Supplementary Appendix

Inhibition of PD-1/PD-L1 and CTLA-4 combination therapy

Comparator arms

All three phase II trials evaluating nivolumab plus ipilimumab, were randomized two-arm trials in the treatment resistant setting, with nivolumab monotherapy as the comparator arm. NRG GY003 compared nivolumab plus ipilimumab versus nivolumab alone in recurrent or persistent ovarian cancer [1]. Nivolumab and ipilimumab monotherapy had been evaluated in previous single-arm phase II trials and case series [2–4]. Alliance A09140111, for treatment-refractory metastatic sarcoma, and IFCT-1501 MAPS2, for platinum-pemetrexed resistant pleural mesothelioma, were both non-comparative studies – evaluating both the combination and nivolumab alone. There was a single small phase II trial of ipilimumab alone in patients with recurrent synovial sarcoma [5]; but no studies of nivolumab alone. There had been no previous trials of either nivolumab or ipilimumab monotherapy in malignant pleural mesothelioma.

There were three phase II trials evaluating the combination of durvalumab plus tremelimumab. CONDOR was a three-arm non-comparative randomized trial in PD-L1 low/negative (TC <25%) recurrent or metastatic head and neck squamous cell carcinoma (HNSCC).[6] There had been several prior phase II trials of durvalumab in HNSCC, from which greater response rates in patients with PD-L1 TC ≥25% had been seen [7,8]. However, there were no prior trials of tremelimumab monotherapy in HNSCC. The clinical trial CO.26 evaluated durvalumab plus tremelimumab versus best supportive care (BSC) for patients with metastatic treatment-refractory colorectal cancer (CRC) in a randomized two-arm study [9]. There had been no prior studies of either agent alone in treatment-refractory CRC. Finally, durvalumab plus tremelimumab was also evaluated in patients with metastatic pancreatic adenocarcinoma in a randomized, two-part, two-arm trial, with durvalumab monotherapy in the other arm [10]. Preliminary safety and efficacy data had been obtained from a phase 1 expansion cohort of durvalumab monotherapy [11]; however, there were no prior studies of tremelimumab monotherapy.

Inhibition of PD-1/PD-L1 and VEGF combination therapy

Comparator arms

There were five trials evaluating patients with metastatic RCC, including two phase II trials and three phase III trials. The phase II trials were single-arm studies evaluating atezolizumab plus bevacizumab in non-clear cell RCC [12] and pembrolizumab plus bevacizumab in pre-treated clear cell RCC [13] respectively. In each phase III trial,
combination therapy was evaluated in first-line metastatic clear cell RCC, and there were two arms with sunitinib as the comparator arm. JAVELIN Renal 101 evaluated axitinib plus avelumab [14], KEYNOTE-426 evaluated pembrolizumab plus axitinib [15] and IMmotion151 evaluated atezolizumab plus bevacizumab [16]. Axitinib monotherapy is approved in the second-line setting [17], but had not been previously evaluated as first-line therapy. Bevacizumab is also approved in pre-treated patients, in combination with interferon alfa, although it was previously evaluated as monotherapy in both the treatment naïve and pre-treated settings [18,19]. Pembrolizumab monotherapy had been evaluated in several phase II trials [20,21]. Atezolizumab [22] and avelumab [23] monotherapy had both been evaluated in expansion cohorts of the phase I trials in both first- and second-line settings.

Pembrolizumab plus lenvatinib was evaluated in KEYNOTE-146, a phase II basket trial in patients with selected advanced solid tumors, including RCC, endometrial cancer, HNSCC, melanoma, NSCLC and urothelial cancer [24,25]. There had been numerous trials of lenvatinib and pembrolizumab monotherapy in most of these indications [26–30]. Pembrolizumab plus axitinib was also evaluated in a single-arm trial in patients with advanced sarcomas. Both pembrolizumab and axitinib had been previously evaluated as monotherapy in phase II trials [31,32]. Finally, IMbrave150 was a phase III trial of atezolizumab plus bevacizumab versus sorafenib as first-line therapy in advanced HCC [33]. Both atezolizumab and bevacizumab had been evaluated as monotherapy for patients with HCC in prior early phase trials [34–36].

