News and Perspectives

Immune checkpoint inhibitors win the 2018 Nobel Prize

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Abstract

The 2018 Nobel Prize in Physiology or Medicine was awarded to Tasuku Honjo and James Allison for their discoveries in cancer immunology. Professor Honjo was awarded due to his discovery of the programmed death molecule-1 (PD-1) on T cells. Professor Allison discovered another important immunosuppressive molecule: cytotoxic T-lymphocyte antigen-4 (CTLA-4). Suppression of T cell activation by PD-1 and/or CTLA-4 is considered one of the major escape mechanisms of cancer cells. Inhibition of these molecules by immune checkpoint inhibitors can successfully activate the immune system to fight cancer. Checkpoint inhibitors have brought about a major breakthrough in cancer immunotherapy, reviving the hope of curing patients with end-stage cancer, including a wide variety of cancer types. In metastatic malignant melanoma, the previous long-term survival of only 5% can now be extended to 50% with anti-PD-1 plus anti-CTLA-4 combined treatment in the latest report. More checkpoint molecules such as lymphocyte-activation gene 3 and T cell immunoglobulin and mucin domain 3 are under investigation. The achievement of Drs. Honjo and Allison in cancer immunotherapy has encouraged research into other immune-pathological diseases.

Like all Nobel Prize winners, Professor Tasuku Honjo and Professor James Allison have been working for a long time to achieve today’s results. Professor Honjo’s team started by studying apoptosis and found programmed death molecule-1 (PD-1) in apoptotic T cells. After long research, they confirmed that mice lacking PD-1 will develop various autoimmune diseases (including lupus-like autoimmune disease, myocarditis, glomerulonephritis, and type 1 diabetes). The co-inhibitory signal provided by the PD-1 pathway regulates the T cell activity to avoid an excessive immune response [1–3]. In contrast, the tumor cell can escape immune surveillance through activating the PD-1 pathway to suppress the effector T cells. Further research has found that the use of antibodies against these molecules can activate the immune system to destroy cancer cells [4]. In the beginning, the major pharmaceutical companies did not have much interest, but Professor Honjo persisted so that finally the PD-1 inhibitor became the main drug for immunotherapy. Professor Allison found cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) on T cells in 1995 and established studies focused on B7/cluster of...
| Cancer type                                | Trial (Phase)       | Published date | Stage         | Line         | Arms                                      | RR (%) | mPFS (months) | mOS (months) | Ref.          |
|-------------------------------------------|---------------------|----------------|---------------|--------------|-------------------------------------------|--------|---------------|--------------|---------------|
| Cutaneous melanoma                        | CA184-002 (III)     | 2010           | Advanced      | 2nd line     | Ipilimumab + gp100                         | 6%     | 2.8           | 10.0         | [12]          |
|                                           |                     |                |               |              | Ipilimumab                                | 11%    | 2.9           | 10.1         |               |
|                                           |                     |                |               |              | Gp100                                      | 2%     | 2.8           | 6.4          |               |
|                                           | CA184-024 (III)     | 2011           | Metastatic    | 1st line     | Ipilimumab + DTIC                          | 15%    | ND            | 11.2         | [13]          |
|                                           |                     |                |               |              | DTIC                                       | 10%    | ND            | 9.1          |               |
|                                           | KEYNOTE-006 (III)   | 2015           | Advanced      | 2nd line     | Pembrolizumab Q2w                          | 34%    | 5.5           | NR           | [14,15]       |
|                                           |                     |                |               |              | Pembrolizumab Q3w                          | 33%    | 4.1           | NR           |               |
|                                           |                     |                |               |              | Ipilimumab                                 | 12%    | 2.8           | 16.0         |               |
|                                           | CheckMate066 (III)  | 2014           | Advanced      | 1st line     | Nivolumab + Gp100                          | 40%    | 5.1           | 37.5         | [15,16]       |
|                                           |                     |                |               |              | DTIC                                       | 34%    | 2.2           | 11.2         |               |
|                                           | CheckMate-067 (III) | 2015           | Advanced      | 1st line     | Nivolumab + Ipilimumab                     | 57%    | 11.5          | NR           | [17,18]       |
|                                           |                     | 2017           |               |              | Nivolumab                                  | 44%    | 6.9           | 37.6         |               |
|                                           |                     |                |               |              | Ipilimumab                                 | 19%    | 2.9           | 19.9         |               |
|                                           | CheckMate-037 (III) | 2015           | Advanced      | 2nd line     | Nivolumab                                  | 27%    | 3.1           | 16           | [19,20]       |
|                                           |                     | 2018           |               |              | Chemotherapy                               | 10%    | 3.7           | 14           |               |
