Cancer Research Consortium of West Michigan
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FAST FACTS

EA3161 - A Phase II/III Randomized Study of Maintenance Nivolumab versus Observation in Patients with Locally Advanced, Intermediate Risk HPV Positive OPCA

Eligibility Criteria for Step 1 Randomization

1. Age ≥ 18 years
2. ECOG performance status of 0 or 1.
3. Patients must have oropharynx cancer (AJCC 8) that is p16-positive by immunohistochemistry OR p16 equivocal by IHC and HPV positive by in situ hybridization with the following criteria:
   ≥10 pack-years, stage T1-2N2-N3 or T3-4N0-3 (less than 10 pack-years is considered a non-smoker)
   OR
   <10 pack-years, stage T4N0-N3 or T1-3N2-3.
4. Patients must not have known hypersensitivity to nivolumab or compounds of similar chemical or biologic composition.
5. Patients with a history of allergic reactions attributed to platinumbased chemotherapy agents are excluded.
6. Patients must not have had prior systemic therapy, radiation treatment or surgery for p16 positive OPSCC.
   a. NOTE: Patients who had resection of T1 or T2 carcinoma with no radiation or chemotherapy are eligible if surgery was done 5 years prior to enrollment
7. Patients must not have received previous irradiation for head and neck tumor, skull base, or brain tumors.
8. Patients must not receive investigational agents within 4 weeks of enrollment or at any time while on study.
9. Patients with evidence of distant metastases or leptomeningeal disease (LMD) are excluded.
10. Patients with uncontrolled inter-current illnesses which in the opinion of the investigator will interfere with the ability to undergo therapy including chemotherapy are excluded.
11. Patients with a history of prior or second malignancy are excluded, with the exception of curatively treated non-melanoma skin cancer, or curatively treated cervical cancer; additionally, patients curatively treated for malignancy who remain free at >2 years of follow up, are not excluded.
12. Baseline organ and marrow parameters (must be obtained ≤ 2 weeks prior to randomization).
    • ANC ≥ 1500/mm3 ANC: _____Date of test: _____
    • Hgb ≥ 8.0 g/dL Hgb: _____Date of test: _____
    • Platelet count ≥ 100,000/mm3
    Platelet count: _____ Date of test: _____
    • Creatinine clearance of ≥ 60 ml/min.
    Creatinine: _____Date of test: _____
    Creatinine clearance may be measured or calculated. If calculating, creatinine clearance, use the Cockroft-Gault formula: (140 – Pt. age) x (Pt. weight in kg)/(72 x patient's serum creatinine) (for females, multiply the result by 0.85)
    Actual, not ideal, body weight will be used.
13. Baseline liver function parameters (must be obtained ≤ 2 weeks prior to randomization):
    • Total bilirubin within 1.5 times the normal limits
    ULN: _____ Total Bilirubin: _____ Date of test: _____
    • SGOT (AST) or SGPT (ALT) within 2.0 times the normal limits

AND Alkaline Phosphatase within 1.5 times the normal limits
ULN: _____ AST/ALT: _____ Date of test: _____
ULN: _____ Alk Phos: _____ Date of test: _____

14. Patients must not be pregnant or breast-feeding as chemotherapy, radiation, and immunotherapy may have possible teratogenicity effects; in addition, complications from pregnancy may interfere with the ability of patients to have an uninterrupted therapy. All women of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy. A patient of childbearing potential is any patient, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
    Patient of child bearing potential? _____ (Yes or No)
    Date of blood test or urine study: _____
15. Patients of childbearing potential must use an accepted and effective method of contraception or abstain from sexual intercourse for at least one week prior to the start of treatment, and continue for 5 months after the last dose of protocol treatment. Patients must also not donate ova during this same time period.
16. Patients must have measurable disease as defined in Section 6.1.
17. Patients must have tumor measurements with CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) within 4 weeks prior to Step 1 randomization.
18. Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue disease, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjogren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.
19. Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).
20. Patients must not have a condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone equivalents) or other immunosuppressive medications which are expected to continue during Nivolumab administration. Inhaled or topical steroids and adrenal replacement doses >10 mg/day prednisone equivalents are permitted in the absence of active autoimmune disease.
21. Patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undectable on suppressive therapy, if indicated.
22. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

23. Patients with a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) must have no detectable viral load on a stable antiviral regimen.
24. Patients must not be receiving any other investigational agents.
25. Patient must not have a baseline clinically significant hearing loss, which in the opinion of the investigator would preclude the use of cisplatin.

Eligibility Criteria for Step 2 Registration

1. Patients must have progression per RECIST criteria AND tissueproven progression on Arm B treatment within 12 months after completion of radiation therapy.
2. ECOG performance status of 0 or 1.
3. Patients must not have known hypersensitivity to nivolumab or compounds of similar chemical or biologic composition.
4. Patients must not have received non-protocol anti-cancer therapy after completion of radiation and chemotherapy.
5. Baseline organ and marrow parameters (must be obtained ≤ 2 weeks prior to registration).
   • ANC ≥ 1500/mm3 ANC: _____Date of test: _____
   • Hgb ≥ 8.0 g/dL Hgb: _____Date of test: _____
   • Platelet count ≥ 100,000/mm3
   Platelet count: _____ Date of test: _____
   • Creatinine within institutional limits of normal.
   Creatinine: _____Date of test: _____

6. Baseline liver function parameters (must be obtained ≤ 2 weeks prior to registration):
   • Total bilirubin within 1.5 times the normal limits
   ULN: _____ Total Bilirubin: _____ Date of test: _____
   • SGOT (AST) or SGPT (ALT) within 2.0 times the normal limits
   AND Alkaline Phosphatase within 1.5 times the normal limits
   ULN: _____ AST/ALT: _____ Date of test: _____
   ULN: _____ Alk Phos: _____ Date of test: _____
7. Patients must not be pregnant or breast-feeding as chemotherapy, radiation, and immunotherapy may have possible teratogenicity effects; in addition, complications from pregnancy may interfere with the ability of patients to have an uninterrupted therapy.
   All patients of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.
   A patient of childbearing potential is any patient, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
   Patient of child bearing potential? _____ (Yes or No)
   Date of blood test or urine study: _____
8. Patients of childbearing potential must use an accepted and effective method of contraception or abstain from sexual intercourse for at least one week prior to the start of treatment, and continue for 5 months after the last dose of protocol treatment. Patients must also not donate ova during this same time period.
9. Patients must have measurable disease as defined in Section 6.1 at the time of documented progression.
   a. NOTE: For patients that have undergone salvage surgery for disease recurrence, measurable disease is not required at the time of registration to Step 2.

10. Patients must have tumor measurements with CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) within 4 weeks prior to Step 2 registration.
    a. NOTE: Patients that have undergone salvage surgery for disease recurrence prior to step 2 are not required to have measurable disease post-resection, but must have CT of neck and CT of chest (or CT of neck and FDG PET/CT if standard of care) after salvage surgery and within 4 weeks prior to step 2 registration to establish a baseline prior to Nivolumab.

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