Phase I and dose ranging, phase II studies with IPH2201, a humanized monoclonal antibody targeting HLA-E receptor CD94/NKG2A

Lesley Seymour MD PhD
Director, Investigational New Drug Program
NCIC Clinical Trials Group, Kingston
Professor of Oncology, Queens University

NCIC CTG : drug and some funding to support a planned study

I have no other conflicts to declare

10:45 - 12:45
Plenary session 2
New frontiers in immunotherapy (1): Checkpoint targets

Chairs: ***Alexander Eggermont****, Villejuif, France &* ***Alex A. Adjei****, Buffalo, NY, USA*

10:45 - 11:05 (O2.1) Educational overview and recent CTLA4, PD1, and PD-L1 data
Alexander Eggermont*, Cancer Institute Gustave Roussy, Univerite Paris-Sud, Villejuif/Paris-Sud, France*

11:05 - 11:25 (O2.2) PDL1 blockade in metastatic bladder cancer
Thomas Powles*, Barts Cancer Institute, London, UK*

11:25 - 11:45 (O2.3) Combined CTLA4 and PD-1 pathway blockade for treatment of advanced cancer
Mario Sznol*, Yale University, New Haven, CT, USA*

11:45 - 12:05 (O2.4) Deconstructing the complexity of human tumor immunology
Priti Hegde*, Genentech, South San Francisco, CA, USA*

12:05 - 12:25 (O2.5) Novel immunostimulatory antibodies: What's next?
Aurelien Marabelle*, Léon Bérard Cancer Center, Lyon, France*

12:25 - 12:45 General discussion
All presentations of this session

Plenary session 8
New frontiers in immunotherapy (2): New targets and agents beyond checkpoint inhibition

Chairs: ***Giorgio Trinchieri****, Frederick, MD, USA &* ***Lillian Siu****, Toronto, ON, Canada*

16:20 - 16:40 (O8.1) Signaling pathways that underlie T-cell co-stimulation and co-inhibition for cancer immunotherapy
Ignacio Melero*, Universidad de Navarra, Pamplona, Spain*

16:40 - 17:00 (O8.2) Putting adoptive T cell therapy on the path to regulatory approval
Antoni Ribas*, UCLA's Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA*

17:00 - 17:20 (O8.3) Targeting tumor-associated macrophages in cancer patients
Dominik Ruettinger*, Hoffmann-La Roche, Penzberg, Germany*

17:20 - 17:40 (O8.4) Immunoscore: a prognostic and predictive tool
Jerome Galon*, Laboratory of Integrative Cancer Immunology, INSERM UMRS1138, Cordeliers Research Center, Paris, France*

