesser improvement in OS of 9 % (HR 0.91, 95 % confidence interval 0.85–0.97, *p* value significant) based on the most recent Cochrane database review by Mocellin et al. [30].

Post-hoc analyses in E1684 indicated that the greatest reduction in risk of relapse occurred early with this therapy—raising the possibility that the value of the HDI regimen's induction phase was both necessary and perhaps sufficient for this treatment benefit. Three prospective randomized trials have evaluated the efficacy of a truncated treatment course in relation to the full year of treatment or observation: Hellenic He13A/98 (modified induction only versus modified induction and maintenance) [14], E1697 (HDI induction only versus observation) [16], and a recently reported Oxford UK phase II study (HDI induction only vs. HDI induction and maintenance) [34]. Hellenic He13A/98 study authors chose a

non-inferiority design and elected to use modified induction/maintenance doses: 25 % dose-reduced induction (IV 15 MU/m^2 rather than 20 MU/m^2) and a flat maintenance (SC 10 MU rather than 10 MU/m^2) with an otherwise unchanged administration schedule. Although Hellenic He13A/98 authors concluded that the modified induction-only regimen was non-inferior to the extended induction/maintenance therapy, the relatively lower percentage of stage III patients enrolled (58 %) and lack of an observation control arm and lower doses of IFN-α used are noteworthy. E1697 was terminated early for futility at interim analysis of 1150 patients of a planned enrollment of 1420. At ASCO 2011, authors reported not noting any significant improvement in either recurrence-free or 5-year survival for the truncated treatment schedule. A recently published British randomized phase II study of HDI induction versus HDI induction/maintenance in 194 patients (77 % lymph node positive) reached similar conclusions with borderline statistical superiority of the 1-year versus the 1-month treatment in terms of the OS of patients in this study.

Other authors have sought to answer the alternative question of whether prolonged duration of therapy might confer greater treatment benefit. Given the toxicity and frequency of treatment with HDI, studies of longer than one year of this regimen have not been undertaken; however, the greater potential facility of treatment with pegylated species and the familiarity of lower dosage regimens with recombinant IFN are used for hepatitis C, studies evaluating longer durations of treatment have utilized PegIFN or lower dosages of IFN-α: E1690 [11], WHO 16 [27], EORTC 18952 [17], 18991 [18] and the Nordic IFN trial [19]. Neither ECOG E1690 nor the European WHO trial 16 demonstrated any RFS/OS benefit with 2–3 years of lower dose IFN (3 MU TIW). Although EORTC 18952 concluded that adjuvant intermediate-dose IFN-α2b given for an extended duration failed to improve distant metastasis-free interval (DMFI), distant metastasis-free survival (DMFS), or OS, post hoc analysis noted a survival benefit for patients with stage IIB/C disease suggesting that lower tumor burdens predicted for IFN response. However, both the Nordic IFN trial and EORTC 18991 concluded that adjuvant IFN (IFN-α2b and PegIFN, respectively) improved RFS but not OS after 1 year of therapy with no incremental benefit from additional treatment. A separate finding from subgroup analysis in EORTC 18991 of RFS/DMFS/OS benefit in patients with ulcerated primaries and/or microscopic nodal metastases is being prospectively evaluated in EORTC 18081 (adjuvant PegIFN for 2 years compared to observation in ulcerated node-negative patients).

HDI and PegIFN are approved by American, European (HDI only, not PegIFN) and Australian health authorities for the adjuvant treatment of high-risk resected melanoma conventionally accepted to comprise either node-positive disease or node-negative disease with a primary of Breslow thickness T2b or greater. Both HDI (given for 1 year) and PegIFN (given for 2 years) improve the RFS from 30 % (HDI) to 13 % (PegIFN). Treatment related toxicity is considerable with both regimens—leading to delays or discontinuation in ~50 % of treated patients.

4 Other Adjuvant Therapeutic Options—Vaccines, Chemotherapy, and Radiotherapy

Other adjuvant immunotherapy modalities that have been evaluated include other cytokines and nonspecific immune stimulants (BCG, Corynebacterium parvum, levamisole including combinations with DTIC). Other than isolated, non-reproducible results in early phase studies, these trials have been largely negative. These data are reviewed in detail elsewhere [35].

