Durable response of multiple myeloma and non-small cell lung cancer with simultaneous, biologically targeted treatment

Advances in therapy have improved outcomes for several incurable cancers. However, with improved survival the risk of developing second cancers becomes more clinically relevant and is further enhanced by some novel life-extending therapies, e.g. the immunomodulatory drug (IMiD) lenalidomide in multiple myeloma (Jones *et al.*, 2016; Jonsdottir *et al.*, 2017). Available published data and our clinical experience suggest that in the era of classical chemotherapy outcome for patients with two active incurable cancers was mostly dismal. However, little is reported on how management of patients with two simultaneously active cancers may be impacted by availability of modern biological therapies.

We report here on a 68-year-old male patient treated for multiple myeloma in our clinic since 2006 . In 2017, the patient was diagnosed with non-resectable [T3 N0 M1b (bilateral lung lesions and soft tissue chest wall metastasis)] squamous subtype non-small cell lung cancer (NSCLC) by image-guided biopsy. The myeloma was reasonably controlled (partial response) at time of NSCLC diagnosis with an ongoing carfilzomib/daratumumab/dexamethasone 5th-line therapy. Prior treatments included lenalidomide, bortezomib, high-dose melphalan and autologous stem cell transplant, pomalidomide and dexamethasone, thalidomide, cisplatin, adriamycin, cyclophosphamide, and etoposide (DT-PACE), to which the myeloma was either refractory or the patient intolerant due to toxicity (Fig 1). Relevant medical history included chronic thrombocytopenia of likely autoimmune pathogenesis and deep vein thrombosis and extensive pulmonary embolism in 2016, contributing to persistent dyspnoea. Patient performance status at time of NSCLC diagnosis was ECOG 1.

Non-small cell lung cancer predictive biomarker analysis demonstrated 70% Programmed Death Ligand 1 (PDL1) expression (22C3 clone) with next generation sequencing (NGS) analysis using the Foundation Medicine platform demonstrating no actionable oncogenic drivers, a tumour mutational burden (TMB) of 83 mutations/Mb, and a number of somatic variants, including *TP53* G245N and S121F mutations.

Following inter-disciplinary tumour board discussion, and noting both the ≥50% PDL1 expression and high TMB status, pembrolizumab therapy was commenced for his NSCLC at 200 mg flat-dose every 21 days, as per the FDA and EMA licensed indication (Herbst *et al.*, 2019). Of note, shortly before, the FDA had halted all anti-PD1 combination trials in myeloma because of excess deaths for anti-PD1 in combination with IMiDs, and risk/benefit ratio was discussed in the tumour board and with the patient (Mok *et al.*, 2019; Usmani *et al.*, 2019). Concurrent myeloma therapy did not contain IMiDs and pembrolizumab was started under close monitoring (ASH_Clinical_News, 2017). First re-staging after three months of pembrolizumab showed a partial response of the NSCLC lesions (Fig 2). The patient had no significant immune-related adverse events, other than a grade 1 skin rash with pruritus.

In contrast to the NSCLC, the myeloma did not respond to pembrolizumab and paraprotein levels continued to rise over 10 months of concurrent pembrolizumab and anti-myeloma therapy until clinical progression, with transfusion-dependent anaemia and severe dyspnoea and fatigue, resulting in reduced performance status [Eastern Cooperative Oncology Group (ECOG) 2]. The patient reported no immune-related adverse events and response evaluation by computed tomography imaging continued to demonstrate an ongoing partial response of the NSCLC.

No approved and/or suitable anti-myeloma treatments were available at the time and NSCLC excluded the patient from participation in clinical trials. A bone marrow myeloma fluorescence *in situ* hybridisation analysis was performed based on emerging data on venetoclax activity in myeloma, and a t (11;14) translocation was detected (Kumar *et al.*, 2017).

Off-label treatment with venetoclax/daratumumab/dexamethasone in parallel with pembrolizumab was discussed in the multi-disciplinary tumour board and with the patient, who expressed a strong wish to pursue therapy. Venetoclax was started in July 2018 with a weekly dose increase from 400 to 1200 mg daily as per published trial data with dexamethasone 40 mg weekly, alongside ongoing pembrolizumab NSCLC therapy. Daratumumab 16 mg/kg i.v. monthly was continued following patient request.