**Inhibition of BRAF and MEK combination therapy**

*Rationale for combinations*

The clinical activity of combination BRAF and MEK inhibitor seen in metastatic BRAF-mutated melanoma resulted in the evaluation of this combination in other cancers known to harbor oncogenic BRAF V600E mutations. In BRAF V600E mutated NSCLC, pre-clinical studies had demonstrated the role for BRAF inhibition, and also the potential sensitivity to MEK inhibition [37–39]. The combination of BRAF and MEK inhibition, however, had not been extensively evaluated in the pre-clinical setting. In BRAF V600E mutated anaplastic thyroid cancer, pre-clinical mouse and cell line models demonstrated the improved efficacy of combination BRAF and MEK inhibition compared with BRAF inhibition alone [40].

*Comparator arms and primary endpoints*

The trial evaluating dabrafenib plus trametinib in metastatic BRAF mutated NSCLC was a multicohort phase II trial [41]. Cohort A investigated dabrafenib monotherapy in both pre-treated and untreated patients, cohort B investigated dabrafenib plus trametinib in pre-
treated patients, whilst cohort C investigated dabrafenib plus trametinib in first-line patients [42,43]. Trametinib monotherapy had not been previously evaluated for \(BRAF\) mutated NSCLC. ROAR was a basket trial of dabrafenib plus trametinib in nine different \(BRAF\) \(V600E\) mutated rare cancers, including anaplastic thyroid cancer. There had been no prior studies of dabrafenib or trametinib monotherapy in anaplastic thyroid cancer, although dabrafenib has been studied in \(BRAF\) \(V600E\) mutated papillary thyroid cancers [44]. The primary endpoint in the two phase II trials of dabrafenib and trametinib was ORR, assessed as appropriate and clinically meaningful.

**Inhibition of HER2 combination therapy**

*Rationale for combinations*

In salivary gland cancers, there was no pre-clinical data indicating the potential efficacy of the combination over monotherapy. This may be in part, due to the relative rarity of salivary gland cancers.

*Utility of biomarkers*

The MyPathway trial included a basket for patients with advanced solid tumors harboring HER2 alterations that included HER2 amplification, overexpression and/or mutation. Furthermore, these HER2 alterations could be locally assessed by any Clinical Laboratory Improvement Amendments (CLIA) certified test which would subsequently be assessed for eligibility by the medical monitor [45]. Specifically for colorectal cancer patients, HER2 alterations were limited to HER2 amplification, as assessed by a CLIA certified test. This could include fluorescence or chromogenic in situ hybridization (FISH/CISH), next-generation sequencing (NGS) or immunohistochemistry (IHC) [46].

*Comparator arms and primary endpoints*

There were also no prior studies of monotherapy treatment in either tumor type. However this should be considered in the context of pre-clinical data suggesting lack of efficacy for monotherapy in HER2-amplified colorectal cancer, as described above [47,48].

*Other combination therapies*

ISA 101 is a synthetic long-peptide HPV-16 vaccine, and was evaluated in combination with nivolumab in a single-arm phase II trial [49]. Eligible patients had incurable HPV-16-positive cancer, and included oropharyngeal, cervical, vulvar, vaginal, penile or anal primary tumors. The rationale for the combination therapy was on the basis of pre-clinical data demonstrating HPV-specific T-cell responses with ISA 101 in cervical cancer models [50,51]. However, in the early phase trials of ISA 101 monotherapy in patients with HPV-16 induced
gynecological cancers, there was no tumor regression [52,53]. It was hypothesized that this may be due to a tumor-induced immunosuppressive environment, and combination with anti-PD-1 therapy could improve efficacy [53]. Although there had been no pre-clinical models which evaluated the combination therapy. There were no prior studies of ISA 101 monotherapy in non-gynecological cancers, whilst nivolumab had previously been approved as monotherapy in unselected squamous cell carcinoma of the head and neck [54].

Pembrolizumab plus talimogene laherparepvec (T-VEC) combination therapy was investigated in a single-arm phase II trial for patients with pre-treated locally advanced or metastatic sarcoma [55]. T-VEC, an oncolytic immunotherapy, is approved in patients with advanced melanoma as monotherapy [56]. However, T-VEC monotherapy had not previously been evaluated in patients with sarcoma, whilst pembrolizumab monotherapy had been evaluated in patients with advanced sarcomas in a single-arm phase II trial [32]. There was also no pre-clinical data investigating the combination therapy, although the combination had been evaluated in a clinical trial for patients with metastatic melanoma [57].

References


