ImmunoScience Academy

Partnering for Education & Optimizing Treatment in ImmunoScience

SUMMARY

ImmunoScience Academy Spring Meeting

31 March 2021

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To stop or not to stop… that's the question

The ImmunoScience Academy (ISA) Spring meeting took place in a fully virtual setting at the studios of Roularta Healthcare. Dr. Paul Lacante, EU Cluster Medical Head / Medical Lead Benelux, welcomed the audience on behalf of BMS and explained that ISA's mission is to provide education and enhance multidisciplinary initiatives within the immunoscience field. A multidisciplinary panel with varying areas of expertise shared their views during this meeting, which Lies Martens professionally moderated.
Prof. Dr. Guy Jerusalem (Head of oncology medicine department, CHU Sart Tilman, Liège) shared the main meeting objectives. To have a correct idea of when to stop treatment with a checkpoint inhibitor, we should first understand the immunology behind the long duration of treatment with those checkpoint inhibitors. Secondly, we will discuss the available data on treatment duration in melanoma and non-small cell lung cancer (NSCLC) tumours. Next, we need to consider the psychological and emotional factors in patients treated with checkpoint inhibitors. Lastly, we will discuss the role of local therapy following checkpoint inhibition in patients with oligometastatic recurrence.

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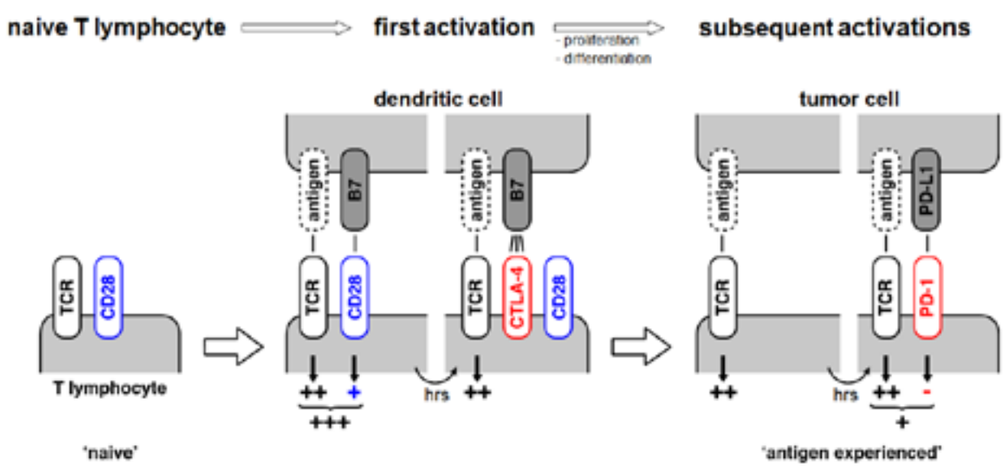
The immunology behind long duration of treatment with PD-1 blockade

Prof. Dr. Pierre Coulie (Immunology, De Duve Institute, UCL, Brussels) commented on the immunology behind long duration, which can be long duration of treatment or long duration of response. A long duration of immune response is a consequence of immune memory, i.e., the maintenance of a pool of memory T cells. A clinical response can be of long duration due to the immunological memory, but there are other possible mechanisms. Concerning the long duration of treatment, it is essential to realise that a long-acting CTLA-4 or PD-1 blockade is not required for a prolonged immune response.

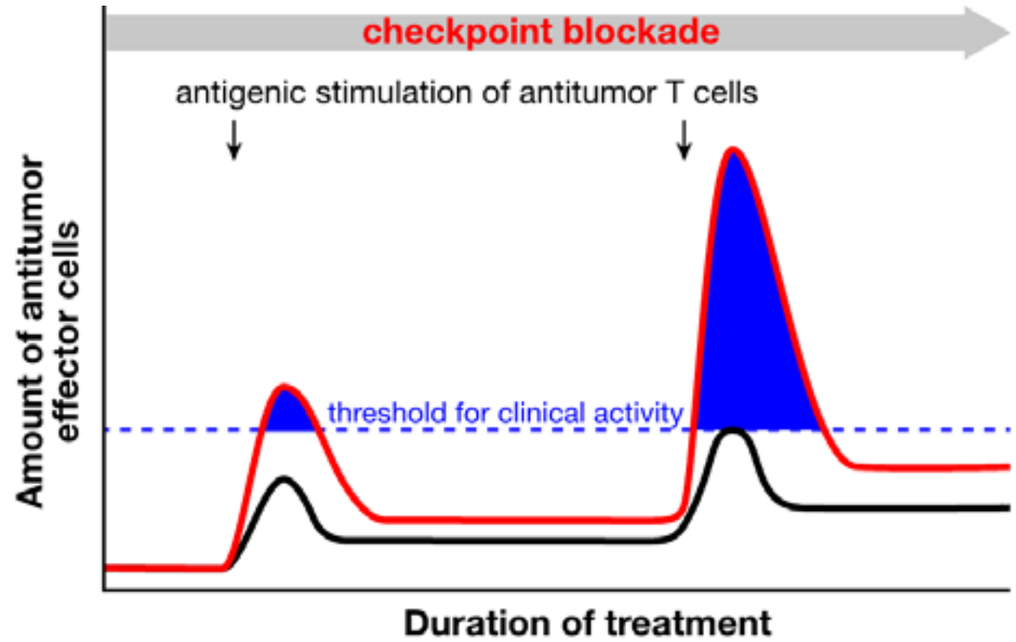
Prof. Dr. Coulie explained that treatment with immunostimulatory antibodies, i.e. current checkpoint blockade, could be stopped when a readily available and functional anti-tumour immunity has been built and has eliminated all tumour cells or will be able to eliminate or control new metastases. Unfortunately, today, such responses can't be measured in patients. In the context of CTLA-4 or PD-1 blockade, this requires a productive contact between tumour antigens and T cells and concurrently blocking antibodies to CTLA-4, PD-1 or PD-L1 (Figure 1).



Wei S, et al. *Cancer Discovery* 2018; 8: 1069–86; Chen D & Mellman I, *Immunity* 2013; 39:1–10; Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264; Sharma P et al. *Science* 2015;348:56-61.

FIGURE 1 *Antigenic stimulation and CTLA-4 or PD-1 blockade*

Both CTLA-4 and PD-1 only come to the T cell surface following T cell receptor (TCR) activation. In vivo, TCR activation of anti-tumour T cells is certainly not permanent. It will depend on the release of tumour antigens by dying tumour cells and capturing these antigens by antigen-presenting cells that will activate the T cells. When T cells can be directly re-stimulated by the tumour cells themselves, they need to have access to the tumour in a non-immunosuppressive microenvironment. It is therefore impossible to predict when exactly anti-tumour T cells will be activated in a given patient. It is expected that during checkpoint blockade, concomitant chemotherapy / radiotherapy / targeted therapy, which destroy tumour cells, increase the probability of activating anti-tumour T cells (Figure 2).



Buchbinder E and Desai A, *Am J Clin Oncol* 2016; 39: 98–106; Ott P, et al. *Clin Cancer Res* 2013;19:5300–9.

FIGURE 2 *Delayed clinical response to immunostimulatory antibodies*

Under physiological conditions, CTLA-4 and PD-1 are present on the surface of activated T cells, which is not valid for regulatory T cells that constitutively express high levels of surface CTLA-4. But we still don't know whether they are essential for the clinical responses to anti-CTLA-4 antibodies in humans, explained Prof. Coulie. Thus, the main effects of CTLA-4 or PD-1 blockades in cancer immunotherapy are only expected following anti-tumour T cell activation, which implies any kind of tumour antigen presentation. When and where anti-tumour T cells are activated in a given patient is unpredictable, justifying long-duration checkpoint blockade. This physiology of T cell activation increased or decreased but never initiated by co-receptors likely explains that the observed clinical effects of CTLA-4 or PD-1 blockades can be delayed. It supports the combination of CTLA-4 / PD-1 blockades with other treatment modalities that will destruct tumour cells.

During the discussion, a question was asked how immunoresistance could be overcome. Prof. Coulie tried to give a short answer, as this is a vast topic. He explained that it often happens, either through immunoresistance, such as downregulation of tumour antigen expression or through local immunosuppression. Much research is being done on these pathways in trying to combine appropriate inhibitors with currently available checkpoint blockade.

Conclusions

The immunology behind long duration of treatment with PD-1 blockade

- Under physiological conditions, CTLA-4 and PD-1 are present on the surface of activated T cells.
- The main effects of CTLA-4 or PD-1 blockades in cancer immunotherapy are only expected following anti-tumour T cell activation, which implies tumour antigen release.
- When and where anti-tumour T cells are activated in a given patient is unpredictable, justifying long-duration checkpoint blockade.
- Anti-tumour T cell activation depends on tumour antigen release. This likely explains that the observed clinical effects of CTLA-4 or PD-1 blockades can be delayed and supports the combination of CTLA-4 / PD-1 blockades with direct modalities of tumour cell destruction.

References: Wei S, et al. Cancer Discovery 2018; 8; 1069–86; Chen D & Mellman I, Immunity 2013; 39:1–10; Pardoll DM. Nat Rev Cancer. 2012;12:252-264; Sharma P et al. Science. 2015;348:56-61; Buchbinder E and Desai A, Am J Clin Oncol 2016; 39: 98–106; Ott P, et al. Clin Cancer Res 2013;19:5300–9.