The patient's myeloma responded rapidly to venetoclax (Fig 1), reaching partial response after two and very good partial response after four cycles of therapy. Haemoglobin levels normalised and severe dyspnoea resolved. Three-weekly pembrolizumab continued without any immune-related adverse events. When the FDA halted venetoclax trials in myeloma in March 2019, based on excess deaths in the venetoclax/bortezomib/dexamethasone arm of the BELLINI trial, findings were discussed by the multidisciplinary board and with the patient and the decision was made to continue

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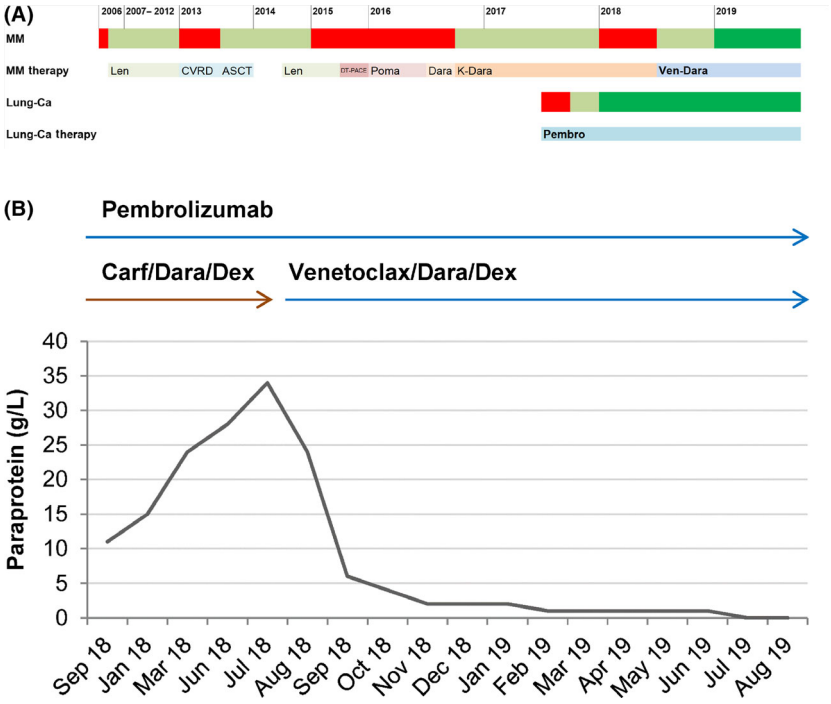

Fig 1. (A) Timelines of myeloma (MM) and non-small cell lung cancer (Lung-Ca) status and treatment. Red colour in MM and Lung-Ca status bars indicates active disease, light green partial response, dark green very good partial response. (B) Time line of anti-MM therapy and paraprotein response before and after therapy with venetoclax.