Cancer vaccines are subdivided based on the nature of the antigen(s) or cell(s) incorporated —whole cell/cell lysate (autologous, allogeneic), dendritic cell (DC), peptide, ganglioside, and DNA vaccines. Of the randomized trials of allogeneic cell-based vaccines evaluated in the adjuvant setting, most have yielded negative results and this approach is no longer being pursued [36]. Peptide vaccines typically utilize melanocyte lineage antigens (MART-1, gp100, tyrosinase) or cancer–testis antigens (NY-ESO-1, MAGE-A3) and include adjuvants or Toll-like receptor (TLR) ligands without which tolerance would result. Promising leads in early phase studies have not increased RFS compared to placebo in randomized trials. A large phase III trial of a MAGE-A3 vaccine is underway in patients with stage III B/C melanoma whose tumors are positive for the MAGE-A3 germ line lineage antigen. This vaccine contains a proprietary immune-stimulant AS15 and elicits robust CD8 + cytotoxic T-cell responses. However, recent reports indicate that the trial failed to meet its DFS end point at interim analysis though the trial will continue until the second coprimary end point (DFS in gene signature-positive subpopulation) is assessed [37]. Other cancer vaccines currently in phase III trials for melanoma include Vical's Allovectin-7® (NCT00395070), Amgen's Talimogene laherparepvec, and OncoVEXGM-CSF® (NCT00769704). Although final data have not been released, interim reports indicate that Vical's Allovectin-7® failed to improve either primary (24 week overall response rate) or secondary (overall survival) efficacy end points compared to chemotherapy [38].

Three phase III trials have reviewed the role of adjuvant chemotherapy after surgical resection. Neither RFS nor OS benefits have been obtained with this approach. In the most recent of these (E1673), neither BCG alone nor the DTIC/BCG combination improved RFS/OS over observation in stage I–III patients [39-41]. Combinations of chemotherapy with immunotherapy (biochemotherapy, BCT) are associated with higher response rates when compared to DTIC, although no survival advantage has been demonstrated and toxicity is greater [42]. Adjuvant BCT was evaluated before the negative data from the use of BCT versus chemotherapy in metastatic melanoma was available. In S008, a randomized phase III trial by South West Oncology Group (SWOG), the reference one-year HDI was compared to three cycles of cisplatin, vinblastine, DTIC, IL-2, and IFN-α2b in patients with high-risk resected melanoma (stage IIIA-C, 100 % node positive). At ASCO 2012, the authors reported that compared to standard HDI in this high-risk cohort, biochemotherapy improved RFS (HR 0.77) with no discernible influence upon OS at a median follow-up of 6 years. Grade 3 constitutional toxicity was higher in the HDI arm, but grade 4 toxicity was noted in 40 % of patients receiving BCT [43].

Acral/mucosal melanoma is a distinct clinical entity associated with mutations in KIT at a higher frequency [15–20 % (mucosal) and 10–20 % (acral)] than present in cutaneous melanomas (2 %) [44-46]. Given the relative rarity of acral/mucosal melanoma outside Asia, prior US/European adjuvant trials have neither selectively evaluated the role of adjuvant therapy in this population nor have mucosal melanoma been separately delineated in previously reported trials. A Chinese phase II study compared HDI versus temozolomide/cisplatin chemotherapy to observation in high-risk resected mucosal melanoma and noted that although both HDI and chemotherapy improved RFS/OS compared to surgery alone, HDI appeared less effective than chemotherapy in RFS terms [47]. Although yet to be validated in a phase III trial, this observation underscores the different biology of acral/mucosal melanoma and may drive differential responses to adjuvant HDI.

Melanoma has long thought to be a radiotherapy (RT) resistant tumor—largely since the 1970s when cell survival curves for human cancer cell lines were first published which showed a broad shoulder for melanoma cell lines and implied high level of damage repair. Investigators assumed that melanoma was less likely to respond to conventionally fractionated radiation (2–2.5 Gy/fraction) and that hyperfractionation (≥4 Gy/fraction) was required to result in equivalent outcomes. RTOG 83-05 prospectively randomized 126 patients with measurable disease to either hyperfractionated or conventionally fractionated radiation schedules [48]. However, the study was closed prematurely for futility as complete and partial remission rates were similar in both arms indicating that not only is melanoma a radio-responsive disease, but conventional fractionation schedules may be equivalent to hyperfractionated schedules for treatment of the disease. RT has been shown to reduce the risk of loco-regional relapse. The ANZMTG trial was a prospective multicenter phase III study in which 250 patients with high-risk disease were randomized to either observation or regional nodal basin RT (48 Gy in 20 fractions). RT significantly reduced risk of loco-regional recurrence although survival was reduced, albeit in a non-statistically significant fashion—a result that is poorly understood at this time [49].

Currently, given HDI's role in reducing local and systemic recurrence risk, RT is primarily indicated to reduce the risk and morbidity of local recurrence in patients who either decline or are unsuitable for HDI. Based on several studies including the ANZMTG trial, clinicopathologic features that predispose to local recurrence despite adequate surgical margins have been identified and include:

- Extra-capsular lymph node extension.
- Involvement of four or more nodes.
- Bulky disease (exceeding 3 cm in size).
- Cervical lymph node location.
- Recurrent disease.

