Antitumor activity and safety of pembrolizumab in patients with PD-L1-positive nasopharyngeal carcinoma: Interim results from a phase 1b study (Presentation 3150)

Head & Neck invited discussion, Saturday, 18 December 2015 – 14:30-15:40

Discussant Brigette B.Y. Ma

Professor, Department of Clinical Oncology
Medical Director (Oncology), Phase 1 Clinical Trial Centre
Prince of Wales Hospital, Hong Kong
Chinese University of Hong Kong
Disclosure slide

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The ‘A to Z guide’ to reported NPC drug trials in the literature

- Azacitadine
- Axitinib
- Bevacizumab
- Bortezomib
- Bleomycin
- Cetuximab
- Carboplatin
- Capecitabine
- Cyclophosphamide
- Docetaxel
- Doxorubicin
- Epirubicin
- Etoposide
- Erlotinib
- 5Fluorouracil
- Gefitinib
- Gemcitabine
- Hydroxyurea
- Ifosfamide
- Irinotecan
- Methotrexate
- Mitomycin C
- MK-2206
- Mitoxantrone
- Nedaplatin
- Oxaliplatin
- Pembrolizumab (PD-1 inhibitor)
- Pazopanib
- Paclitaxel
- Pemetrexed
- Sorafenib
- Sunitinib
- Temozolomide
- T-cell therapy
- Vaccines
- Vinorelbine
Another Star on the Walk of Fame?

Winner
(drug registration for NPC)
Q1: PD-1 as therapeutic target in EBV+ve NPC?

- PD-L1 is upregulated in EBV+ve NPC: (Unpublished data, Prof KW Lo, CUHK)
- Prognostic significance of PD-L1 expression in advanced NPC = conflicting. Our data in expanded cohort (unpublished) did not suggest this.

Figure 1 (unpublished confidential data, Prof KW Lo, CUHK)

EBV infection upregulates PD-L1 in vitro

- LMP-1 upregulates PD-L1 via STAT3, MAPKs/AP-1, NF-κB in vitro
- PD-L1 expression was upregulated after IFN-γ

Fang 2014 Oncotarget;5(23):12189-202
Q2: Are the patients similar to the ones in NPC endemic areas?

- **Heterogeneous** group of patients:
  1) ‘Advanced (unresectable and/or metastatic) solid tumor, failure of prior therapy...PD-L1 +ve in >1% tumor or stromal cells’ - ? Proportion of M1 versus locoregionally recurrent disease.
  2) 33% had 5 or more lines of prior therapy. But 2 patients had ‘0’ line of prior therapy - ? Why
  3) Patients: 37% (n=8) non-Asians
  4) 22% WHO type 1 NPC – keratinizing, not usually associated with EBV (Endemic area: Predominantly non-keratinizing NPC, EBV is ubiquitous)
Q2: How much ‘early signal’ is meaningful enough for this NPC population to warrant further development?

- Primary endpoint: ORR (RECIST) - **25.9%** (95% CI, 11.1-46.3).
- Grade 5: 1 sepsis. Grade 3-4: pneumonitis, hepatitis (? Hepatitis B carrier)
- **Median response duration: 10.8 months** (range 4.8-10.8). PFS at 12 months 28.9%
- Responses seen also in WHO type 1 NPC.
- Pseudoprogression: Problem of tumor swelling for patients with base-of-skull disease with temporal lobe/ carotid invasion?
What’s the ballpark figure for response and duration for monotherapy in phase II studies of multiply treated metastatic or recurrent NPC?

This is not intended to be a direct cross trial comparison......
Phase II Axitinib alone in previously treated NPC

- Interim result of 34 evaluable Chinese patients
- > 90% M1 disease
- 100% undifferentiated NPC
- Mean/ Median: 3 prior line of chemo. No naïve patients.
- ORR (RECIST) – 20.5% (34 evaluable pts).
- Median time to progression: 5.1 months (95% CI 3.9 – 5.9m)
- OS at 12 months: 43.5%
- Grade 3 toxicity < 5%, no Grade 4/5

How about chemo?