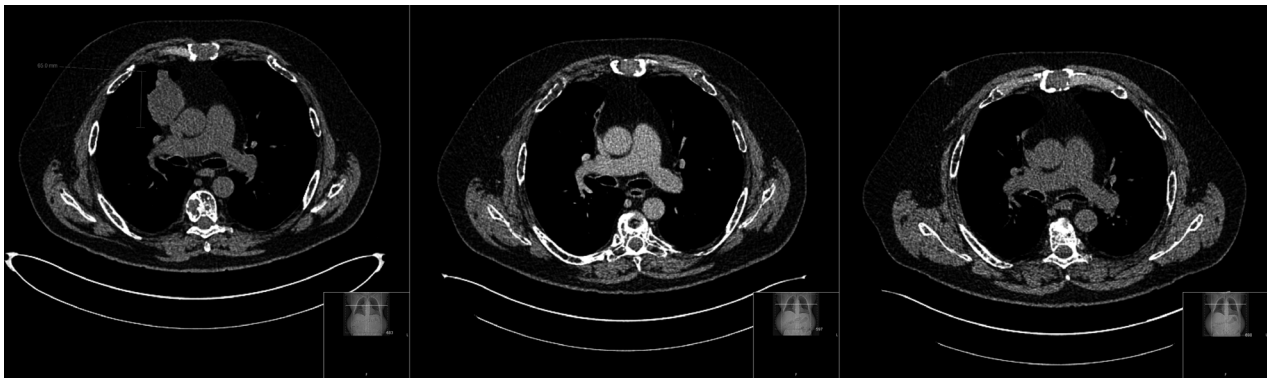

Fig 2. NSCLC before (left) after (middle) 3 months and (right) after 18 months of pembrolizumab therapy.

therapy under close observation (FDA_News, 2019). The patient experienced no clinically significant infections throughout the venetoclax therapy. At the time of this report, the patient enjoyed good performance status (ECOG 0). The myeloma and NSCLC have remained in ongoing stable remission for over 12 and over 18 months respectively with ongoing venetoclax and parallel pembrolizumab therapy, without major breaks and without immune-related adverse events or other safety concerns.

Without pembrolizumab or venetoclax, care for this patient would have likely been limited to palliation both at the time of NSCLC diagnosis and myeloma progression, because of reduced performance status and relevant co-morbidities. Co-administration of pembrolizumab and venetoclax/daratumumab/dexamethasone was primarily driven by medical urgency, but both treatments were also rationally selected for respective tumour biologies, specifically high PDL1 and TMB in NSCLC and translocation t(11;14) in myeloma, which may have contributed to their safe and effective administration. Very recently updated safety data from BELLINI, not available at start of venetoclax in our patient, confirms excess trial deaths were not observed in the t(11;14) target group, to which our patient belonged. Safety concerns over pembrolizumab in the KEYNOTE-185 trial were accompanied by lack of efficacy for the pembrolizumab– IMiD combination (Usmani *et al.*, 2019). Immune cell exhaustion caused by myeloma or anti-myeloma therapy such as dexamethasone has been discussed as a potential reason, suggesting pembrolizumab be used earlier in the therapy of myeloma. In our patient, the lack of response of the myeloma was paralleled by an excellent response of the NSCLC to pembrolizumab, making immune cell exhaustion an unlikely cause for lack of anti-myeloma activity in this case. Interestingly, the NSCLC responded rapidly to pembrolizumab

despite ongoing weekly 40 mg dexamethasone administered for myeloma. Whether CD38 blockade on the lung tumour cells through daratumumab may have enhanced cytotoxic T-cell function and contributed to the excellent response of the NSCLC to pembrolizumab, as recently reported for an *in-vivo* model of lung cancer, is unknown (Chen *et al.*, 2018).

In summary, management of simultaneously active cancers is a challenge that is becoming increasingly frequent. Our case demonstrates the safe and effective parallel management of concurrent malignancies with treatments that target the respective tumour biologies, strongly supporting their further development, in particular venetoclax for t(11;14) myeloma.

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Author contibutions

MFK and SP performed the research, designed and wrote the manuscript; JC performed data analysis; all authors contributed to patient's care.

Conflicts of interest

MFK: Abbvie – consultancy; Bristol-Myers Squibb – consultancy, travel support; Chugai – consultancy; Janssen – consultancy, honoraria; Amgen – consultancy, honoraria; Takeda – consultancy, travel support; Celgene Corporation – consultancy, honoraria, research funding. SP: Research grant/ Funding (institution): Boehringer Ingelheim, Epizyme, BMS, Clovis Oncology, Roche, Lilly, Takeda; Honoraria (self): Boehringer Ingelheim, AstraZeneca, Roche, Takeda, Chugai Pharma; Advisory/ Consultancy: Boehringer Ingelheim, Roche, Novartis, Pfizer, AstraZeneca, BMS, MSD, Guardant Health, AbbVie; Travel/ Accommodation/ Expenses: Boehringer Ingelheim, BMS, Merck Sharp & Dohme. The remaining authors declare no conflicts of interest.

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