5 Ongoing Adjuvant Trials

The current spectrum of adjuvant clinical trials spans several classes of agents including standard (HDI and pegIFN) and novel immunotherapeutic agents including checkpoint

inhibitors (anti-CTLA-4, anti-PD1, and anti-PDL1); new targeted molecular signaling inhibitor therapies (BRAF, MEK); and novel vaccine approaches. These are summarized in Table 2.

Based on observations in EORTC 18952/18991 of selective OS/RFS benefits in patients with node-negative ulcerated primary melanomas who received adjuvant IFN (IFN-α2b and PegIFN), the EORTC has designed a prospective randomized trial—EORTC 18081—to compare 2 years of PegIFN to observation in 1200 patients with node-negative melanoma and ulcerated primaries greater than 1 mm thickness (T2-4bN0M0). Accrual has commenced.

The discovery of the critical role of oncogenic driver mutations has profoundly altered the therapeutic landscape of many malignancies including melanoma. Prior histopathologic nomenclature (superficial spreading, nodular, lentigo maligna, acral lentiginous) is increasingly being replaced by genetically defined subgroups (BRAF, NRAS, KIT, and for uveal melanoma, GNAQ/GNA11). Somatic mutations in BRAF have been described in approximately 40–60 % of malignant melanomas, especially those that arise from intermittent sun-exposed skin [50-53]. Most prevalent are missense mutations in valine 600. These single base alterations most often substitute glutamine for valine (V600E, 80–90 %), with other substitutions being less common—lysine for valine (V600K, 5–12 %) and arginine/aspartic acid for valine (V600 R/D, respectively, <5 %). Regardless of type, these mutations result in enhanced BRAF kinase activity and increased activity of downstream targets such as MEK [54, 55].

Inhibitors of BRAF (vemurafenib and dabrafenib) and MEK kinases (trametinib) have significantly improved survival in patients with advanced disease, although acquired resistance is common and tumor progression occurs in most patients [56-58]. Proven activity in the former setting has led to interest in the adjuvant arena; currently, there are several studies evaluating RAF/MEK inhibitors either singly or in combination for adjuvant treatment of melanoma. COMBI-AD (NCT01682083) and BRIM-8 (NCT01667419) are randomized, double-blind phase III studies enrolling high-risk stage III patients to placebo versus combined RAF/MEK inhibition with dabrafenib and trametinib (COMBI-AD) or RAF inhibition alone with vemurafenib (BRIM-8). Primary end points are RFS (COMBI-AD) and disease-free survival (BRIM-8) with the proposed duration of treatment in both studies being 12 months. Investigators from Memorial Sloan Kettering Cancer Center are performing a phase II adjuvant study of 4 cycles of monthly dabrafenib in resected stage IIIC BRAF-mutated patients with RFS as a primary end point (NCT01682213). Chinese investigators are comparing imatinib to a modified IFN-α2b schedule in KIT-mutated patients (NCT01782508). These trials are slated to open in 2013 with estimated completion between 2014 and 2016.

T-cell responses to antigen presentation are modulated by a system of positive and negative feedback loops following initial antigen presentation. Following binding of cognate ligands to CD4+ T-cell receptors, T cells are primed but require a second “costimulatory” signal between B7-1/B7-2 (CD80/86) on antigen presenting cells (APCs) and T-cell CD28 for full activation. CD28 transmits a stimulatory signal, while CTLA-4 transmits an inhibitory signal

—with the functional outcome depending on the relative engagement of APC with CD28 versus CTLA-4. PD-L1 is ubiquitously expressed on tumors and engages with T-cell PD-1 to downregulate CD8+ T-cell responses possibly through suppression of PI3K/AKT activation [59]. CTLA-4 and PD-1 are negative regulators of T-cell responses that function in initiator and effector phases of the T-cell response, respectively. By blocking negative regulators of the immune response, CTLA-4 (and PD-1) inhibitors enhance CD8+ T-cell proliferation and response.

Ipilimumab (Yervoy™, Medarex Inc/Bristol-Myers Squibb) is a humanized IgG1K monoclonal antibody that competitively inhibits CTLA-4 negative regulatory checkpoint. Ipilimumab has been evaluated in two randomized trials in metastatic melanoma patients: against a gp100 peptide vaccine in the second line (3 mg/kg) and against dacarbazine in the first line (10 mg/kg) [60, 61]. Of these, both trials demonstrated improved OS and PFS with durable responses in a minority of treated patients. Use is associated with a novel pattern of side effects involving skin, liver, bowel, and/or endocrine system—collectively termed immune-related adverse events (irAEs). Ipilimumab use is also associated with a variety of radio-graphic response patterns, distinct from those observed with traditional cytotoxic chemotherapy [62].