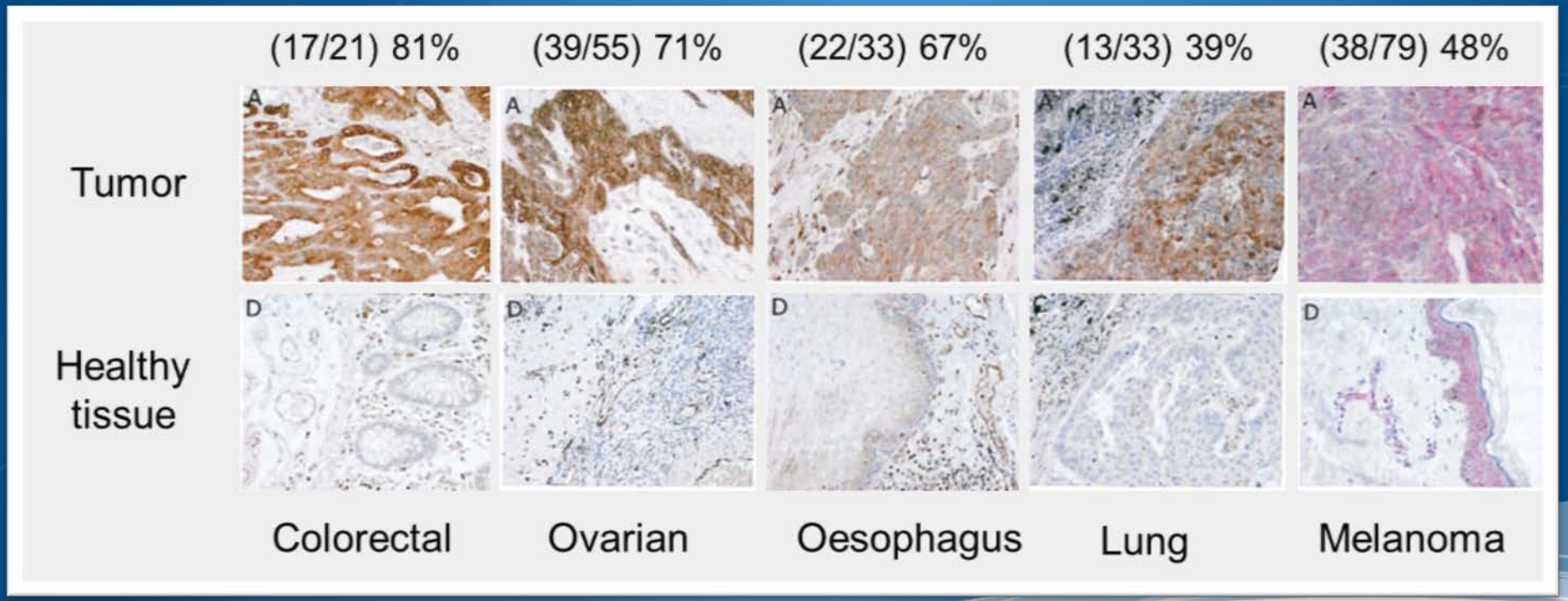
17:40 - 18:00 General discussion
All presentations of this session

"Breaking Tolerance": Inhibiting Immune Inhibition – Novel Targets

- CD94/NKG2A is a heterodimer complex between CD94 and NKG2A (natural killer group 2 member A)
  - Peripheral and tumour infiltrating NK cells
  - Cytotoxic T cells
- NK cells - major ligands are MHC 1
  - Always at least one inhibitory receptor
    - CD94/NKG2A - ligand HLA-E
    - KIR2DL – HLA-C
    - KIR3DL – HLA-B or A3
  - Activating
    - CD94/NKG2C – HLA-E
    - KIR2DS – HLA-C
    - KIR3DS – HLA-Bw4

HLA-E

- Non classical major histocompatibility complex class I molecule
- Expressed on cell surface of most leukocytes and large variety of transformed cells



