تقيم كلية الصيدلة / جامعة بغداد
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Innovative Approaches to Multiple Cancers: Keytruda

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يوم الاحد المصادف ١٦/٢/٢٠٢٥
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1. Introduction

•Overview of the workshop objectives

1. Introduction

- Pembrolizumab [Keytruda (US)], a humanized monoclonal antibody against the programmed death receptor-1 (PD-1) protein, has been developed by Merck & Co for the treatment of cancer.
- It is a lyophilized powder, and reconstituted in 0.9% sodium chloride solution to a final concentration of 1–10 mg/mL for intravenous use. It is stable for 4 hours at room temperature, and 24 hours when refrigerated.33 It is administered as a 30-minute intravenous infusion.
- Pembrolizumab has been tested clinically in a series of KEYNOTE studies. Currently, pembrolizumab is tested in 12 categories of malignancies (bladder, breast, colorectal, esophagus, gastric, head and neck, hematology, lung, melanoma, ovarian, pediatric, other solid tumors) to determine its clinical efficacy.

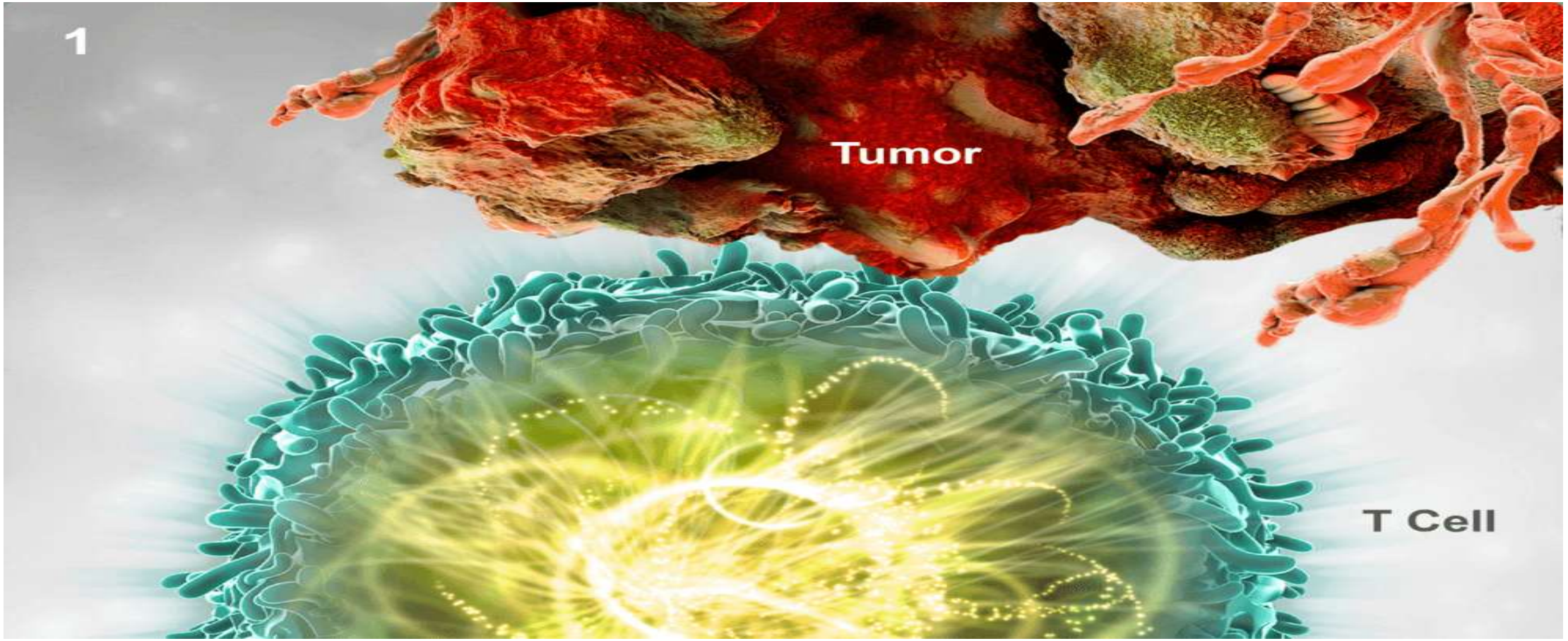
2. The Science Behind Keytruda (Pembrolizumab)

- Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks interaction with its ligands, PD-L1 and PD-L2. This binding results in the activation of T-cell–mediated immune responses against tumor cells. Blocking PD-1 activity resulted in decreased tumor growth in genetically identical mouse tumor models.
- Anti-PD-1 therapies represent a novel therapeutic approach to the treatment of cancer, reactivating the immune response by blocking the interaction between PD-1 and its ligands

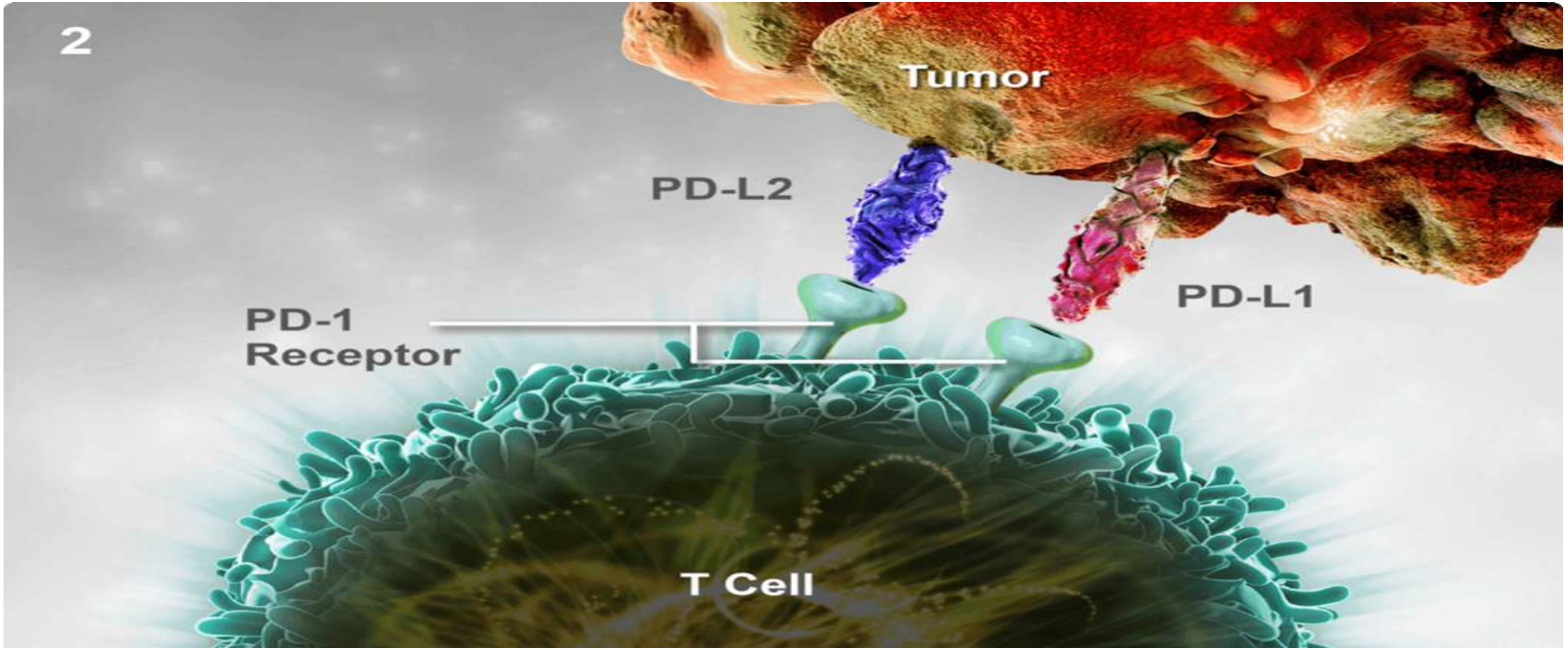
3. How it boosts the immune response against cancer ?

- The programmed death receptor-1 (PD-1) is a surface molecule expressed on antigen-stimulated T-cells , as well as monocytes, B cells, natural killer T cells, and dendritic cells .
- In normal tissues PD-1 acts as an immune checkpoint receptor, enabling self-tolerance by T-cells and thus preventing autoimmune reactions .
- When unbound, PD-1 allows the normal immune response by T cells to occur . However, binding of PD-1 to its ligands, PD-L1 and PD-L2, suppresses the immune response by inducing downstream signaling that inhibits the proliferation of T-cells, cytokine release and cytotoxicity.
- Abnormal PD-L1 expression on the surface of tumour cells, including melanoma cells, activates PD-1 and suppresses cytotoxic T cell activity; this T cell tolerance allows the tumour cells to avoid recognition and attack by the immune system .

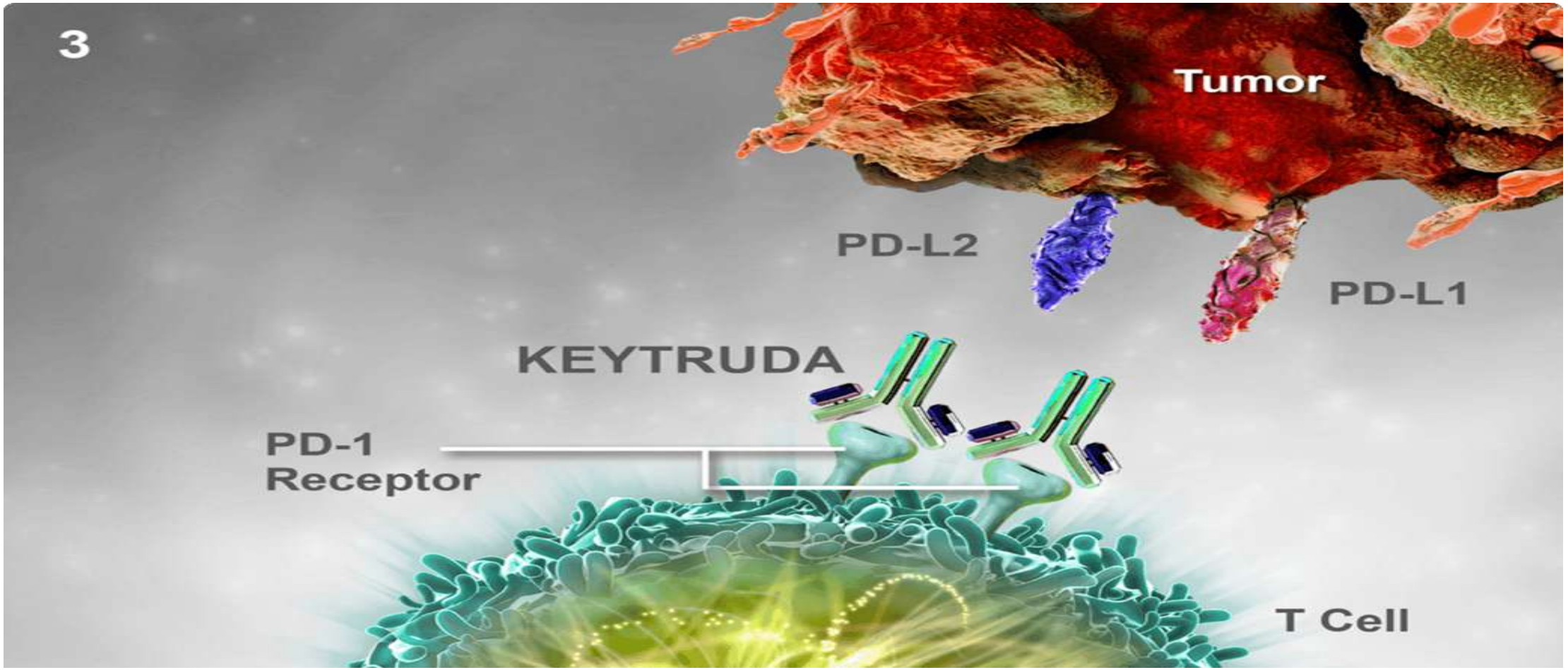
Normal Immune Response



Tumor evasion and T-cell deactivation



T –cell reactivation with Keytruda



- **KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma** in adults who have received prior platinum-containing chemotherapy
- KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10
- KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent **head and neck squamous cell carcinoma (HNSCC)** in adults whose tumours express PD-L1 with a CPS ≥ 1
- KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy
- KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced **renal cell carcinoma (RCC)** in adults