| Cutaneous Squamous cell carcinoma         | NCT02760498 (I/II)  | 2018           | Metastatic    | 1st line     | Cemiplimab                                 | 47%    | NR            | NR           | [21]          |
| Merkel cell carcinoma                     | NCT02267603 (II)    | 2016           | Advanced      | 1st line     | Pembrolizumab                              | 56%    | 67%           | NR           | [22]          |
| Renal cell carcinoma                      | CheckMate-025 (III) | 2015           | Advanced      | 2nd line     | Nivolumab                                  | 25%    | 4.6           | 25           | [23]          |
|                                           |                     |                |               |              | Everolimus                                 | 5%     | 4.4           | 19.6         |               |
| Non-small cell lung cancer -Nonsquamous   | CheckMate-214 (III) | 2018           | Advanced      | 1st line     | Nivolumab + Ipilimumab                     | 42%    | 11.6          | NR           | [24]          |
|                                           |                     |                |               |              | Sunitinib                                  | 27%    | 8.4           | 26           |               |
|                                           | CheckMate-057 (III) | 2015           | Advanced      | 2nd line     | Nivolumab + chemotherapy                    | 19%    | 2.3           | 12.2         | [25]          |
|                                           |                     |                |               |              | Docetaxel                                  | 12%    | 4.2           | 9.4          |               |
|                                           | KEYNOTE-024 (III)   | 2016           | Advanced      | 1st line     | Pembrolizumab                              | 44.8%  | 10.3          | 30           | [26,27]       |
|                                           | 2018                |                |               |              | Platinum-based                             | 27.8%  | 6.0           | 14.2         |               |
|                                           | KEYNOTE-189 (III)   | 2018           | Metastatic    | 1st line     | Pembrolizumab + chemotherapy               | 47.6%  | 8.8           | NR           | [28]          |
|                                           |                     |                |               |              | Chemotherapy + placebo                      | 18.9%  | 4.9           | 11.3         |               |
|                                           | IMpower-150 (III)   | 2018           | Metastatic    | 1st line     | Atezolizumab + bevacizum + chemotherapy     | 63.5%  | 8.3           | 19.2         | [29]          |
|                                           |                     |                |               |              | Atezolizumab                                | 48%    | 6.8           | 14.7         |               |
|                                           | IMpower130(III)     | 2018           | Metastatic    | 1st line     | Atezolizumab + chemotherapy                 | 49.2%  | 7.0           | 18.6         | [30]          |
|                                           |                     |                |               |              | Chemotherapy                               | 31.9%  | 5.5           | 13.9         |               |
| Non-small cell lung cancer | CheckMate-017 (III) | 2015 | Advanced | ≥ 2nd line | Nivolumab | 20%<sup>x</sup> | 3.5<sup>x</sup> | 9.2<sup>x</sup> [31] |
|----------------------------|---------------------|------|----------|------------|-----------|----------------|----------------|-------------------|
| IMpower 131 (III)          | 2017                | 1st line | Atezolizumab + chemotherapy<sup>y</sup> | NR        | NR        | NR             | 14.6           |
| KEYNOTE-407(III)          | 2018                | Advanced | Pembrolizumab + chemotherapy<sup>h</sup> | 57.6%<sup>x</sup> | 6.4<sup>x</sup> | 15.9<sup>x</sup> [33] |
| Non-small cell lung cancer | KEYNOTE-010 (I/III) | 2016 | Advanced | ≥ 1st line | Pembrolizumab 2 mg/kg | 30.2%<sup>j</sup> | 5.0<sup>i</sup> | 10.4<sup>j</sup> [34] |
|                            |                     |       |          |            | Pembrolizumab 10 mg/kg | 19%<sup>x</sup> | 5.2<sup>x</sup> | 12.7<sup>x</sup> |
|                            |                     |       |          |            | Docetaxel | 8% | 4.1 | 8.5 |
| OAK (III)                  | 2016                | Advanced | ≥ 2nd line | Atezolizumab | 14% | 2.8 | 13.8<sup>x</sup> [35] |
| CheckMate-026 (III)       | 2017                | Advanced | ≥ 1st line | Pembrolizumab | 26%<sup>y</sup> | 4.2<sup>y</sup> | 14.4<sup>y</sup> [36] |
| Small cell lung cancer    | CheckMate-032 (I/II) | 2018 | Limited or extensive stage | Pembrolizumab | 60.2%<sup>x</sup> | 5.2<sup>x</sup> | 12.3<sup>x</sup> [38] |
| IMpower133 (III)          | 2018                | Extensive stage | Pembrolizumab + Chemotherapy<sup>y</sup> | 64.4% | 4.3 | 10.3 |
| Urothelial carcinoma      | KEYNOTE-045 (III)   | 2017 | Advanced | ≥ 2nd line | Pembrolizumab | 21.1%<sup>x</sup> | 2.1 | 10.3<sup>x</sup> [39] |
| IMvigor211 (III)          | 2018                | Advanced | ≥ 2nd line | Atezolizumab | 23%<sup>y</sup> | 2.4<sup>y</sup> | 11.1<sup>y</sup> [40] |
| CheckMate-275 (II)        | 2017                | Advanced | ≥ 2nd line | Nivolumab | 19.6% | 2.0 | 8.74 [41] |
| NCT01693562 (I/II)        | 2017                | Advanced | Pembrolizumab | 26.7% | 1.5 | 18.2 [42] |
| JAVELIN Solid Tumor (I)   | 2017                | Advanced | ≥ 2nd line | Durvalumab | 17% | 1.6 | 6.5 [43] |
| IMvigor210 (II)           | 2017                | Advanced<sup>z</sup> | Atezolizumab | 23% | 2.7 | 15.9 [44] |
| KEYNOTE-052 (II)          | 2017                | Advanced<sup>z</sup> | Pembrolizumab | 28.9% | 2 | 11.5 [45,46] |
| Head and neck squamous cell carcinoma | CheckMate-141 (III) | 2016 | Advanced | ≥ 2nd line | Nivolumab | 13.3%<sup>x</sup> | 2.0<sup>x</sup> | 7.5<sup>x</sup> [47] |
| KEYNOTE-040 (III)         | 2018                | Advanced | Pembrolizumab | 14.6% | 2.1 | 8.4<sup>x</sup> [48] |
| KEYNOTE-048 (III)         | 2018                | Advanced | Pembrolizumab | 10.1% | 2.3 | 6.9 |

