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Positive Quality Intervention: Tremelimumab-actl (Imjudo®) Patient Management

Description: This document will help to guide the management of patients on tremelimumab in various cancer types.

Background: Tremelimumab-actl is a CTLA-4 blocking antibody that is indicated in combination with durvalumab for adult patients with unresectable hepatocellular carcinoma (uHCC) and in combination with durvalumab and platinum-based chemotherapy for adult patients with metastatic non-small cell lung cancer (mNSCLC) with no EGFR or ALK mutations.[1] The Phase III, open-label, global HIMALAYA study evaluated durvalumab plus single priming high dose of tremelimumab-actl, durvalumab monotherapy, or sorafenib in patients with untreated uHCC. All treatments were given until disease progression or unacceptable toxicity. The median overall survival (OS) was 16.43 months (95% confidence interval [CI], 14.16-19.58) with durvalumab plus tremelimumab-actl, 16.56 months (95% CI, 14.06 to 19.12) with durvalumab, and 13.77 months (95% CI, 12.25-16.13) with sorafenib. OS at 36 months was 30.7%, 24.7%, and 20.2%, respectively. The OS hazard ratio (HR) for durvalumab plus tremelimumab-actl versus sorafenib was 0.78 (96.02% CI, 0.65-0.93). Overall survival with durvalumab monotherapy was non-inferior to sorafenib (HR, 0.86; 95.67% CI, 0.73-1.03). Median progression-free survival (PFS) was not significantly different among all three groups.[2] The open-label, phase III POSEIDON study evaluated tremelimumab-actl plus durvalumab and chemotherapy and durvalumab plus chemotherapy versus chemotherapy alone in first line mNSCLC. PFS was significantly improved with durvalumab plus chemotherapy versus chemotherapy alone (HR, 0.74; 95% CI, 0.62-0.89). A trend for improved OS did not reach statistical significance (HR, 0.86; 95% CI, 0.72-1.02; median, 13.3 v 11.7 months; 24-month OS, 29.6% v 22.1%). Tremelimumab-actl plus durvalumab showed significant improvements in PFS compared to chemotherapy alone (HR, 0.72; 95% CI, 0.60-0.86; median, 6.2 v 4.8 months) and OS (HR, 0.77; 95% CI, 0.65 to 0.92; P 5 .0030; median, 14.0 v 11.7 months; 24-month OS, 32.9% v 22.1%).[3]

PQI Process: Upon order of Tremelimumab-actl[1]

- Dosing
  - Hepatocellular Carcinoma (unresectable) in combination with durvalumab
    - 30 kg or more: Tremelimumab-actl 300 mg as a single dose followed by durvalumab 1500 mg on cycle 1 day 1, then durvalumab 1500 mg as a single agent every 4 weeks
    - <30 kg: Tremelimumab-actl 4 mg/kg as a single dose followed by durvalumab 20 mg/kg on cycle 1 day 1, then durvalumab 20 mg/kg as a single agent every 4 weeks
  - Non-small cell lung cancer (metastatic, no EGFR or ALK mutations) in combination with durvalumab and platinum-based chemotherapy
    - See Durvalumab (Imfinzi®) Therapy Overview PQI for durvalumab management

Tumor Histology	Weight	Tremelimumab-actl Dose (max 5 doses)	Durvalumab Dose	Platinum-based Chemotherapy Regimen
Non-Squamous	≥ 30 kg	75 mg	1500 mg	Carboplatin & nab-paclitaxel OR carboplatin or cisplatin & pemetrexed
	< 30 kg	1 mg/kg	20 mg/kg	
Squamous	≥ 30 kg	75 mg	1500 mg	Carboplatin & nab-paclitaxel OR carboplatin or cisplatin & gemcitabine
	< 30 kg	1 mg/kg	20 mg/kg	

See Supplemental Information for recommended dosage modifications for adverse reactions

	Week[b]																							
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Cycle:	1			2			3			4			5				6				7				8
Tremelimumab-actl[c]	X			X			X			X							X								
Durvalumab[a]	X			X			X			X			X				X				X				X
Chemotherapy	X			X			X			X			X[d]				X[d]				X[d]				X[d]

a. Continue durvalumab until disease progression or intolerable toxicity
b. Dosing internal change from every 3 weeks to every 4 weeks starting at cycle 5
c. If less than 4 cycles of platinum-based chemotherapy is received, the remaining tremelimumab-actl should be given in conjunction with durvalumab every 4 weeks
d. Optional pemetrexed may be given from week 12 until disease progression or intolerable toxicity