- **KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma** in adults.
- KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection
- KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic **non-small cell lung carcinoma (NSCLC)** in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
- KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults.
- KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.
- KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory **classical Hodgkin lymphoma (cHL)** who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

- **Targeted therapies differ from standard chemotherapy in several ways:**
- Targeted therapies act on specific molecular targets that are associated with cancer, whereas most standard chemotherapies act on all rapidly dividing normal and cancerous cells.
- Targeted therapies are deliberately chosen or designed to interact with their target, whereas many standard chemotherapies were identified because they kill cells.
- Targeted therapies are often cytostatic (that is, they block tumor cell proliferation), whereas standard chemotherapy agents are cytotoxic (that is, they kill tumor cells).

4. Comparison with traditional cancer treatments

- Keytruda is a game-changer for cancers with high PD-L1 expression or MSI-high tumors, offering long-term benefits with fewer side effects than chemo.
- Chemotherapy remains the first-line treatment for many cancers but has more side effects.
- Radiation is best for localized cancers but isn’t effective for widespread disease

4. Comparison with traditional cancer treatments

1. More Targeted & Long-Lasting Response

✓ **Activates the immune system** to recognize and attack cancer cells, leading to a long-term response.
✓ Unlike chemotherapy and radiation, Keytruda can provide **durable remission** in some cancers.

2. Fewer Side Effects Compared to Chemotherapy

✓ Avoids the **severe toxicity of chemotherapy**, such as hair loss, nausea, vomiting, and damage to healthy cells.
✓ **Does not suppress bone marrow**, meaning fewer issues with anemia, infection risk, and fatigue.

3. Effective for Certain Hard-to-Treat Cancers

✓ Works well for **advanced, metastatic, and immunogenic cancers** (e.g., melanoma, lung cancer, bladder cancer).
✓ Approved for **MSI-high or dMMR tumors** regardless of cancer type, whereas chemotherapy is often cancer-type-specific.

4. More Convenient Treatment Schedule

✓ Typically given **every 3-6 weeks**, reducing hospital visits compared to chemotherapy (which requires frequent cycles).
✓ Less **overall treatment burden** on the patient.

4. Comparison with traditional cancer treatments

- **5. Less Damage to Healthy Cells Compared to Radiation**
- ✓ Unlike radiation, Keytruda does not damage nearby healthy tissues, **reducing localized side effects** like burns and scarring.
  ✓ No risk of **secondary cancers due to radiation exposure**.
- **6. Works When Chemotherapy Fails**
- ✓ Can be used as a **second-line or combination therapy** when chemotherapy is ineffective or resistance develops.
- **7. Potential for Complete Tumor Regression**
- ✓ Some patients experience **complete and long-term remission** with Keytruda, something less common with chemo or radiation

5. Overview of Pembrolizumab for Melanoma

- Pembrolizumab has shown significant activity in patients with advanced melanoma, particularly those who are refractory to previous treatments such as chemotherapy, BRAF/MEK inhibitors, and ipilimumab. It has been found to be superior to ipilimumab in terms of both efficacy and safety profile .
- Melanoma is an aggressive malignancy. In metastatic melanoma, the median overall-survival (OS) is <12 months, with a 10-year survival of <10%.36 Conventional chemotherapy is ineffective.
- In 135 patients with advanced melanoma who were enrolled in non-randomized cohorts of the large, phase 1 study KEYNOTE 001, pembrolizumab resulted in long-lasting objective responses in 31–51% of patients treated with doses ranging from 2 mg/kg every 3 weeks to 10 mg/kg every 2 weeks, and 81% of patients survived for at least 1 year after starting treatment.