Evaluation in the adjuvant setting is proceeding in both Europe and the USA. EORTC 18071 evaluated ipilimumab 10 mg/kg against placebo in 951 high-risk stage IIIA-C melanoma patients post-resection, and interim results were presented at ASCO 2014 [63, 64]. Specifically in the IIIA cohort, investigators only enrolled patients with >1 mm lymph node involvement. Accrual commenced June 2008 and completed July 2011, and as at June 2014, a median of 2.7 years (and 56 % of events) had elapsed. Ipilimumab use was associated with a 25 % reduction in risk of relapse (HR 0.74, 0.64–0.90). This translated into a 9.0-month (26.1 vs. 17.1 months) improvement in RFS over placebo and a difference in absolute risk of 8 % at 2 years and 12 % at 3 years, respectively. This is similar although three years less mature than the initial report of adjuvant efficacy for high-dose IFN. RFS improvement was noted in all subgroups but was greatest in patients with stage IIIC disease, ulcerated primaries, or microscopic nodal involvement which may be due to the greater relative maturity of the data in this subset. Toxicity profile was consistent with studies of ipilimumab in advanced melanoma though somewhat higher (42 % grade 3/4 events including 7.6 % grade 3/4 colitis, 5.1 % grade 3/4 hypophysitis) and included 5 treatment-related deaths. Although most patients discontinued therapy secondary to intolerance or progression, benefit was seen after a median of 4–5 doses suggesting that the first four induction doses accounted for majority of RFS benefit. Data regarding secondary end points (DMFS and OS) are immature and will be reported later.

ECOG has led an intergroup trial E1609 that is an open-label randomized phase III trial comparing ipilimumab at both the approved dosage level (3 mg/kg) and the higher potentially more active dosage of 10 mg/kg versus HDI in 1600 patients with high-risk melanoma (stages IIIB-C/IV) following resection. Unlike EORTC 18071, E1609 was powered with RFS and OS as coprimary end points and will answer whether ipilimumab 10 mg/kg has RFS (or OS) benefit over IFN, and if so, whether 3 mg/kg is efficacious. Accrual is near complete, and initial results are expected in 2016. These data are awaited

due to the fact that the primary end points of this trial were both OS and RFS, and it has tested the lower and already US FDA-approved dosage of 3 mg/kg of ipilimumab, where the fatal and grade ¾ toxicity rate is anticipated to be substantially lower than for the 10 mg/kg studied in EORTC 18071. Moreover, the comparator IFN therapy is more relevant to the worldwide community where IFN has been adopted as the approved reference standard.

6 Conclusions

Prior efforts in developing an adjuvant option in high-risk resected melanoma have centered on the use of non-selective cytokines. Approaches based on vaccines, cytotoxic chemotherapy, and BCT have largely failed to yield reproducible benefits in randomized studies. RT has a role in selecting patients as delineated above.

HDI (for 1 year) and PegIFN (for 2 years) have reproducibly demonstrated improved RFS and OS resulting in regulatory approval. Treatment-related morbidity is significant with both agents, and ~50 % of patients experience treatment delays, discontinuations, and/or dose adjustments. Efforts to improve the risk/benefit ratio have evaluated lower dose regimens and longer durations of therapy with negative results. EORTC's E18081 will prospectively evaluate whether PegIFN will selectively benefit patients with ulcerated node-negative melanoma.

Advances over the preceding decade have elucidated several molecular driver (BRAF, MEK) and immune tolerogenic mechanisms (CTLA-4, PD-1/PD-L1) important in the growth and proliferation of melanoma. Agents developed based on these approaches (BRAF/MEK/KIT inhibitors, CTLA-4/PD-1/PD-L1 inhibitors) have improved survival in the advanced disease setting and are pending evaluation in the adjuvant setting—COMBI-AD (dabrafenib and trametinib combination vs. placebo in BRAF-mutated patients), BRIM-8 (vemurafenib vs. placebo in BRAF-mutated patients), and NCT01782508 (imatinib vs. modified IFN-α2b schedule in KIT-mutated patients).

Data from EORTC 18071 (ipilimumab 10 mg/kg vs. placebo) reported clinically significant improvement in RFS over placebo with adjuvant ipilimumab compared to placebo in stage III resected melanoma. Data regarding OS is immature at this time. E1609 (ipilimumab 3 mg/kg vs. ipilimumab 10 mg/kg vs. HDI) has nearly completed accrual and results are expected in 2016. Collectively results from these two studies will inform if ipilimumab has a role in the management of high-resected melanoma. These two trials are summarized in Table 3.

Recent work suggests that BRAF-mutated melanomas have greater tumor immunogenicity but paradoxically decreased antitumor immunity suggesting that combinations of targeted and immunomodulatory therapies may have additive, or synergistic, benefits. This approach is being evaluated in the advanced disease setting and if successful may be transposed to the adjuvant setting.