Edwin Hui, B Ma, … TC Chan ASCO J Clin Oncol 33, 2015 (suppl; abstr 6031)
Capecitabine, gemcitabine monotherapy

- Capecitabine monotherapy (Chua 2008)
  - N = 49. Median 4 prior line of chemo
  - 71% had metastatic disease
  - ORR: 37% (95% CI: 23 - 50%)
  - Median time to progression = 5 months
  - PFS 1 yr = 9%

- Gemcitabine monotherapy (Foo 2008)
  - N = 27, previously treated, 78% 1 prior line
  - ORR: 48%
  - Median time to progression = 5.1 months (95% CI: 0.9 – 13.1)
  - Median response duration = 4.25 months, ORR 34%

- Pembrolizumab
  - Median duration of response = 10 m
  - PFS 1 yr = 28.9%, while most would expect TTP around 5 months with monotherapy in this setting....

Chua et al Jpn J Clin Oncol 38 (4):244-249
Ma B et al 2002 Cancer 95 (12):2516-2523.
Q4: Should we further develop this as monotherapy or combination?

- PD-1 inhibition can shrink tumors – probably just like some other agents. The main ‘added value’ = durability of response.

- Preclinical data: immunological basis for activity of chemo, VEGFR-TKI (e.g. Axitinib in rodent melanoma model, Sorafenib in HCC), and PD-1 inhibition may augment response to peptide-induced cytotoxic T-cells, cisplatin.

- Mono or combo? Multiple factors, depends on:
  1) Science
  2) Clinical setting and unmet need:
     - In treatment-naïve: since ‘standard therapy’ is already quite effective, thus combo with ‘standard’ therapy in phase III study using survival as endpoint = favored.
     - In palliation of refractory cases, monotherapy/ combo are feasible, tolerability is the key.
  3) Economics: in countries with heavy government subsidized public healthcare - e.g. combo of two targeted therapy $$$
Q3: Should we select subjects based on tumoral PD-L1 expression?

- My bias = No, at this stage
- Predictive-ness could be tumor-type dependent. Optimal ‘threshold’ has not been determined for NPC, need more data.
- Lack of standardized kit
- PD-L1 expression is dynamic, inducible by changes in microenvironment
- Other factors: Mutational load? T-cell function? Interferon gene expression / plasma cytokine level?
What’s on the horizon?
International Phase II study of Nivolumab in NPC
(Chair: B Ma, CUHK. NCI-CTEP solicitation, CTRG study. US-FDA approved protocol – now open for enrollment)

Eligibility

Metastatic or recurrent non-keratinizing NPC
Any prior line of chemo
No prior PD-L1 therapy

Design

Primary: RR
Secondary: immune-related response, PFS, OS, duration, pEBV DNA clearance, fMRI, tumor PD-L1 expression, immune markers

Plan

1st stage: n = 20, if >= 2 responses, Stage II max 45 pt. 90% to detect ORR 20%

Nivolumab 3mg/kg IV q2W

Until PD or intolerance

https://clinicaltrials.gov/ct2/show/NCT02339558
Safety and Efficacy Study of PDR001 in Patients With Recurrent or Metastatic NPC (industry)

**Eligibility**
- Metastatic or recurrent non-keratinizing NPC
- One line of chemo

**Randomized phase II**
- Physician’s choice comparator chemo
- PDR001

**Plan**
- Primary: PFS.
- Secondary: ORR, duration, OS, duration, plasma biomarkers
- Until PD or intolerance

https://clinicaltrials.gov/ct2/show/NCT02339558
Summary

• Pembrolizumab’s early signal is very promising
• Some grade 4-5 toxicities (immune) encountered – need to find out who could be at risk
• Need confirmatory phase II studies in a more homogeneous population (ethnicity, prior lines, EBV-associated non-keratinizing NPC). This also allows opportunity to study predictive biomarkers that may help to design phase III registrational study
• Need to find out mechanism of resistance to PD-1 inhibitor: immune-monitoring during therapy.
• There has never been a drug registered for advanced NPC – let’s hope this may change soon!