Immunotherapy treatment duration: experience in melanoma

Prof. Dr. Bart Neyns (Head of medical oncology, UZ Brussels) showed that stage IV melanoma patients' prognosis and treatment outcomes evolved positively with anti-PD1 therapies as first-line immunotherapy. The Checkmate 067 study demonstrated a sustained long-term overall survival (OS) at five years in a more significant percentage of patients who received nivolumab plus ipilimumab or nivolumab alone compared to those who received ipilimumab alone (Larkin J. N Engl J Med 2019;381:1535-46). Combining nivolumab and ipilimumab induced a more than 50% survival benefit at five years. Even more important when discussing the duration of treatment is progression-free survival (PFS), explained Prof. Neyns. A big step forward was also here achieved with PD1 blockade or the combination of PD1 and CTLA-4 blockade, inducing a PFS in one out of three patients at five years.

Careful analysis of data from patients experiencing treatment-limiting toxicity showed that even after treatment discontinuation, a large proportion of patients continued to derive benefit from combination therapy. A pooled analysis of randomised phase II and III trials in patients with advanced melanoma who discontinued treatment with nivolumab and ipilimumab because of adverse events during the induction phase showed a comparable PFS at more than 18 months of follow-up (8.4 vs 10.8 months; P = 0.97). The objective response rate was 58.3% for patients who discontinued because of adverse events and 50.2% for patients who did not discontinue (Schadendorf D. J Clin Oncol 2017;35:3807-14). Based on these data, it seems that treatment duration doesn't have an impact on efficacy.

If there is no limiting toxicity or disease progression, can elective treatment discontinuation be considered? Prof. Neyns clearly emphasised that this does not apply to targeted therapy which should be continued in patients with clinical benefit. In most registration trials with immunotherapy, treatment was stopped after two years. Progression-free survival estimates of first-line pembrolizumab (KN006 study; Robert C. in Lancet Oncol 2019;20(9):1239-51) or nivolumab monotherapy (CM067 study) showed that the highest risk of disease progression occurred within the first six months of treatment, whereafter the risk of progression decreased. In the KN006 study, treatment was stopped at the two years landmark, whereas in the CM067 study, treatment was continued beyond two years. The behaviour of the PFS curves was not different whether or not you stop treatment after two years, as shown in figure 3. In the KN006 study, 103 (18.5%) patients completed the protocol-specified two years of pembrolizumab treatment, of which 21 had a complete response, 69 a partial response and 13 stable disease on CT scan. The patients with a partial response had a comparable risk of subsequent progression as patients who had a complete remission. In contrast, patients with stable disease had a higher risk of progression.

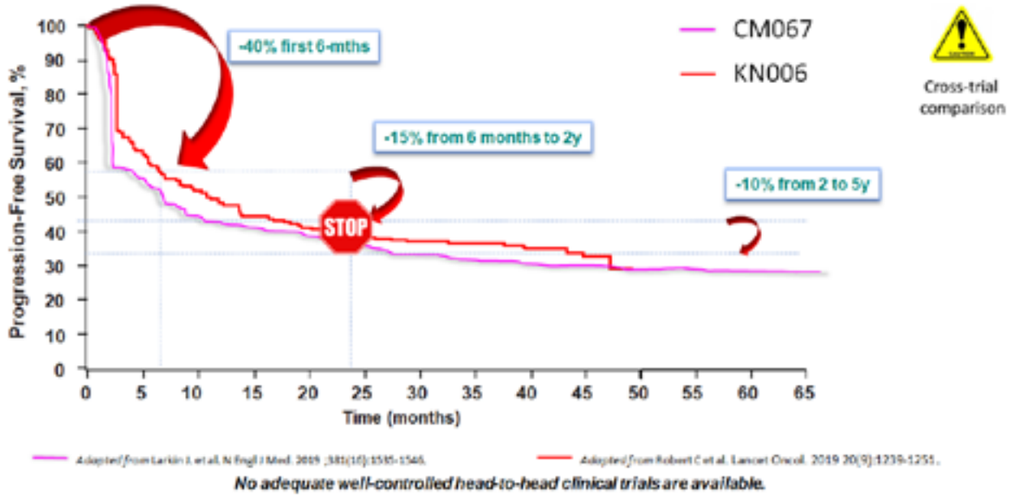


FIGURE 3 *Cross-trial comparison: Overlay PFS estimates of 1L pembrolizumab (KN006) or nivolumab monotherapy (CM067)*

Analysis of real-life data from 185 advanced melanoma patients who electively discontinued anti-PD-1 therapy with pembrolizumab (N = 167) or nivolumab (N = 18) at 14 hospitals across Europe and Australia revealed a similar message (Jansen YJL. In Ann Oncol 2019;1;30(7):1154-61). The duration of anti-PD-1 therapy was shorter (median one year) as compared to clinical trials. In patients with a complete remission and being treated for more than six months, the risk of relapse after treatment discontinuation was low (Figure 4). This is also reflected in the ESMO consensus recommendations stating that elective discontinuation should only be considered after a minimum treatment duration of six months (Keilholz U. in Ann Oncol 2020;31(11):1435-48). Patients achieving a partial remission or stable disease were at higher risk for progression after discontinuing therapy and defining the optimal treatment duration in such patients deserves further study. For these patients, ESMO currently recommends continuing treatment for at least two years.
Retreatment at the time of disease progression following elective treatment discontinuation has demonstrated activity in small case series and should be considered.