(continued on next page)
| Cancer type                          | Trial (Phase) | Published date | Stage  | Line   | Arms                                      | RR (%) | mPFS (months) | mOS (months) | Ref. |
|-------------------------------------|---------------|----------------|--------|--------|-------------------------------------------|--------|--------------|--------------|------|
| Gastric cancer/Gastroesophageal      | ATTRACTION-2 (III) | 2017          | Advanced | 3rd line | Nivolumab                                | 11%    | 1.61<sup>a</sup> | 5.26<sup>+</sup> | [50] |
|                                     |               |                |        |        | Placebo                                   | 0%     | 1.45         | 4.14         |      |
| Hepatocellular carcinoma            | KEYNOTE-059 (II) | 2018          | Advanced | 3rd line | Pembrolizumab                             | 11.6%  | 2.0          | 5.6          | [51] |
|                                     | CheckMate-040 (I/II) | 2017         | Advanced | 1st line | Nivolumab                                 | 20%<sup>c</sup> | 4          | 74%<sup>+</sup> |      |
|                                     | KEYNOTE-224 (II) | 2018          | Advanced | 2nd line | Pembrolizumab                             | 17%    | 28%<sup>i</sup> | 54%<sup>+</sup> | [52] |
|                                     | NCT0271531 (IIb) | 2018         | Advanced | 1st line | Atezolizumab + bevacizum                    | 34%    | 14.9         | NR           | [53] |
| Colorectal cancer-dMMR or MSI-H     | CheckMate-142 (II) | 2017          | Advanced | 2nd line | Nivolumab                                 | 32%    | 14.3         | 73%<sup>+</sup> | [54] |
| Cervical cancer                     | KEYNOTE-158 (II) | 2018          | Advanced | 1st line | Pembrolizumab + Ipilimumab                 | 55%    | 71%<sup>a</sup> | 85%<sup>+</sup> | [55] |
| Tissue agnostic-dMMR or MSI-H       | KEYNOTE-016 (II) | 2018          | Metastatic | 2nd line | Pembrolizumab                             | 54%    | 53%<sup>c</sup> | 64%<sup>+</sup> | [56] |
|                                     | KEYNOTE-016, -164, -012, -028, and -158 | 2018 | Metastatic | 2nd line | Pembrolizumab                             | 39.6%  | ND           | ND           | [57] |
| Breast cancer                       | IMpassion-130 (III) | 2018          | Metastatic | 1st line | Atezolizumab + Nab-paclitaxel              | 56%<sup>a</sup> | 7.2<sup>+</sup> | 21.3         | [58] |
|                                     |               |                |        |        | Nab-paclitaxel                             | 46%    | 5.5          | 17.6         |      |