- The FDA approved pembrolizumab in September 2014 for the treatment of unresectable or metastatic melanoma that has progressed after ipilimumab and, if BRAFV600 mutation positive, a BRAF inhibitor. The approval was later expanded in December 2015 to include initial treatment for these patients .

5. Overview of Pembrolizumab for Melanoma

- In the KEYNOTE-006 trial, pembrolizumab was administered to patients with unresectable stage III/IV melanoma. The trial compared two dosing regimens of pembrolizumab (10 mg/kg every 2 weeks and every 3 weeks) against ipilimumab. The overall response rate (ORR) was 38%, with the highest ORR of 52% in the 10 mg/kg every 2 weeks cohort .
- Responses to pembrolizumab were durable, with 81% of patients remaining on treatment at the time of analysis. This indicates that many patients experienced long-lasting benefits from the therapy .
- **Biomarkers and Predictors**: PDL1 expression was positive in 80% of cases, suggesting that PDL1 expression may serve as a valid predictor of response to pembrolizumab **[5]**. Additionally, tumors with high mutation burdens showed better responses, indicating the potential for personalized treatment approaches .
- In summary, pembrolizumab represents a significant advancement in the treatment of advanced melanoma, offering improved efficacy and safety compared to previous therapies, with ongoing research aimed at optimizing its use and understanding its mechanisms of action.

6. **Overview of Pembrolizumab for Non-Small Cell Lung Cancer (NSCLC)**

- Pembrolizumab was evaluated in the KEYNOTE-001 trial, which included 495 patients with advanced unresectable or metastatic NSCLC. The overall response rate (ORR) was 19.4%, with treatment-naïve patients showing a higher ORR of 24.8% compared to 18% in previously treated patients. The median duration of response was 12.5 months, indicating substantial anti-tumor activity .
- The trial initially did not require testing for EGFR mutations or ALK rearrangements, but later amendments mandated such testing. Among tested patients, EGFR mutations were found in 1.5% and ALK translocations in 2%. The majority of patients (81%) had non-squamous carcinoma **[1]**.
- **PD-L1 Expression as a Biomarker** An exploratory analysis identified a PD-L1 positivity cutoff of 50% as a potential biomarker for predicting responses to pembrolizumab. Patients with tumors expressing 50% PD-L1-positive cells had an ORR of 45.2%, while those with lower expressions had significantly lower ORRs (16.5% for 1-49% and 10.7% for <1%) .
- In this randomized trial, patients with previously treated NSCLC and at least 1% PD-L1-positive tumor cells were assigned to receive either pembrolizumab (2 mg/kg or 10 mg/kg) or docetaxel. The median overall survival (OS) was significantly better in the pembrolizumab groups compared to docetaxel (10 mg/kg: 12.7 months vs. 8.5 months for docetaxel) .
- Adverse events (AEs) of any grade occurred in 63% of patients receiving pembrolizumab at 2 mg/kg and 66% at 10 mg/kg, compared to 81% in the docetaxel group. Grade 3-5 treatment-related AEs were less frequent in the pembrolizumab groups (13% for 2 mg/kg and 16% for 10 mg/kg) compared to 35% for docetaxel. Immune-related AEs were observed in 20% of patients on pembrolizumab .
- Pembrolizumab received FDA approval in October 2015 for the treatment of metastatic NSCLC expressing PD-L1, particularly for patients who have shown disease progression on or after platinum-containing chemotherapy .
- In conclusion, pembrolizumab has demonstrated significant efficacy and safety in treating NSCLC, particularly in patients with high PD-L1 expression, marking a substantial advancement in the management of this challenging malignancy.