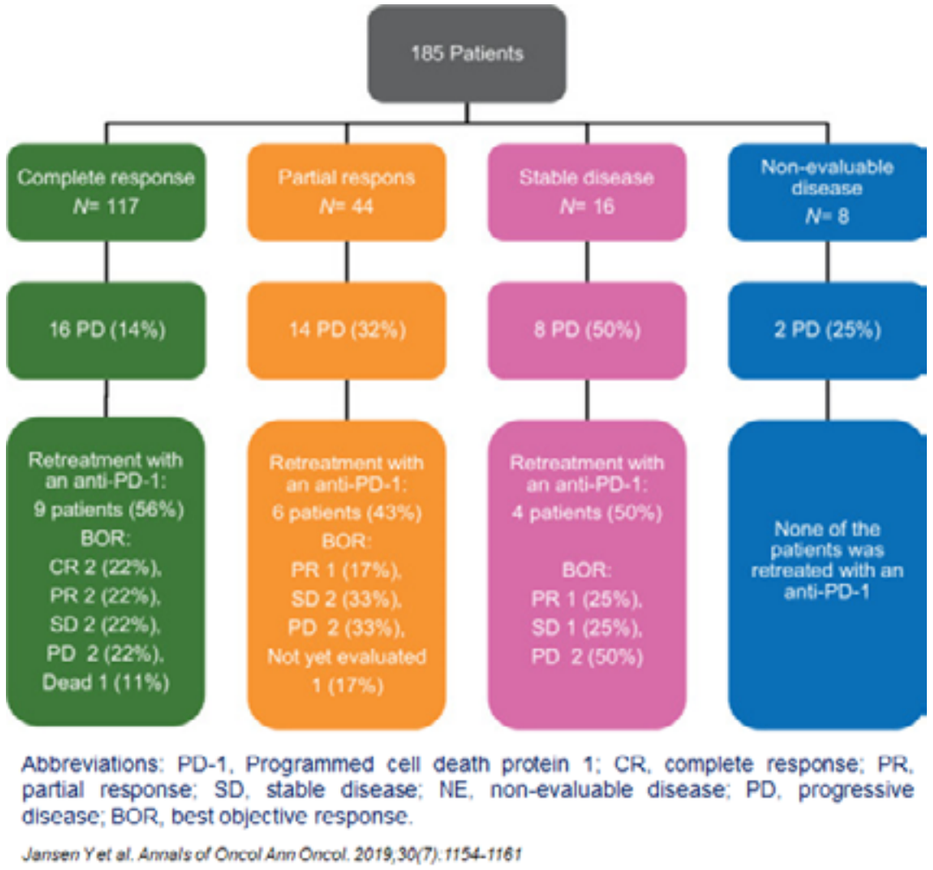


FIGURE 4 *Clinical outcome of advanced melanoma patients after discontinuation of an anti-PD-1 in the absence of disease progression or treatment limiting toxicity*

Prof. Neyns acknowledged that FDG-PET imaging could help to predict long-term outcomes better. In a retrospective analysis of metastatic melanoma patients treated with anti-PD-1-based immunotherapy at one year, patients with a partial response on a CT scan but with a complete metabolic response on an FDG-PET scan had a lower risk of progression, whereas patients with a positive FDG-PET scan in a lesion while stopping treatment were at highest risk of progression (Tan AC. in Ann Oncol 2018;29(10):2115-20). Almost all patients with a complete metabolic response at one year had an ongoing response to therapy after that. FDG-PET scans may have utility in predicting long-term benefit and help guide treatment discontinuation.

Personally, Prof. Neyns prefers to give at least one year of immunotherapy in all patients, so also in those that tolerate treatment well and might be candidates for elective discontinuation.