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Table 1

Phase III studies of IFN-α for advanced melanoma

Study reference	Patients eligible for analysis	Stage	IFN type	Dose and schedule—treatment arm	Median follow-up at reporting (years)	DFS/RFS	OS	% node positive
High dose								
NCCTG 83-7052 [9]	262	II—III (T2-4N0M0 or TanyN+M0)	IFN-α2a versus observation	IM 20 MU/m^2 thrice weekly for 4 months	6.1	HR: 1.20 (HDI vs. observation) (NS)	HR: 1.11 (HDI vs. observation) (NS)	61
ECOG E1684 [10]	287	II–III (T4N0M0 or TanyN+M0)	IFN-α2b versus observation	IV 20 MU/m^2 5 days a week for 4 weeks → then → SC 10 MU/m^2 3 days a week for 48 weeks	12.6	HR: 1.38 (HDI vs. observation) (S)	HR: 1.22 (HDI vs. observation) (S at 6.9 years but NS at 12.6 years)	89
ECOG E1690 [11]	642	II–III (T4N0M0 or TanyN+M0)	IFN-α2b—high dose versus low dose versus observation	High dose: IV 20 MU/m^2 5 days a week for 4 weeks → then → SC 10 MU/m^2 3 days a week for 48 weeks Low dose: SC 3 MU/m^2 2 days a week for 2 years	4.3	HR: 1.28 (HDI vs. observation) (S) 1.19 (LDI vs. observation) (NS)RFS: 44 % (HDI) versus 40 % (LDI) versus 35 % (observation)	HR: 1.0 (HDI vs. observation) (NS) 1.04 (LDI vs. observation) (NS) OS: 52 % (HDI) versus 53 % (LDI) versus 55 % (observation)	74
ECOG E1694 [12]	774	II–III (T4N0M0 or TanyN+M0)	IFN-α2b versus GMK vaccine	IV 20 MU/m^2 5 days a week for 4 weeks → then → SC 10 MU/m^2 2 days a week for 48 weeks	2.1	HR: 1.49 (HDI vs. GMK) (S) RFS: 25 % (HDI) versus 39 % (GMK)	HR: 1.38 (HDI vs. GMK) (S) OS: 78 % (HDI) versus 73 % (GMK)	77
ECOG E2696 [13]	107	II–IV	GMK vaccination with concurrent HDI (Arm A) versus GMK vaccination with HDI beginning D28 (Arm B) versus GMK vaccination alone (Arm C)	HDI: IV 20 MU/m^2 5 days a week for 4 weeks → then → SC 10 MU/m^2 3 days a week for 48 weeks GMK vaccination: GM2-KLH/ QS-21 on D1, 8, 15, 22 then weeks 12, 24,36	2.4	HR: 1.75 (C vs. A) (S) 1.96 (C vs. B) (S) RFS: Not reached (A) versus 30.72 months (B) versus 14.85 months (C)	HR: not reported OS: not reached (A, B or C)	Not reported
Hellenic He13A/98 [14]	364	IIB-C/III (T3/4N0M0 or TanyN+M0)	Modified IFN-α2b induction-only (Arm A) versus modified IFN-α2b induction and maintenance (Arm B)	Non-inferiority design. Modified induction: IV 15 MU/m^2 5 days a week for 4 weeks Modified maintenance: SC 10 MU 3 days a week for 48 weeks	5.3	Median RFS: 24.1 months (Arm A) versus 27.9 (Arm B) (NS, primary non-inferiority endpoint met)	Median OS: 64.4 months (Arm A) versus 65.3 (Arm B) (NS)	58
Italian Melanoma Intergroup [15]	330	III (TanyN1-3M0)	Intensified IFN-α2b (IHDI) every other month versus IFN-α2b for 1 year	IHDI: IV 20 MU/m^2 5 days a week for 4 weeks every other month for 4 cycles Standard HDI: IV 20 MU/m^2 5 days a week for 4 weeks → then → SC 10 MU/m^2 3 days a week for 48 weeks	5.0	Median RFS: 47.9 months (IHDI) versus 35.6 months (HDI) (NS) 5 year RFS: 45.8% (IHDI) versus 44.3 % (HDI)	Median OS: 88.7 months 5 year OS: 60.1 % (IHDI) versus 82.6 % (HDI) (NS)	100