Abbreviations: RR: Response Rate; mPFS: median Progression-Free Survival; mOS: median Overall Survival; Ref: Reference; ND: not documented; NR: not reported; DTIC: Dacarbazine.

<sup>a</sup> Chemotherapy: DTIC or carboplatin/paclitaxel.
<sup>b</sup> Progression-free survival rate at 6 months.
<sup>c</sup> In intermediate- and poor-risk patients.
<sup>d</sup> Chemotherapy: pemetrexed + platinum.
<sup>e</sup> Chemotherapy: paclitaxel + carboplatin.
<sup>f</sup> Chemotherapy: carboplatin + nab-paclitaxel.
<sup>g</sup> Chemotherapy: carboplatin + paclitaxel.
<sup>h</sup> Chemotherapy: paclitaxel or nab-Paclitaxel + carboplatin.
<sup>i</sup> Among population with a tumor proportion score of ≥50%.
<sup>j</sup> Among population with a PD-L1 expression level of ≥5%.
<sup>k</sup> Chemotherapy: carboplatin + etoposide.
<sup>l</sup> Chemotherapy: paclitaxel or docetaxel or vinflunine.
<sup>m</sup> In the IC2/3 population.
<sup>n</sup> Cisplatin ineligible.
<sup>o</sup> Chemotherapy: Methotrexate, docetaxel, cetuximab.
<sup>p</sup> Systemic therapy: platinum + 5-FU + cetuximab.
<sup>q</sup> Combined positive score (CPS) ≥20 population.
<sup>r</sup> In the dose-expansion phase.
<sup>s</sup> 9-month OS rate.
<sup>t</sup> 12-month PFS rate.
<sup>u</sup> 6-month OS rate.
<sup>v</sup> 12-month OS rate.
<sup>w</sup> 24-month PFS and OS rate.
<sup>x</sup> Statistically significant compared to control arm.
differentiation 28 (CD28)/CTLA-4 [5,6]. When CTLA-4 bound to the ‘B7 family’ on the surface of the antigen presenting cell, the T cell was suppressed. This mechanism to regulate the immune response to maintaining self-tolerance can also be misused by cancer cells. Therefore, Professor Allison and his team developed CTLA-4 blockade for cancer treatment and got success in melanoma after 13 years of research [7]. Professors Honjo and Allison both won the first Tang Award for Biotechnology and Medicine in 2014 [8]. The two Tang Award winners rely on their enthusiasm for scientific research, their persistence in the research effort, the search for a variety of possible opportunities, and the realization of their theories and achievements. The spirit of perseverance is truly admirable.