HLA-E expression prognostic in gynecologic tumours

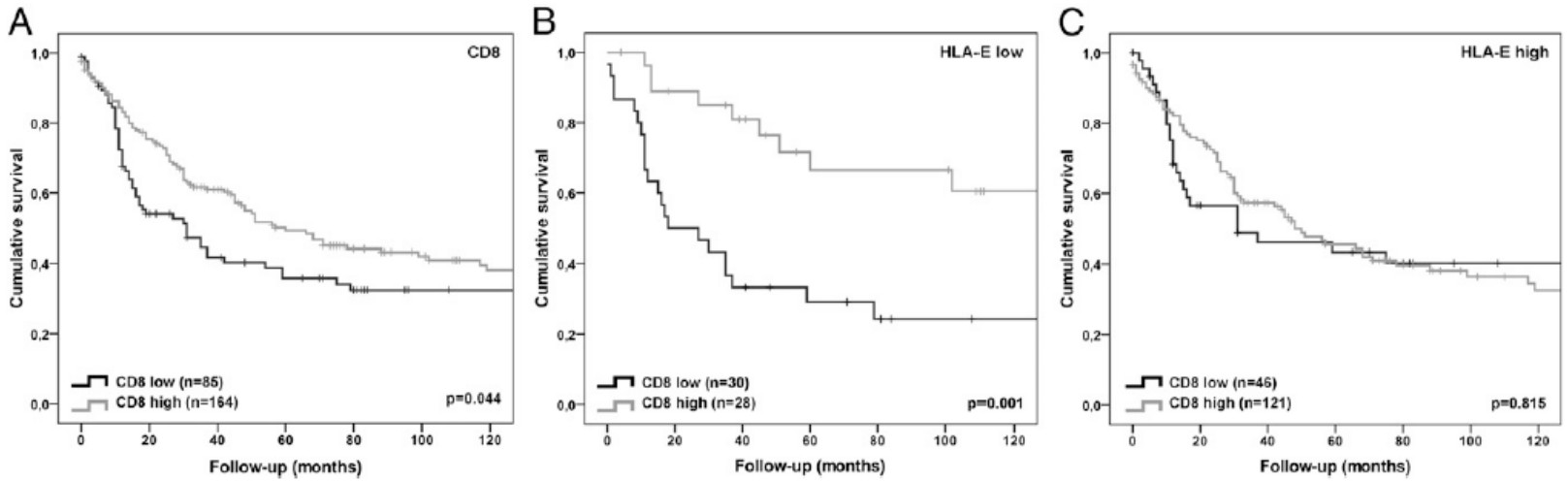


Fig. 4. Kaplan–Meier survival curves of ovarian cancer. Overall survival in months of 249 patients with ovarian cancer for whom two or more cores were available is plotted. (*A*) Infiltrating $CD8^+$ T cells were counted and stratified in two groups with a cutoff on the lowest tertile. Patients with a high CTL count showed a better survival than those with low CTL counts ($P = 0.044$, log rank test). (*B* and *C*) Subsequently, HLA-E expression was added as parameter, dividing the population into HLA-E low expression (lowest quartile) (*B*) and high HLA-E expression (*C*). The beneficial effect of high CTL counts on survival was not attributable for those cancers with high HLA-E ($P = 0.815$, log rank). Consequently, the beneficial role of high CTL infiltration of the whole cohort was the result of a small subpopulation of patients with low expression of HLA-E.

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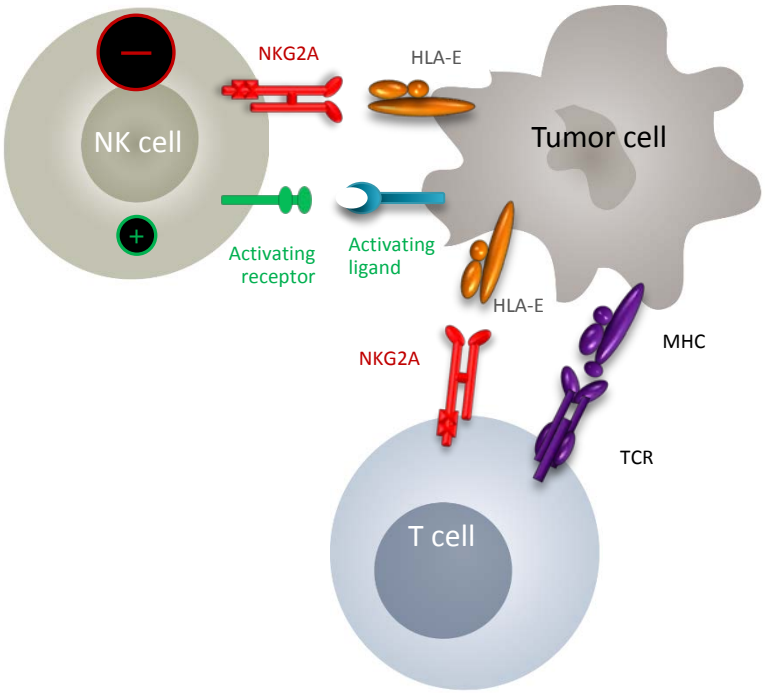
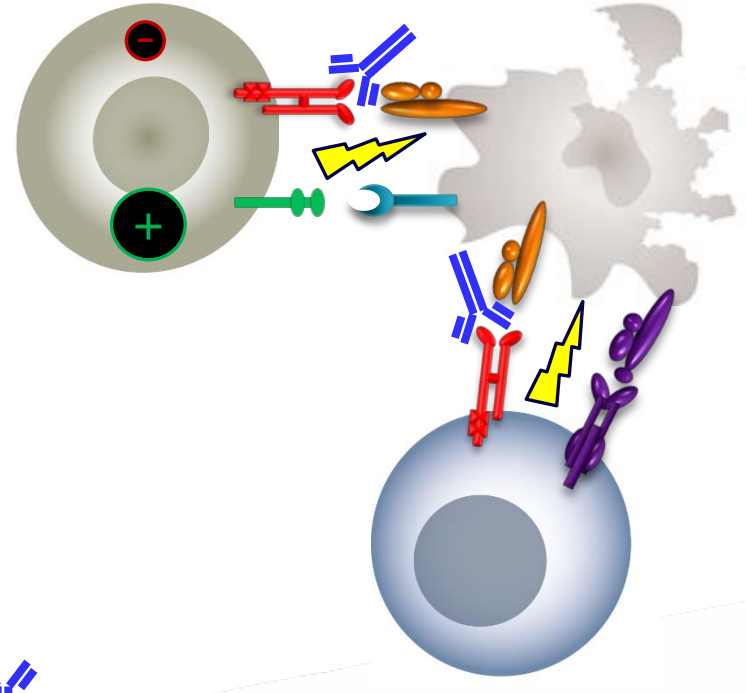
IPH2201: First in Class MAb targeting NKG2A