Overview of Pembrolizumab for Lymphomas

- Lymphomas are heterogeneous malignancies with varying genetic mutations and microenvironments. In Hodgkin lymphoma, the neoplastic Reed Sternberg cells constitute less than 1% of the tumor, with the remaining tumor bulk made up of infiltrating immune cells, including T-cells and myeloid cells. The expression of PDL1 is a notable feature in many lymphomas, including Hodgkin lymphoma, where chromosome 9p24 amplification may lead to increased PDL1 and PDL2 expression .
- In a phase 1B study, pembrolizumab was administered to 10 patients with relapsed or refractory primary mediastinal B-cell lymphoma. The treatment involved 10 mg/kg every 2 weeks, with responses assessed after 12 weeks and then every 8 weeks. The study reported that 60% of patients experienced at least one adverse event (AE) .
- **Hodgkin Lymphoma Treatment**: A phase 2 study focused on 31 patients with relapsed or refractory classical Hodgkin lymphoma who had not responded to previous brentuximab vedotin therapy. These patients received pembrolizumab at the same dosage. The study found that the overall response rate (ORR) was 64%, with complete responses in 16% and partial responses in 48%. The most common AEs included hypothyroidism (16%), diarrhea (13%), and pneumonitis (10%) .
- **Safety in Allogeneic HSCT Recipients**: Pembrolizumab has been cautiously used in patients who have undergone allogeneic hematopoietic stem cell transplantation (HSCT). While initial trials excluded these patients due to concerns about graft versus host disease (GVHD), some cases have shown that pembrolizumab can be safely administered without exacerbating GVHD, although careful monitoring is essential .
- **Mechanism of Action**: Pembrolizumab is a humanized monoclonal IgG4 kappa anti-PD1 antibody that works by blocking the PD1 receptor, which is crucial for tumor cells to evade the immune response. This blockade enhances T-cell activation and anti-tumor immunity, making it an important therapeutic strategy for lymphomas .
- In summary, pembrolizumab has demonstrated significant efficacy and safety in treating various lymphomas, particularly Hodgkin lymphoma and B-cell lymphomas, with ongoing studies to further establish its role in these malignancies.

7.Survival Rates and Patient Response Data for Pembrolizumab (Keytruda)

- **Non-Small Cell Lung Cancer (NSCLC)**:
  - In the KEYNOTE-010 trial, patients with previously treated NSCLC showed significant improvements in overall survival (OS) when treated with pembrolizumab compared to docetaxel. The median OS was:
    - Pembrolizumab 2 mg/kg: 10.4 months
    - Pembrolizumab 10 mg/kg: 12.7 months
    - Docetaxel: 8.5 months
    - The differences were statistically significant ($p < 0.0001$) .
  - The median progression-free survival (PFS) was comparable across treatment groups, with:
    - Pembrolizumab 2 mg/kg: 3.9 months
    - Pembrolizumab 10 mg/kg: 4.0 months
    - Docetaxel: 4.0 months .

7.Survival Rates and Patient Response Data for Pembrolizumab (Keytruda)

- **Melanoma**:
  - In the KEYNOTE-006 trial, pembrolizumab demonstrated superior outcomes compared to ipilimumab. The estimated 12-month OS rates were:
    - Pembrolizumab 2-weekly: 74.1%
    - Pembrolizumab 3-weekly: 68.4%
    - Ipilimumab: 58.2%
    - These results indicate a significant survival advantage for pembrolizumab .
  - The estimated 6-month PFS was also higher in the pembrolizumab groups (47.3% and 46.4%) compared to ipilimumab (26.5%) .
- **Overall Response Rates (ORR)**:
  - In advanced melanoma, a pooled analysis of KEYNOTE-001 showed an ORR of 34%, with a complete response (CR) rate of 6% at a median follow-up of 14.8 months .
  - For NSCLC, the ORR was reported to be between 19-25%, indicating a notable response to pembrolizumab in this patient population .

8. **Combination Therapies and Their Impact in Pembrolizumab Treatment**

- Pembrolizumab (Keytruda) has been studied not only as a monotherapy but also in combination with other agents to enhance its efficacy in treating various malignancies. Here's a summary of the combination therapies and their impacts based on the provided contexts:
- **Combination with Chemotherapy**:
  - In the KEYNOTE 021 study, pembrolizumab was combined with platinum-based chemotherapy for patients with advanced non-small cell lung cancer (NSCLC). This combination aimed to improve overall response rates (ORR) and survival outcomes compared to chemotherapy alone .
- **Combination with Other Immunotherapies**:
  - The KEYNOTE 029 study explored the combination of pembrolizumab with the CTLA4 checkpoint inhibitor ipilimumab in advanced melanoma. This combination was particularly aimed at patients who had failed first-line anti-PD1 or anti-PDL1 therapy, potentially leading to improved outcomes in a challenging patient population .