- Monitor ACTH, creatinine, glucose, hepatic enzymes, and thyroid function at baseline and prior to each dose
- Tremelimumab-actl comes in 25 mg/1.25 mL and 300 mg/15 mL single-dose vials (both are 20 mg/mL)
- Withdraw the necessary volume from the vials and transfer to a sterile intravenous bag of 0.9% Sodium Chloride or 5% Dextrose; gently inverting diluted solution to ensure proper mixing, do not shake vials or diluted solution
    - Final diluted concentration should be between 0.1 and 10 mg/mL
    - Maximum diluent volume for 300 mg dose is 150 mL, for 4 mg/mL dosing the maximum diluent volume is 80 mL[4]
    - After preparation can be stored for up to 24 hours in room temperature or under refrigeration
- Infuse tremelimumab-actl intravenously through a low protein binding 0.2 to 0.22-micron filter over 60 minutes, do not administer other drugs through attached infusion lines
- Durvalumab with tremelimumab-actl: Infuse tremelimumab-actl first over 60 minutes, observe patient for at least 60 minutes, then administer durvalumab over 60 minutes on the same day
- Durvalumab and tremelimumab-actl with platinum-based chemotherapy/pemetrexed: Infuse tremelimumab-actl first over 60 minutes, observe patient for at least 60 minutes (cycle 1), then administer durvalumab over 60 minutes; if no infusion reactions occurred during the Cycle 1 then durvalumab can be infused immediately after the temelimumab-actl, with a 30-minute wait between the durvalumab and starting the platinum-based chemotherapy
- Common adverse effects (AEs) (all grades) are itching (23%), abdominal pain (20%), decreased appetite (17-28%), diarrhea (22-27%), nausea (12-42%), rash (27-32%), hypothyroidism (13-14%), and infusion reaction (2.6-2.9%)
    - Permanent discontinuation of tremelimumab-actl due to AE occurred in 14% of patients with hepatocellular carcinoma and 17% of patients with NSCLC
    - Use of irAE Assessment Tool for immune-related adverse events

Patient-Centered Activities:

- Provide Intravenous Cancer Treatment Education (IVE) Sheet
- Educate patient on common AEs and when to contact the care team
- Females of reproductive potential should use effective method of birth control during treatment and 3 months after the last dose
- Additional Imjudo® Resources are available
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Imjudo (tremelimumab-actl) Prescribing Information.
2. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. *NEJM Evidence*. 2022;1(8). doi:https://doi.org/10.1056/evidoa2100070.
3. Johnson M, Byoung, Cho C, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. *J Clin Oncol*. 41:1213-1227. doi:https://doi.org/10.1200/JCO.22.
4. Imfinzi Imjudo Hepatocellular Carcinoma Dosing. Imfinzi Imjudo. Accessed April 2024. https://www.imfinzihcp.com/hepatocellular-carcinoma/dosing.html.

Supplemental Information:
Dose Modification for Adverse Reactions

Adverse Reaction	Severity	Dose Modification
Pneumonitis	Grade 2	Hold until Grade 1 or 0 after corticosteroid taper; discontinue if not resolved within 12 weeks of initiating steroids or unable to 10 mg prednisone or less (or equivalent)
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2	Hold until Grade 1 or 0 after corticosteroid taper; discontinue if not resolved within 12 weeks of initiating steroids or unable to 10 mg prednisone or less (or equivalent)
	Grade 3 or 4	Permanently discontinue
Intestinal perforation	Any Grade	Permanently discontinue
Hepatitis with no tumor involvement of the liver	ALT or AST increases to more than 3 and up to 8 times the ULN or total bilirubin increases to more than 1.5 and up to 3 times ULN	Hold until Grade 1 or 0 after corticosteroid taper; discontinue if not resolved within 12 weeks of initiating steroids or unable to 10 mg prednisone or less (or equivalent)
	ALT or AST increases to more than 8 times ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver*	AST or ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times ULN or AST or ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times ULN	Hold until Grade 1 or 0 after corticosteroid taper; discontinue if not resolved within 12 weeks of initiating steroids or unable to 10 mg prednisone or less (or equivalent)
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Hold until clinically stable or permanently discontinue depending on severity
Nephritis with renal disfunction	Grade 2 or 3 increased blood creatinine	Hold until Grade 1 or 0 after corticosteroid taper; discontinue if not resolved within 12 weeks of initiating steroids or unable to 10 mg prednisone or less (or equivalent)
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Hold until Grade 1 or 0 after corticosteroid taper; discontinue if not resolved within 12 weeks of initiating steroids or unable to 10 mg prednisone or less (or equivalent)
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2-4	Permanently discontinue
Neurological Toxicities	Grade 2	Hold until Grade 1 or 0 after corticosteroid taper; discontinue if not resolved within 12 weeks of initiating steroids or unable to 10 mg prednisone or less (or equivalent)
	Grade 3 or 4	Permanently discontinue
Infusion related reactions	Grade 1 or 2	Interrupt or slow rate of infusion
	Grade 3 or 4	Permanently discontinue

* If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement