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

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SINGAPORE 2015 ESMO ASIA 18-21 DECEMBER SINGAPORE

Disclosure slide

- Grants/research support: Novartis, Merck Serono
- Honoraria or consultation fees: Novartis, Merck Serono

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

- Azacitadine
- Axitinib
- Bevacizumab
- Bortezomib
- Bleomycin
- Cetuximab
- Cisplatin
- 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 ?

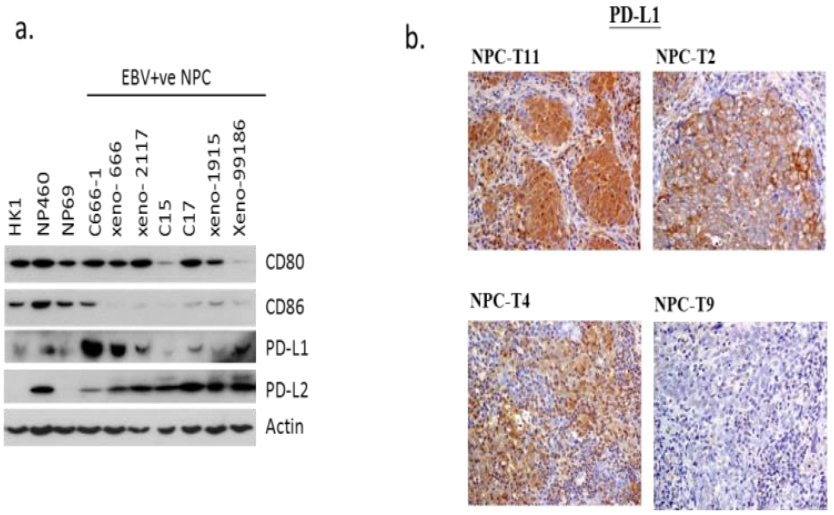
Winner

(drug registration for NPC}

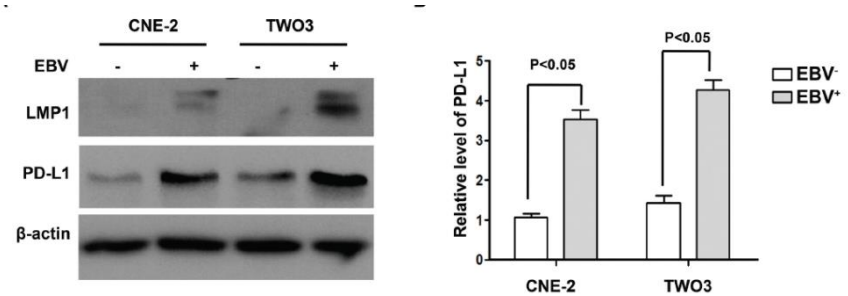
Q1: PD-1 as therapeutic target in EBV+ve NPC ?

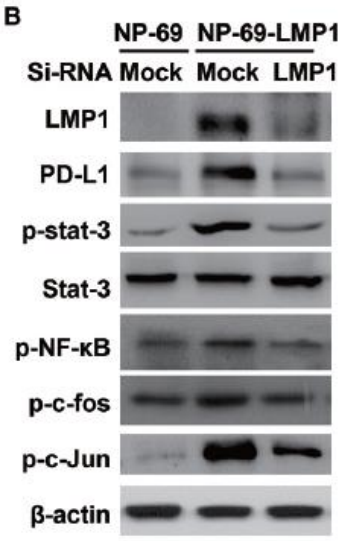
- **PD-L1 is upregulated in EBV+ve NPC**: (*Unpublished data, Prof KW Lo, CUHK*)
- **Prognostic significance of PD-L1 expression in advanced NPC = conflicting**. *Our data in expanded cohort (unpublished) did not suggest this.*

Figure 1 (unpublished confidential data, Prof KW Lo, CUHK)



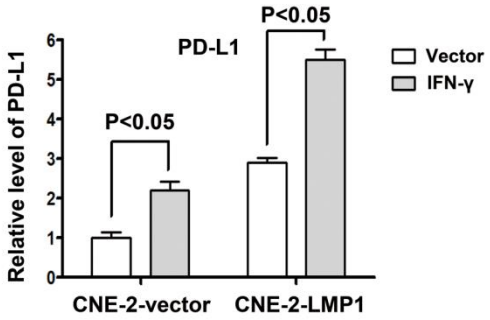
- **EBV infection upregulates PD-L1 in vitro**