Study reference	Patients eligible for analysis	Stage	IFN type	Dose and schedule—treatment arm	Median follow-up at reporting (years)	DFS/RFS	OS	% node positive
E1697 [16]	1150 (1420 planned enrollment)	IIB-C/III (T2-4N0M0 or TanyN1a/2aM0)	Induction HDI versus observation	HDI induction: IV 20 MU/m^2 5 days a week for 4 weeks	Not reported	Median RFS: 6.8 years (HDI induction) versus 7.3 years (observation) (NS)	5 year OS: 82 % (HDI induction) vs. 85 % (observation) (NS)	19
S0008 [28]	402	IIIA-IIIC	HDI vs. biochemotherapy (IL-2, IFN, cisplatin, vinblastine, and dacarbazine)	HDI: IV 20MU/m2 5 days a week for 4 week→then→C 10MU/m2 3 days a week for 48 weeks Biochemotherapy: Dacarbazine 800 mg/m^2 (day 1); Cisplatin 20 mg/m^2, Vinblastine 1.2 mg/m^2, IL-2 at 9 MU/m^2 continuous IV infusion (days 1-4); IFN 5MU/m2 (day 1-5, 8, 10, 12). Repeated every 21 days for 3 cycles.	7.2	Median RFS: 4.0 years (biochemotherapy) vs. 1.9 years (HDI) (S) 5 year RFS: 39 % (biochemotherapy) vs. 48 % (HDI) (S)	Median OS: 9.9 years (biochemotherapy) vs. 6.7 years (HDI) (S) 5 year OS: 56 % (biochemotherapy) vs. 56 % (HDI) (NS)	24
Intermediate dose								
EORTC 18952 [17]	1388	II–III (T4N0M0 or TanyN+M0)	IFN-α2b for 1 year versus 2 years versus observation	Induction: IV 10 MU 5 days a week for 4 weeks Maintenance: SC 10 MU 3 days a week for 1 year *OR* SC 5 MU 3 days a week for 2 years	4.7	DMFI: HR: 0.93 (13 month versus observation) (NS) 0.83 (25 month versus observation) (S)	DMFS: HR: 0.95 (13 month versus observation) (NS) 0.85 (25 month versus observation) (NS)	74
EORTC 18991 [18]	1256	III (TanyN+M0)	PegIFN versus observation	Induction: SC 6 μg/kg/week for 8 weeks Maintenance: SC 3 μg/kg/week for 5 years	7.6	34.8 months (IFN) versus 25.6 months (observation); S	Not reported	100
Nordic IFN [19]	855	IIB-IIIB (T4N0M0 or TanyN1-2M0)	IFN-α2b for 1 year versus 2 years versus observation	Observation (A) versus SC 10 MU 5 days a week for 4 weeks then SC 10 MU 3 days a week for 1 year (B) versus SC 10 MU 5 days a week for 4 weeks then SC 10 MU 3 days a week for 2 years (C)	6.0	23.2 months (A) versus 37.8 months (B) versus 28.6 months (C) IFN versus observation and IFN 1 year versus observation (S); IFN 2 year versus observation (NS)	56.1 months (A) versus 72.1 months (B) versus 64.3 months (C) (NS)	81
Low dose								
Austrian Melanoma Cooperative Group (AMCG) [20]	311	II (T2-4N0M0)	IFN-α2a versus observation	SC 3 MU 7 days a week for 3 weeks → then → SC 3 MU 3 days a week for 1 year	3.4	RFS/DMFS not reported Rate of relapse: (24.0 % LDI vs. 36.3 % obs)	Not reported	0
French Melanoma Cooperative Group (FCGM) [21]	499	II (T2-4N0M0)	IFN-α2a versus observation	SC 3 MU 3 days a week for 18 months	>3	HR: 0.74 (LDI versus observation) (S)	HR: 0.70 (LDI versus observation) (S)	0

Study reference	Patients eligible for analysis	Stage	IFN type	Dose and schedule—treatment arm	Median follow-up at reporting (years)	DFS/RFS	OS	% node positive
WHO Melanoma Program Trial 16 [22]	444	III (TanyN+M0)	IFN-α2a versus observation	SC 3 MU 3 days a week for 36 months	7.3	NS	NS	100
Scottish Melanoma Cooperative Group [23]	96	II—III (T3-4N0M0 or TanyN+M0)	IFN-α2a versus observation	SC 3 MU 3 days a week for 6 months	>6	NS	NS	Not reported
EORTC 18871/DKG 80-1 [24]	728	II–III (T3-4N0M0 or TanyN+M0)	IFN-α2b versus IFN-γ versus ISCADOR M® versus. observation	IFN-α2b: SC 1 MU every other day for 12 months IFN-γ: SC 0.2 mg every other day for 12 months	8.2	NS	NS	58
UKCCCR/AIM HIGH [25]	674	II–III (T3-4N0M0 or TanyN+M0)	IFN-α2a versus observation	SC 3 MU 3 days a week for 24 months	3.1	NS	NS	Not reported
DeCOG [26]	840	III (T3anyN +M0)	IFN-α2a	SC 3 MU 3 days a week for 18 months (A) versus 5 years (B)	4.3	5 year DMFS 81.9 % (A) versus 79.7 % (B) (NS)	5 year OS 85.9 % (A) versus 84.9 % (B) (NS)	Not reported
DeCOG [27]	444	III (TanyN+M0)	IFN-α2a	SC 3 MU 3 days a week for 24 months (A) versus SC 3 MU 3 days a week for 24 months + DTIC 850 mg/m^2 every 4–8 weeks for 24 months (B) versus observation (C)	3.9	HR: 0.69 (A) versus 1.01 (B) versus 1.0 (C)	HR: 0.62 (A) versus 0.96 (B) versus 1.0 (C)	100 %