Professor Allison’s research results are mainly used in melanoma, and with anti-PD-1 drugs for the treatment of lung cancer and kidney cancer. Professor Honjo’s research results have now been widely applied in almost all cancers, including head and neck cancer, lung cancer, liver cancer, stomach cancer, urinary tract cancer, lymphoma, and skin cancer. Clinical trials are also actively undergoing in other cancer types. The combination of two immuno-drugs is more effective, but the side effects are relatively greater. Immuno-therapy provides optimistic long-term efficacy compared to traditional chemotherapy or targeted therapy in some patient groups. For example, melanoma is the most widely studied and best-performing disease, with the CTLA-4 immunologic drug (ipilimumab, marketed as Yervoy) successfully allowing 21% of patients to survive for more than 10 years [9]. Because of the recent development of PD-1 drugs, current official reports have only tracked results for about five years. As of now, though, PD-1 drugs can help 30% of patients with terminal disease survive for more than five years [10]. The combination of the two drugs has succeeded in allowing more than 50% of patients to survive for more than three years [11].

After the astonishing improvement reported in melanoma, very many clinical trials have begun in different cancer types, especially in solid cancers with poor prognosis. We list the pivotal trials in Table 1, and these data shape the landscape of cancer treatment in the early 21st century. Besides malignant melanoma [13,15–18], there have been major advances in renal cell carcinoma [24], lung cancer [26–30,32,33,38], urothelial carcinoma [44–46], head and neck squamous cell carcinoma [49], and triple negative breast cancer [59]; in these, immune checkpoint inhibitors have become part of the first-line standard treatment. In other cancer types such as hepatocellular carcinoma [52–54], gastric/gastroesophageal junctional cancer [51], colorectal cancer with microsatellite instability—high (MSI-H) or mismatch repair deficient (dMMR) feature [55,56], and cervical cancer [57], immune checkpoint inhibitors play important an role beyond that of first-line therapy. In some rare cancer types with limited effective regimens, such as cutaneous squamous cell carcinoma [21] and Merkel cell carcinoma [22], immune checkpoint inhibitors can yield an amazing response rate and median overall survival. Furthermore, the US Food and Drug Administration (FDA) granted accelerated approval to anti-PD-1 (pembrolizumab, marketed as Keytruda) for first tissue-agnostic indication in adult and pediatric patients with advanced MSI-H or dMMR solid tumors beyond first-line [58,59]. Furthermore, immunotherapy is moving beyond advanced disease, with studies in consolidation.
therapy in lung cancer [65] and adjuvant therapy in melanoma [61–64] Table 2. We look forward to more positive results in early stage disease that will benefit millions of cancer patients. In conclusion, immune checkpoint inhibitors are writing a whole new chapter in the history of fighting cancer, changing treatment guidelines in many different types of cancer, providing long-term survival, and creating the possibility of a cure for cancer patients who previously had little hope.

Although more and more immune drugs are used in various cancer research studies and clinical trials, these drugs also have side effects, including immune-related adverse reactions which differ completely from those of chemotherapy. We should be alert to the early signs of the complications of immunotherapy and treat patients accordingly so to continue to improve the odds of survival.

We should all follow the enthusiastic, dedicated, and persevering spirit of these two pioneers. The inventions of these Nobel Prize winners truly benefit our patients.

Congratulations again to Professor James Allison and Professor Tasuku Honjo for winning the Nobel Prize in Physiology or Medicine.

**Conflicts of interest**

The authors declare no conflicts of interest.

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