NK and T cell inhibition by NKG2A

Anti-NKG2A

Activation through NKG2A blockade

Phase I study in Rheumatoid Arthritis

Data Kindly Provided by:
L Favre-Kontula, Novo Nordisk A/S, Søborg, Denmark
N Wagtmann and P. Dodion, Innate Pharma, France

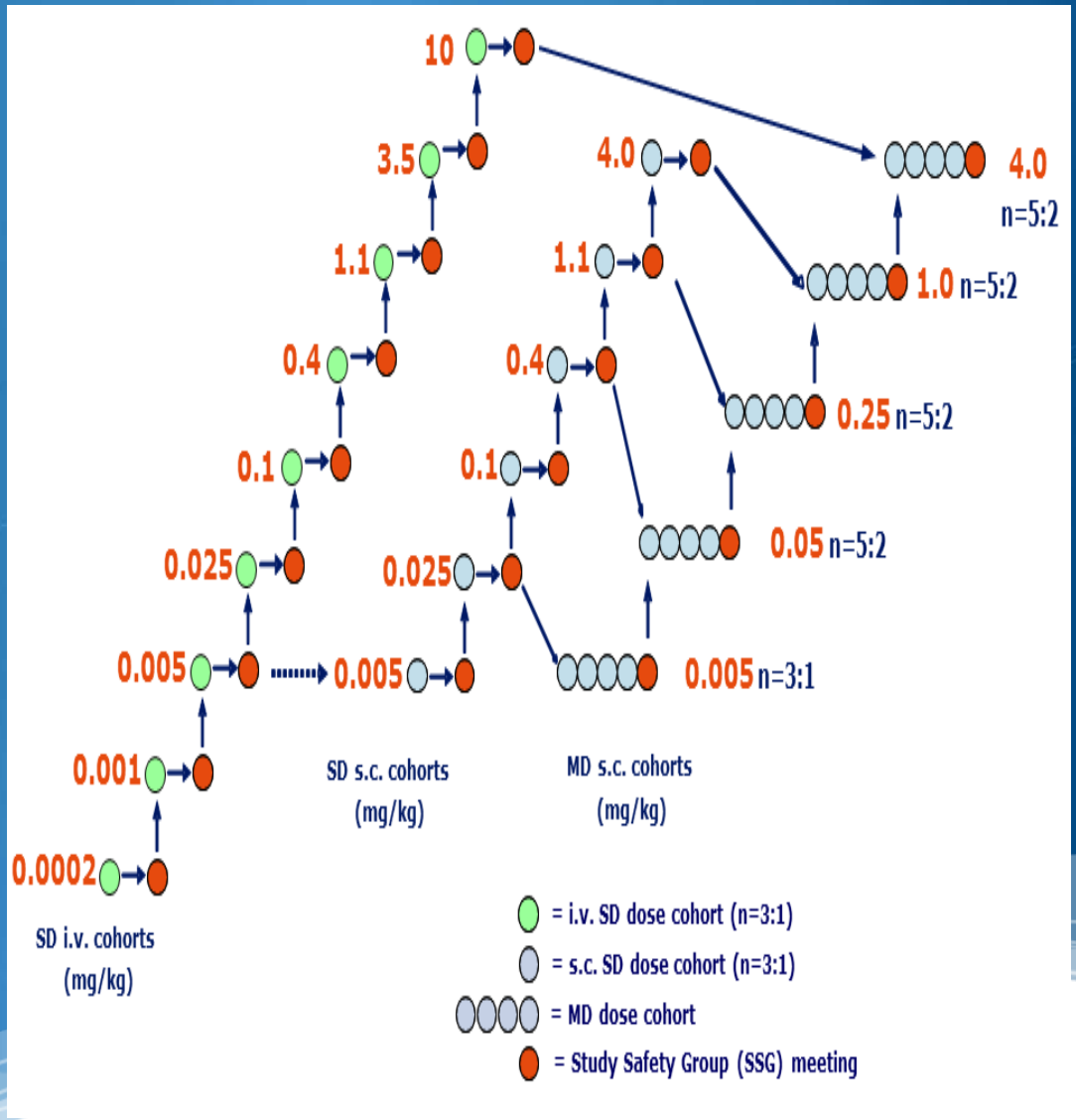
Preclinical Summary

- Dose dependent increase in NK cell activation
  - Restricted to CD94/NKG2A+ effector cells
- In ex-vivo studies increases killing of autologous blasts
- “IPH2201” pretreated NGK2A+ NK cells prevent tumour engraftment in in-vivo mouse models
- “IPH2201” has anti-tumour activity in established xenograft models

IPH2201 does not bind to CD94/NKG2A in mice, so a surrogate rat anti-mouse NKG2A-blocking monoclonal antibody and a mousified version of this mAb, were used for *in vivo* efficacy studies.
These antibodies increase mouse NK-cell cytolytic activity *in vitro*.

Phase I study of IPH2201

- Patients with rheumatoid arthritis
- Randomized, double-blind, placebo-controlled