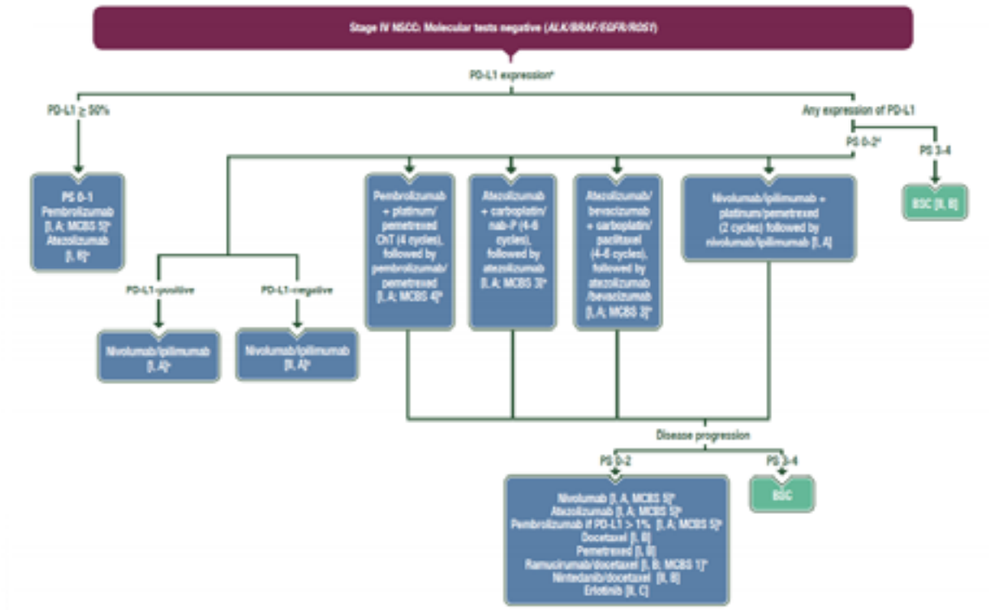
Conclusions

WHEN TO STOP IMMUNOTHERAPY IN MELANOMA?

- Stopping anti-PD1 immunotherapy may be considered in advanced melanoma patients who benefit from therapy and do not experience treatment-limiting toxicities with an acceptable low risk for progression within the first three years following treatment discontinuation.
- The optimal duration of a PD-1 treatment has not been established and may vary between patients:
  - The largest body of evidence relates to an arbitrary treatment duration of two years (KN006 study).
  - Real-world data support a shorter duration of therapy, as equally safe with respect to progression-free survival.
  - A complete response on CT can be used as the main driver in decision making (KN001 study).
  - FDG-PET scan after one year of therapy can aid decision making in patients with partial and complete response.
- Rather than prospective trials investigating arbitrary duration of therapy, predictive algorithms incorporating baseline clinical and tissue biomarkers and on-therapy response characteristics (FDG-PET) may allow making individualised decisions on optimal treatment duration.

Immunotherapy treatment duration: experience in non-small cell lung cancer

The current ESMO guidelines indicate that immunotherapy in stage IV NSCLC patients without an oncogene addiction should be continued until there is tumour progression. At that moment, a second-line treatment or best supportive care can be offered (Figure 5) (Planchard D. Ann Oncol 2018;29(suppl 4):iv192–237).
Prof. Dr. Johan Vansteenkiste (Respiratory oncology unit, department of pulmonology, UZ Leuven & Leuven Lung Cancer Group) called this an ostrich action, without any horizon. In the absence of a randomised controlled study, he tried to answer the question on immunotherapy treatment duration based on available data.



Planchard D. Ann Oncol 2018;29(suppl 4):iv192–237 & e-Update Sept 15, 2020

FIGURE 5 *Treatment algorithm for stage IV NSCC, molecular tests negative (ALK/BRAF/EGFR/ROS1).*

According to Prof. Vansteenkiste, an exploratory analysis of the Checkmate 153 study, a community-based phase IIIb/IV study, brings some insights. (Waterhouse DM. in J Clin Oncol 2020;38(33):3863-73). Patients with previously treated advanced NSCLC received nivolumab monotherapy. All patients on treatment at one year (N=252), regardless of response status, were randomly assigned to continue nivolumab until disease progression or unacceptable toxicity (N=127) or to stop nivolumab with the option of on-study retreatment after disease progression (one-year fixed duration, N=125). Of these, 89 and 85 patients in the continuous and one-year fixed-duration arms, respectively, had not progressed. At a minimum follow-up of 13.5 months, median PFS (24.7 months vs. 9.4 months; HR 0.56 [95% CI, 0.37 to 0.84] and median OS [not reached vs. 28.8 months; HR 0.62 [95% CI, 0.42 to 0.92]) were longer with continuous versus one-year fixed-duration treatment. These data suggest that continuation of nivolumab after one year improves treatment outcomes. Prof. Vansteenkiste emphasised that these data should be interpreted with caution as this was no preplanned study hypothesis with a moderate number of patients. Nevertheless, these data suggest that one year of immunotherapy appears to be insufficient in patients with NSCLC.

Follow-up data from patients receiving two years of immunotherapy in more recent clinical trials confirmed this. In the KEYNOTE-010 study, 79/690 (11.4%) patients with PD-L1 ≥1% received two years of pembrolizumab as a second- or third-line treatment. The three-year survival rate from the time of pembrolizumab discontinuation was 83%. After five years of follow-up, there were still 38 patients without disease progression. Of the 21 patients with disease progression who had received a second course of pembrolizumab, 15 were still alive (Herbst RJ. 2020 in J Clin Oncol; 38(14):1580-90). In the KEYNOTE-024 study, 39/690 patients (25.3%) with PD-L1 ≥50% had two years of pembrolizumab as a first-line treatment. The three-year survival rate from the time of pembrolizumab discontinuation was 81%. At five years of follow up, there were 15 patients without disease progression. Twelve patients with disease progression had received a second course of treatment, and of them, eight were still alive, five of whom were without disease progression (Brahmer J. in Annals of Oncology 2020;31(suppl_4): S1142-S1215). Currently, a two-year immunotherapy treatment seems to be a reasonable approach in NSCLC, acknowledged Prof. Vansteenkiste.

In a retrospective exploratory analysis with data from two clinical trials of anti-PD-1 treatments, the dept of response was grouped by percentage of maximum tumour shrinkage (Q1 = 1%-25%, Q2 = 26%-50%, Q3 = 51%-75%, and Q4 = 76%-100%) (Figure 6). A greater dept of response was associated with longer PFS and OS (McCoach CE. in Annals of Oncology 2017;28:2707–14). This can be an additional outcome measure for clinical trials, and may allow better comparisons of treatment activity, said Prof. Vansteenkiste.

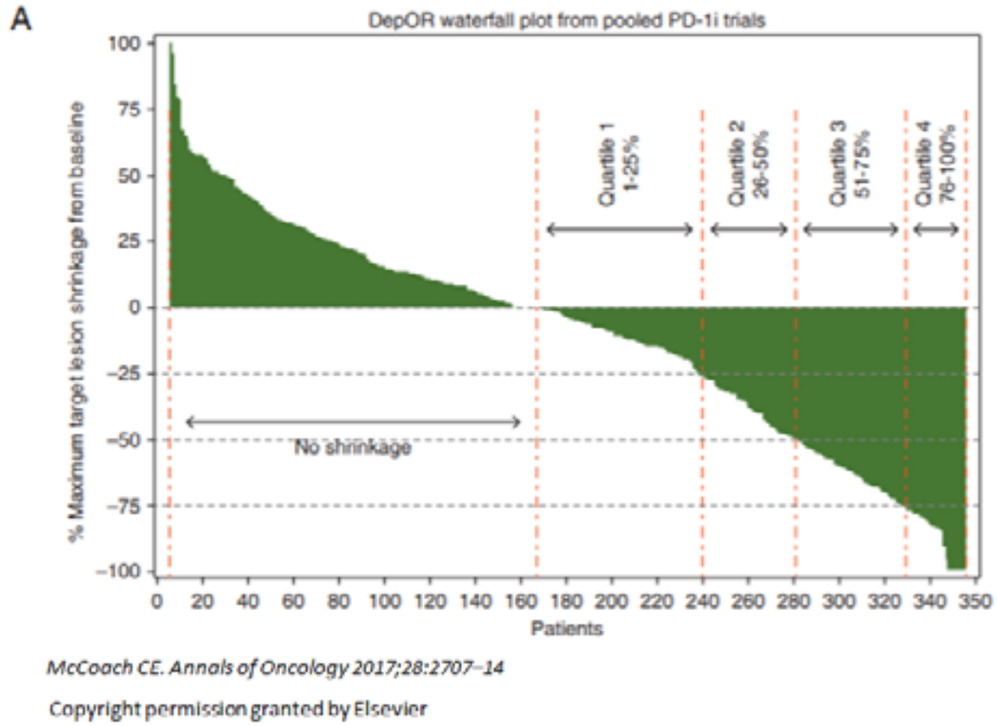


FIGURE 6 *Waterfall plot of pooled analysis of two PD-1 inhibitor trials*

During the discussion, the question was posed if it is reasonable to stop treating a patient in complete remission. Prof. Vansteenkiste mentioned that lung cancer differs from melanoma, as remission in NSCLC is rarely seen. Patients with a partial or a complete response can be grouped to decide for follow-up. Based on available evidence, it is very likely that one year of immunotherapy is not enough. In clinical practice, we mostly give immunotherapy for a maximum of two years. We follow the evidence of the current clinical trials in the absence of better ones.

Conclusions

When to stop immunotherapy in NSCLC?

- Limited data exist on the optimal duration of immunotherapy in NSCLC.
- Based on an exploratory analysis of the Checkmate 53 study, one year of immunotherapy seems insufficient in patients with NSCLC.
- Follow up data of recent clinical trials suggest that two year immunotherapy is a reasonable approach in NSCLC.
- A greater depth of response is associated with better outcomes for patients on immunotherapy. Depth of response may provide an additional outcome measure for clinical trials and may allow better comparisons of treatment activity.