← **LMP-1 upregulates PD-L1 via STAT3, MAPKs/AP-1, NF-κB in vitro**

PD-L1 expression was up-regulated after IFN-γ



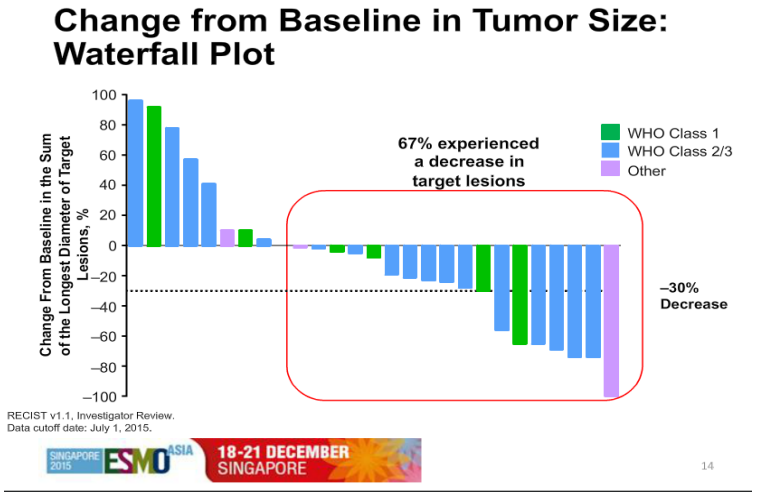
Fang 2014 Oncotarget;5(23):12189-202

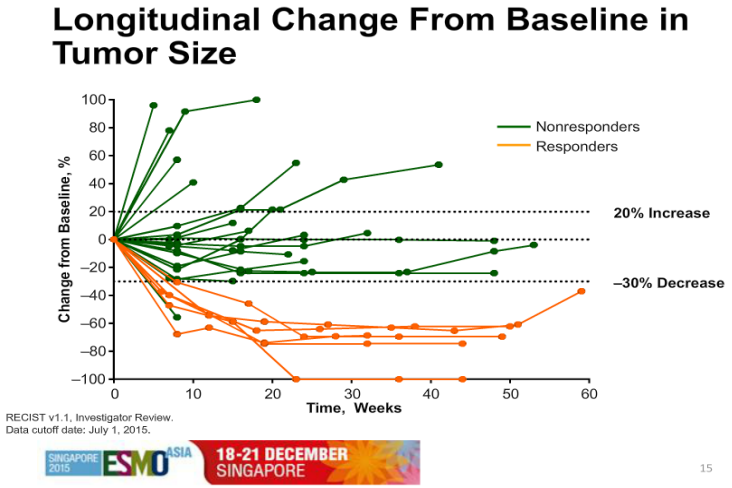
Q2: Are the patients similar to the ones in NPC endemic areas ?

- **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 ?





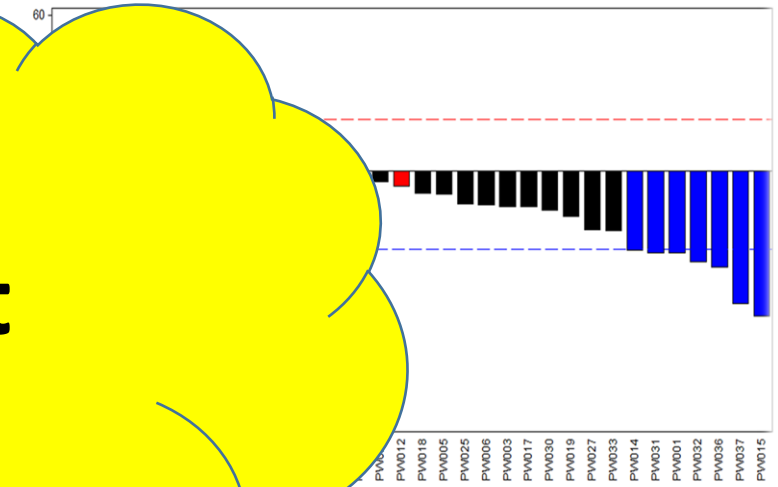
What's the ballpark figure for response and duration for monotherapy in phase II studies of multiply treated metastatic or recurrent NPC ?

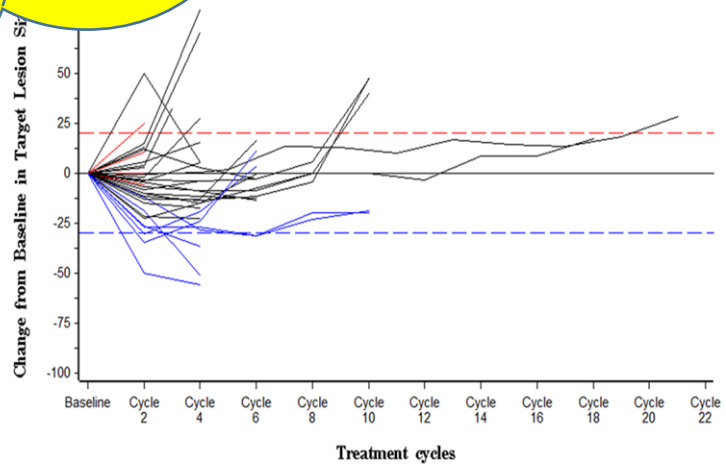
This is not intended to be a direct cross trial comparison……

Phase II Axitinib alone in previously treated NPC

- Interim result of 3
- > 90% M1 diseas
- 100% undiffe
- Mean/ Me
  patients.
- ORR (RECIST)
- Median tim
  5.9m)
- OS at 12 months: 43.
- Grade 3 toxicity ≤ 5%, no Grade 4/5

How about chemo ?