8. Combination Therapies and Their Impact in Pembrolizumab Treatment

- **Targeted Therapy Combinations**:
  - In the KEYNOTE 022 study, melanoma patients with the BRAFV600 mutation were randomized to receive either a combination of dabrafenib and trametinib or the same combination plus pembrolizumab. This study aimed to assess whether adding pembrolizumab could enhance the efficacy of targeted therapies in this specific genetic context .
- **Combination with Other Novel Agents**:
  - The KEYNOTE 037 study investigated the use of pembrolizumab in combination with indoleamine 2,3-deoxygenase inhibitors (epacandostat and indoximod) across various malignancies. This approach aimed to leverage different immune pathways to improve patient responses .
- **Impact on Toxicity Management**:
  - The management of toxicities is crucial when combining therapies. For severe (grade 3) or life-threatening (grade 4) toxicities, cessation of therapy is recommended, highlighting the importance of monitoring patients closely when using combination therapies

9. Managing Side Effects and Toxicity

- **Immune-Related Adverse Events (AEs)**:
  - **Common AEs**: These include thyroid dysfunction, pneumonitis, hepatitis, and skin reactions. Fatigue is also reported in up to 20% of patients. Immune-related AEs can occur in any organ and may arise even after treatment cessation due to the prolonged immune response .
- **Management of Thyroid Dysfunction**:
  - **Hypothyroidism**: Regular monitoring of thyroid function is recommended, as hypothyroidism can be subtle with asymptomatic increases in thyroid-stimulating hormone (TSH) levels. Hormonal replacement therapy may be necessary for patients diagnosed with hypothyroidism .
- **Management of Pneumonitis**:
  - **Pneumonitis**: This serious AE can present as pulmonary infiltrates or severe pneumonia. Management depends on the severity:
    - **Grade 1**: Close clinical and radiologic monitoring is usually sufficient.
    - **Grade 2**: Treatment with corticosteroids is warranted.
    - **Grade 3 and 4**: High-dose corticosteroids are required, and treatment with pembrolizumab should be permanently discontinued .

9. Managing Side Effects and Toxicity

- **Management of Hepatitis**:
  - **Hepatitis**: Monitoring liver function tests is essential. If significant liver enzyme elevation occurs, corticosteroids may be indicated, and treatment with pembrolizumab may need to be paused or discontinued depending on severity **[1]**.
- **Skin Reactions**:
  - **Severe Skin Reactions**: These can be life-threatening and require immediate medical attention. Management may involve topical or systemic corticosteroids, depending on the severity of the reaction .
- **General Management Strategies**:
  - **Monitoring**: Regular monitoring for AEs is crucial, especially for patients receiving long-term treatment. This includes routine blood tests and clinical evaluations to detect any emerging toxicities early .
  - **Patient Education**: Educating patients about potential AEs and encouraging them to report any new symptoms promptly can facilitate early intervention and management.