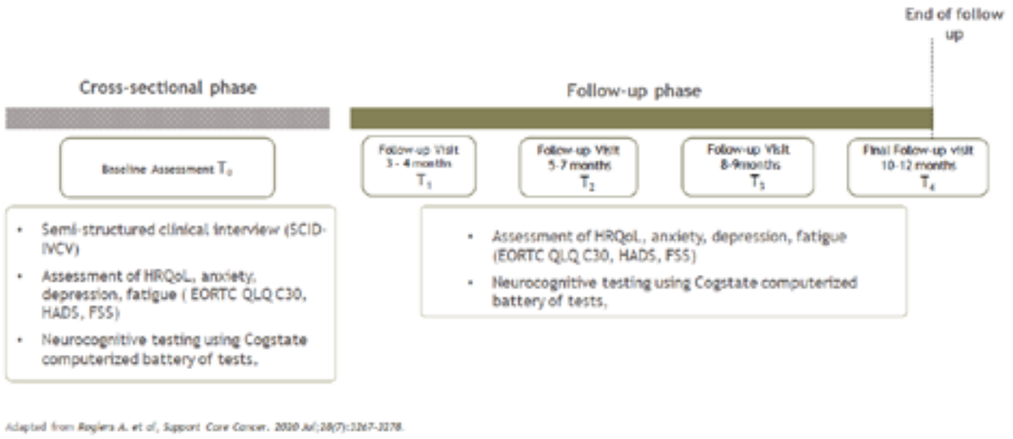
Emotional impact of stopping successful immunotherapy

Prof. Dr. Anne Rogiers (Neurocognitive Remediation Clinic, department of Psychiatry, Brugmann University Hospital, Brussels) started her presentation with a clear statement. Of the 12 million cancer survivors in Europe, 80% have persisting problems. Cancer diagnosis and survivorship were first described by Dr. Fitzhugh Mullan (N Engl J Med 1985), using the metaphor of the four seasons of cancer (Figure 7). The diagnosis is a rollercoaster of emotions, where the patient is confronted with his own mortality. The treatment phase is referred to as acute survival and is characterised by fear that cancer will not respond to treatment, anxiety about the future and physical symptoms.

This treatment phase is followed by the follow-up phase or extended survival, a phase of watchful waiting, fear of recurrence, and long-term physical symptoms and emotional issues. The fourth season is the permanent survival phase, where long-term survivors are in permanent survival, and cancer can be considered as permanently arrested. But the impact of cancer may persist, including late toxicity effects of cancer treatment as well as persisting emotional and cognitive problems and social issues such as loss of employment, obtaining a mortgage or insurance.

FIGURE 7 *The four seasons of cancer*

Prof. Rogiers conducted a single centre observational longitudinal study in the first-generation metastatic melanoma survivors treated with pembrolizumab to assess Health-Related Quality of Life (HRQoL), emotional burden and neurocognitive function (Support Care Cancer 2020;28(7):3267-78). Survivors were defined as patients with unresectable AJCC stage III or IV melanoma who achieved a durable remission after at least six months of pembrolizumab treatment. The primary study objective was to investigate HRQoL, the emotional burden and the neurocognitive outcome in advanced melanoma survivors treated with immune checkpoint inhibitors to provide a foundation for adapted psychosocial care. The social impact and fatigue were secondary objectives of the study. The study design is shown in figure 8.



Adapted from Rogiers A. et al, Support Care Cancer. 2020 Jul;28(7):3267-3278.

FIGURE 8 *Pilot study in the first generation of metastatic melanoma survivors treated with pembrolizumab*

Of the 25 patients that completed baseline assessment (18 female; median age 58 years), 24 completed the 1-year follow-up phase. The median time since diagnosis was 30 months; the median time since initiation of pembrolizumab was 19 months. At all visits, survivors reported a significantly impaired global HRQoL (P=0.005), physical function (P=0.001), role function (P=0.005), emotional function (P=0.04), cognitive function (P=0.00025) and social function (P=0.005) compared with the European mean of the healthy population (Hinz et al., Acta Oncol. 2014;53(7):958-965). Patients also reported significantly more fatigue (P=0.05), pain (P=0.05), insomnia (P=0.05) and constipation (P=0.05) as well as financial difficulties (P=0.02).

There was also an important emotional impact. During the first year after stopping treatment, all patients reported fear of cancer recurrence (daily worrying) due to uncertainty of patients and caregivers about treatment outcomes in terms of overall survival (OS). Fear can lead to avoidance of control visits. The clinical interview revealed that 12 patients (48%) had cancer-related post-traumatic stress disorder, of whom 7 (36%) survivors developed transient suicidal ideation. According to the Hospital Anxiety and Depression Scale, emotional distress was reported by 17 survivors (71%) at one year follow-up up. The neuropsychological testing revealed that one in three survivors suffered from overall cognitive impairment as defined in the protocol on at least one time-point. Also, the social impact can't be ignored, with 40 % of patients dealing with financial problems related to the disease and 32 % reported worrying about their family. These data clearly show that metastatic melanoma survivors, treated successfully with pembrolizumab, are at risk for emotional distress and neurocognitive impairment with a persistent impact on their HRQoL. Timely detection to offer tailored care is indicated.