Edwin Hui, B Ma, …TC an ASCO J Clin Oncol 33, 2015 (suppl; abstr 6031)

Capecitabine, gemcitabine monotherapy

- Capecitabine mono… (Chua 2008)
- N = 49. Media…
- 71% had…
- ORR: **37%**
- Median ti… **5** months
- PFS 1 yr = **9%**

…py (Foo …% 1 chemo …tion **4.25** …y (Ma 2002)

Pembro – median duration of response 10 m, PFS 1yr = 28.9%, while most would expect TTP around 5 months with monotherapy in this setting….

Chua et al Jpn J Cli… …ol 38 (4):244-249

Foo et al 2002 Ann Oncol 13 (1):150-156
Ma B et al 2002 Cancer 95 (12):2516-2523.

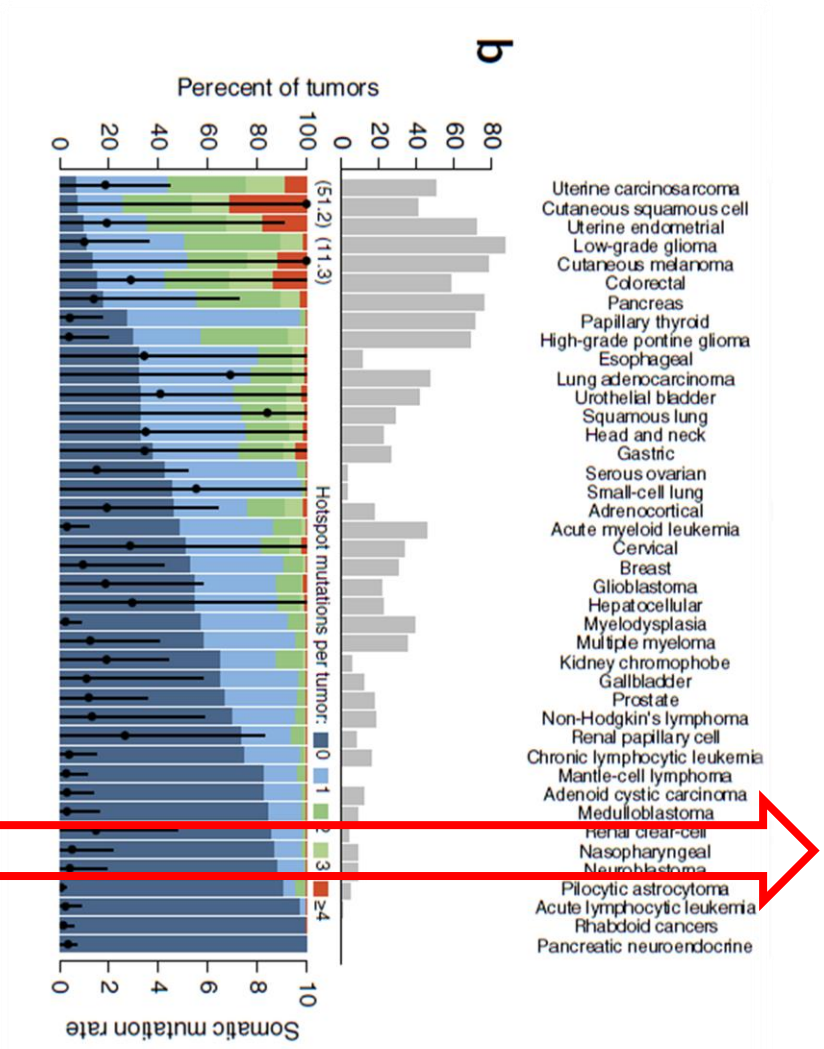
Q4: Should we further develop this as monotherapy or combination ?

- 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 $$$

Oncoimmunology. 2015 Jan 22;4(4)
Hepatology. 2015 May;61(5):1591-602
Int J Oncol. 2015 Jan;46(1):28-36.
PLoS One. 2013 Dec 19;8(12):e84927

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 ?