- 3 cohorts
  - Single dose iv
  - Single dose sc
  - Multiple dose sc
- 92 patients
  - 68 IPH2201
  - 24 placebo



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Most frequent adverse events *

Preferred Term	Single dose IV		Multiple dose SC	
	Placebo (N=9)	IPH2201 (N=27)	Placebo (N=9)	IPH2201 (N=23)
Nasopharyngitis	22%	48%	56%	43%
Headache	22%	7%	0	26%
Dizziness	11%	7%	11%	4%
Rhinitis	11%	7%	0%	0%
Inject. site erythema	0%	0%	0	22%
Oral Herpes	0%	0%	0	13%
Diarrhoea	0%	0%	11%	9%

* Most frequent: defined as occurring in >5% of the IPH2201 treatment groups sorted by decreasing frequency in the IPH2201 SD IV group

Adverse Event Summary

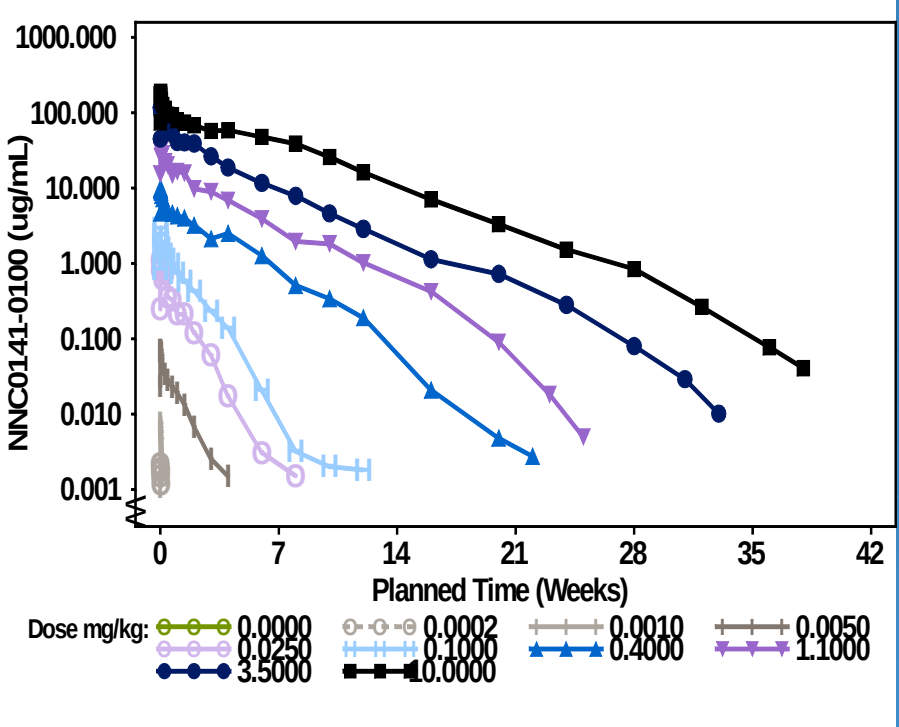
- No DLT identified up to the highest tested dosage (10 mg/kg SD IV, 4 mg/kg SD SC and MD SC)
- No AE leading to treatment discontinuation
- Only 7 ‘severe’ – all unrelated
  - 3 placebo
  - 4 IPH2201
    - 2 episodes of transient tooth ache, one tooth extraction and one injury of meniscus.