During the discussion, the question was asked how psychosocial care for patients should be organised. Prof. Rogiers explained that empowerment of the patients as well as awareness of the family and treating physicians is essential. The patients need to put some hope in the first announcement of cancer diagnosis, especially in this rapidly evolving immunotherapy field. Most patients don't need a psychologist at the cancer diagnosis, as their main focus is survival. In that stage, they need their treating physicians and the oncology nurses. Psychosocial care becomes more important when patients are 'cured'. Prof. Rogiers sees a vital role for the oncology nurse within a multidisciplinary team, as she is there for the patient from the diagnosis onwards.

Conclusions

Emotional impact of stopping successful immunotherapy

- Emotional issues are in accordance with the uncertainty of the caregiver, especially in the new field of immunotherapy.
- The highest risk of emotional impact is just after the oncological control visit during the first year after stopping treatment.
- It is essential to organise survivorship care in parallel with the oncological control visits. If untreated, the emotional impact can persist for several years. If treated, it resolves.
- The social impact of cancer treatment is underestimated:
  - Financial problems, job loss
  - Changed family relationships
- Timely detection and offering tailored care are mandatory to make the best of survivorship. making individualised decisions on optimal treatment duration.

Oligometastatic recurrence under / following anti-PD1 and the role of local therapy

Using case examples, Prof. Neyns and Prof. Vansteenkiste demonstrated that patients with oligoprogressive disease that did well on anti-PD1 therapy have a good prognosis after local treatment (surgical resection and/or local ablative therapy).

MELANOMA

A retrospective multi-institutional analysis presented at the ESMO 2020 congress demonstrated that patients with stage IV melanoma with disease progression in a single tumour lesion after initial response to immunotherapy could be effectively treated with local therapy (Versluis JM. Ann Oncol 2020;31(suppl_4): S672-S710). The study analysed data from 294 patients with solitary progression on anti-PD-1 (67%), anti-CTLA-4 (13%), the combination of anti-PD-1 and anti-CTLA-4 (15%) and other ICI combinations (5%). The best overall response prior to progression was stable disease (15%), partial response (55%) and complete response (30%). Local therapy was mainly surgery (56%), radiotherapy (35%) or both (5%). The median time to secondary progression after treatment of the solitary progression in the overall population was 33 months. The median OS during immunotherapy was not reached; the estimated 3-year OS was 79%. In patients with progression off immunotherapy, the combination of local therapy and restart of immunotherapy successfully delayed further progression. Overall survival was not yet improved compared to single-modality treatment. Local therapy and immunotherapy continuation in patients with solitary progression on immunotherapy did not improve time to second progression but did improve OS. These data suggest that local therapy might benefit patients with stage IV melanoma and solitary progression under or following immunotherapy.

NSCLC

Radiotherapy might augment systemic antitumoral responses to immunotherapy. This was evaluated in a pooled analysis of two randomised trials (PEMBRO-RT (phase 2) and MDACC (phase 1/2)) in metastatic NSCLC patients treated with pembrolizumab with or without radiotherapy (Theelen WS. Lancet Oncol 2020; doi: 10.1016/S2213-2600(20)30391-X). The most frequently irradiated sites were lung metastases (39%), intrathoracic lymph nodes (21%) and lung primary disease (17%). Best abscopal response was 19.7% with pembrolizumab versus 41.7% with pembrolizumab plus radiotherapy (odds ratio [OR] 2.96; 95% CI 1.42 – 6.20; p=0·0039). The median PFS was 4.4 months with pembrolizumab alone versus 9.0 months with pembrolizumab plus radiotherapy (HR 0.67; 95% CI 0.45 – 0.99; p=0·045), and median OS was 8.7 months with pembrolizumab versus 19.2 months with pembrolizumab plus radiotherapy (HR 0.67; 95% CI 0.54 – 0.84; p=0·0004).

A small retrospective analysis showed that oligoprogression predominantly occurred at the primary lesion site or at the locoregional lymph nodes (Kagawa Y. Cancer Sci 2020;111(12):4442–52). In this analysis, no difference in outcome with local ablative therapy was seen.

A retrospective multicentre cohort of stage IV NSCLC patients with oligoprogressive disease immunotherapy and concurrent stereotactic radiotherapy demonstrated that after one year, 80% of the patients were still alive and more than half (55%) were still on the same immunotherapy (Kroeze SGC. Radiat Oncol 2021;16(4)).

During the discussion, a comment was made if immunotherapy should be stopped during the local treatment. Prof. Vansteenkiste mentioned that checkpoint inhibition is usually continued in NSCLC patients. Prof. Neyns indicated that this is an individual decision based on the patient profile and usually guided by PET/CT imaging. If there are still lesions visible on the scan, he would continue immunotherapy.

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