Chang 2015, Nature biotech, November


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)

TITLE: Multicenter Phase II Study of Nivolumab in Previously Treated Patients with Recurrent and Metastatic Nasopharyngeal Carcinoma

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P2C-MN026 / Mayo Clinic Cancer Center P2C
P2C-TX035 / University of Texas M D Anderson Cancer Center P2C
P2C-CA189 / University of California Davis Comprehensive Cancer Center P2C
P2C-FL065 / H Lee Moffitt Cancer Center P2C
P2C-IL057 / University of Chicago Comprehensive Cancer Center P2C
P2C-OH007 / Ohio State University Comprehensive Cancer Center P2C

Statistician:
Nathan R. Foster
Mayo Clinic Cancer Center
Telephone: 507-284-5051
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Document history:
NCI initial submission: 12/8/2014
Consensus Review Reply:

NCI-Supplied Agent: Nivolumab (BMS-936558, MDX-1106, and ONO-4538) (NSC #748726)

IND #: TBD

Eligibility	Design	Plan
Metastatic or recurrent non-keratinizing NPC Any prior line of chemo No prior PD-L1 therapy	Primary: RR Secondary: immune-related response, PFS, OS, duration, pEBV DNA clearance, fMRI, tumor PD-L1 expression, immune markers	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

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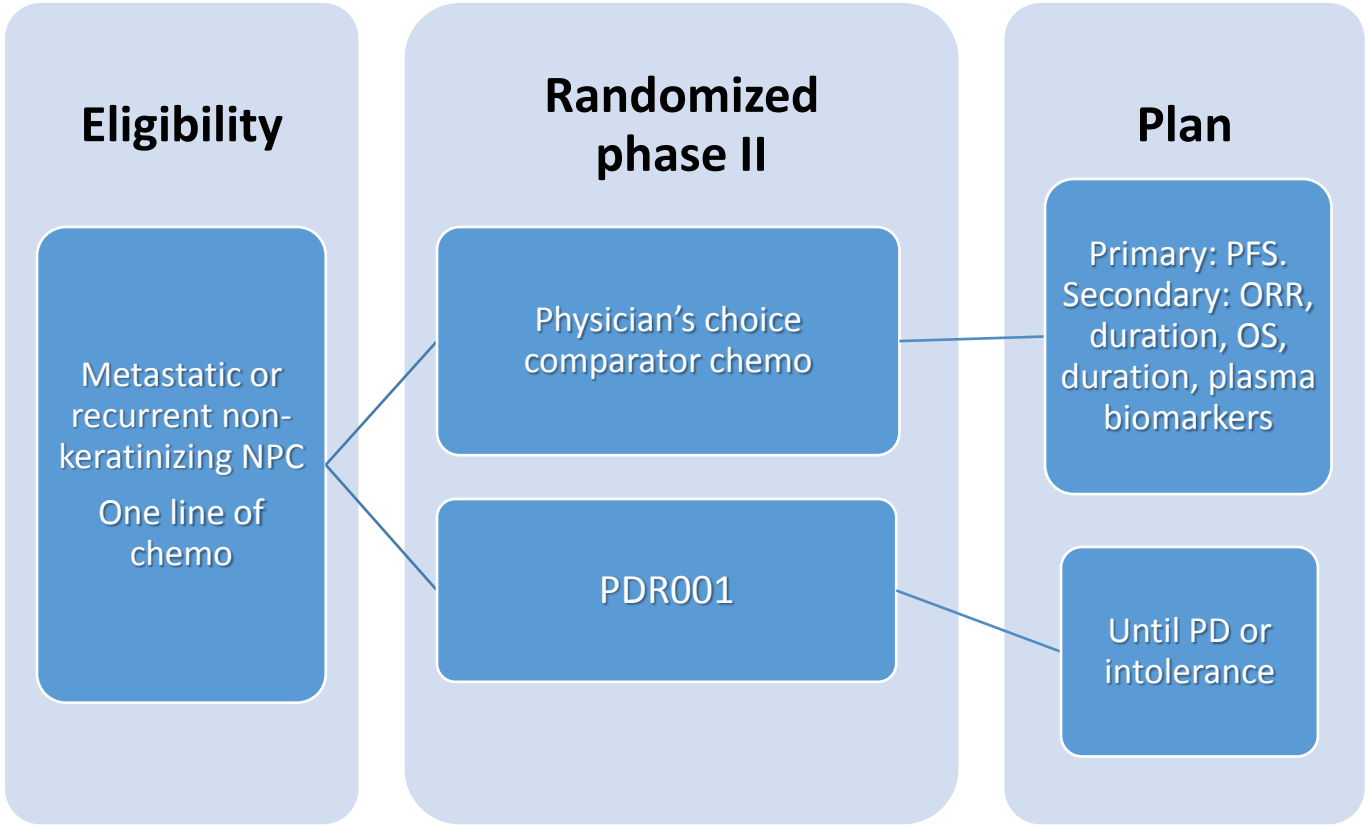
https://clinicaltrials.gov/ct2/show/NCT02339558

Safety and Efficacy Study of PDR001 in Patients With Recurrent or Metastatic NPC (industry)



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 !