Key: *NS* not significant; *S* significant; *HR* hazard ratio; *DFS* disease free survival; *OS* overall survival

Table 2

Phase III studies of Ipilimumab for advanced melanoma

Study reference	Patients eligible for analysis	Study design	Endpoints	Dose and schedule—treatment arm	Median Follow-up at Reporting (years)	RFS and OS	Grade 3/4 Toxicity (ipilimumab vs. placebo)
IImmunotherapies							
EORTC 18071 (NCT00636168)	951	Phase III, randomized, open-label study in T2b-4bN1-3M0 melanoma following resection Stage breakdown (% in ipilimumab and placebo arms) •IIIA (restricted to ≥1 mm LN involvement): 21 %/ 18 % •IIIB: 45 %/43 % •IIIC: 35 %/38 %	Primary—RFS Secondary—OS, DMFS, quality of life, quality-of-life-adjusted survival	Ipilimumab vs. placebo Ipilimumab:*Induction*—10 mg/kg q3 weeks for 4 doses *Maintenance*—10 mg/kg q3 montds for a maximum of 36 months	2.7	RFS (ipilimumab vs. placebo): •Median 26.1 months vs. 17.1 months •HR: 0.75 (0.64-0.90) (S) •1-year: 63.5 % vs. 56.1 %. •2-year: 51.5 % vs. 43.8 %. •3-year: 46.5 % vs. 34.8 %.	Grade 5 AE: 1 % (in both groups) Grade 4 AE: 8 % vs. 3 % All Grade 3/4 irAE: 41 % vs. 2.5 % Cutaneous: 4.5 % vs. 0.0 % Gastrointestinal: 16 % vs. 0.8 % •Colitis: 7.6 % vs. 0.2 % •Hepatic: 10.7 % vs. 0.2 % Endocrine: 8.5 % vs. 0.0 % •Hypophysitis: 5.1 % vs. 0.0 % •Hypothyroidism: 0.2 % vs. 0.0 % Resolution: •Cutaneous: 89.1 % vs. 92.9 % •Gastrointestinal: 93.8 % vs. 94.4 % •Hepatic: 94.8 % vs. 80.0 % •Endocrine: 56.0 % vs. 80.0 %
E1609 (NCT01274338)	1500	Phase III, randomized, open-label study in high-risk (IIIB-C or resected IVA) resected melanoma *Biomarker evaluation: •Ipilimumab—MDSC, Treg, IL-17 •HDI—S100B	Primary—RFS and OS Secondary—Toxicity, global quality of life	Ipilimumab in 2 dose levels vs. HDI Ipilimumab: *Induction*–3 or 10 mg/kg q3weeks for 4 doses *Maintenance*—3 or 10 mg/kg q6weeks until week 48 then q12weeks afterwards HDI: *Induction*—I.V. 20MU/m^2 5 days a week for 4 weeks *Maintenance*—S.C. 10MU/m^2 3 days a week for 48 weeks	N/A	N/A	N/A

Key: *NS* not significant; *S* significant; *HR* hazard ratio; *DFS* disease free survival; *RFS* relapse free survival; *OS* overall survival; *irAE* immune-related adverse events