10. **Patient Support and Monitoring in Pembrolizumab Treatment**

- **Regular Monitoring**:
  - **Thyroid Function**: Patients receiving pembrolizumab should have their thyroid function monitored regularly. This is important because hypothyroidism can develop subtly, often indicated by an increase in thyroid-stimulating hormone (TSH) levels before actual declines in thyroxine levels occur. Early detection allows for timely intervention, such as hormonal replacement therapy if needed .
- **Monitoring for Immune-Related AEs**:
  - **General Monitoring**: Patients should be monitored for a range of immune-related AEs, including fatigue, pneumonitis, hepatitis, and skin reactions. Fatigue is reported in up to 20% of patients, and specific management strategies may be required for endocrine AEs like hypothyroidism and diabetes mellitus, which typically do not necessitate discontinuation of pembrolizumab treatment .
  - **Severity Assessment**: For severe (grade 3) or life-threatening (grade 4) toxicities, treatment cessation is recommended. This includes any recurring severe toxicity or moderate toxicity that does not resolve with appropriate treatment within three months .
- **Patient Education and Support**:
  - **Informing Patients**: Educating patients about potential AEs and the importance of reporting new symptoms is vital. This proactive approach can facilitate early detection and management of any adverse effects, enhancing patient safety and treatment outcomes.
  - **Support Systems**: Establishing a support system, including access to healthcare professionals for questions and concerns, can help patients navigate their treatment journey more effectively.
- **Clinical Trials and Research**:
  - **Ongoing Studies**: Participation in clinical trials, such as those mentioned in the KEYNOTE studies, can provide patients with access to additional monitoring and support while contributing to the broader understanding of pembrolizumab's efficacy and safety in various malignancies .

Conclusion & Key Takeaways

- **Pembrolizumab**
- Pembrolizumab is a humanized anti-PD1 monoclonal antibody with no cytotoxic activity.
- Administered intravenously, it shows dose-proportional pharmacokinetics.
- Effective in various malignancies, including melanoma and NSCLC, with ongoing clinical trials.
- **Melanoma**
- Melanoma has a poor prognosis with conventional chemotherapy being ineffective.
- Activating mutations in the MAPK pathway are common in melanoma.
- Immune checkpoint blockade, particularly targeting CTLA4, has shown promise in treatment.
- **Pembrolizumab Monotherapy in Melanoma**
- Initial studies showed an overall response rate (ORR) of 38% in advanced melanoma.
- Responses were durable, with a significant percentage of patients remaining on treatment.
- Subsequent trials confirmed pembrolizumab's efficacy compared to chemotherapy.

Conclusion & Key Takeaways

- **Pembrolizumab in NSCLC**
- Pembrolizumab has shown significant efficacy in NSCLC, especially in PD-L1 positive tumors.
- The ORR and survival rates improved with higher PD-L1 expression levels.
- Pembrolizumab is FDA approved for metastatic NSCLC after platinum-based chemotherapy.
- **Molecular Landscape in NSCLC for Response to Pembrolizumab**
- High nonsynonymous mutation burden correlates with better response to pembrolizumab.
- Neo-antigen recognition is crucial for T-cell response and treatment efficacy.
- Smoking history does not predict response, but mutation patterns do.
- **Pembrolizumab in MMR Deficient Cancers**
- Pembrolizumab shows efficacy in MMR deficient colorectal and non-colorectal cancers.
- Higher mutation loads in tumors correlate with better treatment responses.
- **Pembrolizumab in Advanced Merkel-Cell Carcinoma**
- Pembrolizumab demonstrates activity in both MCPyV positive and negative tumors.
- The ORR was significant, with manageable adverse events reported.
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Conclusion & Key Takeaways

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- **Pembrolizumab in Lymphomas**
- Pembrolizumab shows promise in various lymphomas, particularly Hodgkin lymphoma.
- High ORR and manageable toxicity were observed in clinical trials.
- **Pembrolizumab in the Context of Allogeneic HSCT**
- Pembrolizumab may be safe for use in patients post-allogeneic HSCT with careful monitoring.
- No significant exacerbation of graft versus host disease (GVHD) reported.
- **Other Trials of Pembrolizumab as a Single Agent**
- Pembrolizumab shows variable efficacy across different cancers, with PDL1 expression as a key biomarker.
- Adverse events are common, but many patients experience durable responses.
- **Toxicities of Pembrolizumab**
- Immune-related adverse events are prevalent, with grade 3-4 occurring in up to 5% of patients.
- Late-onset immune-related AEs can occur even after treatment cessation.
- **Management of Toxicities**
- Regular monitoring for endocrine AEs is essential; specific treatments may be required.
- Prompt recognition and management of pneumonitis are crucial for patient safety.
- Ongoing studies are exploring combination therapies to enhance treatment efficacy.

THANK YOU