Table 3

Ongoing adjuvant studies in high-risk resected melanoma

Study reference	Estimated enrollment	Study design	Primary endpoint	Secondary endpoint(s)	Dose and schedule—treatment arm	Start date	Estimated completion
Immunotherapies							
Ipilimumab vs. HDI (E1609; NCT01274338)	1500	Phase III, randomized, open-label study in high-risk (IIIB-C or resected IVA) resected melanoma *Biomarker evaluation: •Ipilimumab—MDSC, Treg, IL-17 •HDI—S100B	RFS, OS	Toxicity, global quality of life	Ipilimumab in 2 dose levels vs. HDI Ipilimumab: *Induction*—3/10 mg/kg q3weeks for 4 doses *Maintenance*—3/10 mg/kg q6weeks until week 48 then q12weeks afterwards HDI: *Induction*—I.V. 20MU/m^2 5 days a week for 4 weeks *Maintenance*—S.C. 10MU/m^2 3 days a week for 48 weeks	June 2008	September 2014
E1609 (NCT01274338)	1500	Phase III, randomized, open-label study in high-risk (IIIB-C or resected IVA) resected melanoma *Biomarker evaluation: • Ipilimumab – MDSC, Treg, IL-17 • HDI—S100B	RFS, OS	Toxicity, global quality of life	Ipilimumab in 2 dose levels versus HDI Ipilimumab: *Induction*—3/10 mg/kg q3 weeks for 4 doses *Maintenance*—3/10 mg/kg q6 weeks until week 48 then q12 weeks afterward HDI: *Induction*—I.V. 20 MU/m^2 5 days a week for 4 weeks *Maintenance*—S.C. 10 MU/m^2 3 days a week for 48 weeks	May 2011	May 2018
Pegylated IFN-α2b (EORTC 18081; NCT01502696)	1200	Phase III, randomized, open-label study in ulcerated node-negative (T2b-4bN0M0) melanoma	RFS	OS, DMFS, quality of life	Pegylated IFN-α2b 3 μg/kg weekly injections for 2 years	April 2012	April 2020
Nivolumab vs. Ipilimumab (CheckMate 23; NCT02388906)	800	Phase III, randomized, double-blind placebo-controlled study in resected stage III B/C melanoma	RFS	OS	Nivolumab 3 mg/kg q2 weeks + Ipilimumab matched placebo q3 weeks for 1 year Ipilimumab 3 mg/kg q3 weeks + Nivolumab matched placebo q2 weeks for 1 year	March 2015	June 2020
Pembrolizumab (KEYNOTE 054; NCT02362594)	900	Phase III, randomized, double-blind placebo-controlled study in resected stage III melanoma *Biomarker evaluation: •Pembrolizumab—PD-L1 expression	RFS and RFS in PD-L1 positive tumors	DMFS (and DMFS in PD-L1 positive tumors); OS (and OS in PD-L1 positive tumors)	Pembrolizumab 200 mg q3 weeks for 1 year Matched placebo in same schedule	July 2015	September 2023
Vaccines							
MAGE-A3 vaccine (NCT00796445)	1349	Phase III, randomized, open-label study in T2b-4bN0M0 melanoma *Biomarker evaluation: •Expression of MAGE-A3 Antigen-specific cancer immunotherapeutic (ASCI) gene signature	DFS	OS, DMFS, anti-MAGE-A3 and antiprotein D seropositivity status, quality of life	MAGE-A3 vaccine with 2 adjuvants including QS-21 (Stimulon™, Agenus) and a proprietary Toll-like receptor 9 agonist (VaxImmune™, Coley Pharmaceuticals)	December 2008	October 2016
Molecularly targeted agents							

Study reference	Estimated enrollment	Study design	Primary endpoint	Secondary endpoint(s)	Dose and schedule—treatment arm	Start date	Estimated completion
Dabrafenib (NCT01682213)	23	Non-randomized open label phase II study in high-risk (IIIC) resected BRAF V600E/K mutant melanoma	RFS	OS, safety, toxicity	Dabrafenib 150 mg B.I.D. per cycle (28 days) for 4 cycles	September 2012	September 2014
Imatinib (NCT01782508)	40	Non-randomized open label phase II study in high-risk (IIB-IIIC) resected CKIT mutant melanoma	RFS	OS	Imatinib 400 mg daily versus modified IFN-α2b	August 2012	December 2014
Vemurafenib (BRIM8, NCT01667419)	725	Phase III, randomized, double-blinded study in high-risk (IIC or IIIA-C) resected BRAF V600E mutant melanoma	DFS	OS, DMFS, quality of life, pharmacokinetics, safety, toxicity	Vemurafenib 960 mg B.I.D. vs. placebo for 12 months	September 2012	June 2016
Dabrafenib and Trametinib (COMBI-AD, NCT01682083)	850	Phase III, randomized, double-blinded study in high-risk (IIIA-C) resected BRAF V600E/K mutant melanoma	RFS	OS, DMFS, FFR, safety, toxicity	Dabrafenib 150 mg B.I.D. ANDTrametinib 2 mg once daily vs. placebos for 12 months	November 2012	July 2015
Crizotinib (NCT02223819)	30	Open label phase II study in high-risk uveal melanoma as determined by gene expression profiling (Castle Biosciences, class II)	RFS	OS, disease specific survival, toxicity	Crizotinib 250 mg B.I.D. per 4 week cycle for 12 cycles	August 2014	August 2016
Dabrafenib and Trametinib (COMBI-NEO, NCT02231775)	84	Randomized open-label phase II study of neoadjuvant and adjuvant Dabrafenib /Trametinib and surgery compared to surgery alone in clinical stage IIIB-C or oligometastatic stage IV melanoma	1 year RFS	N/A	Dabrafenib 150 mg B.I.D. and Trametinib 2 mg daily for 8 weeks prior to surgery; then surgery; then Dabrafenib/Trametinib in patients with stable/responding disease for an additional 44 weeks	October 2014	October 2017

Key: *NS* not significant; *S* significant; *HR* hazard ratio; *DFS* disease free survival; *RFS* relapse free survival; *OS* overall survival; *irAE* immune-related adverse events