Serious Adverse Events

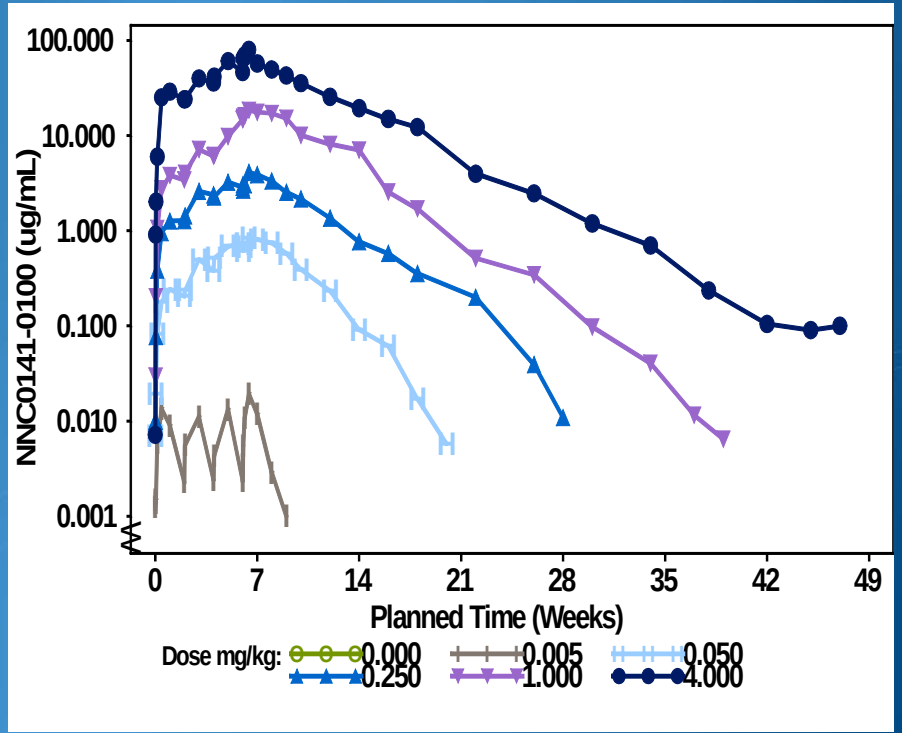
- None were considered related to either placebo or IPH2201 and all occurred after off-treatment
- Placebo
  - Headache: 1 patient (SD IV)
  - Amnesia: 1 patient in (SD SC)
- IPH2201
  - Meniscus injury: 1 patient (SD IV)
  - Abdominal pain, night sweats, dyspnea: 3 events in 1 patient (MD SC)

IPH2201 Pharmacokinetics

Single dose IV



Multiple dose SC



- Approximately dose-proportional for dose levels between 1 and 10 mg/kg
- The apparent half-life is concentration dependent with longer half-life at higher concentrations
- For the highest dose levels, the apparent t½ approaches the general half-life for IgG mAbs (~ 3 weeks)
- 3-6 fold accumulation after administration of 4 doses at dose levels from 0.05 to 4 mg/kg

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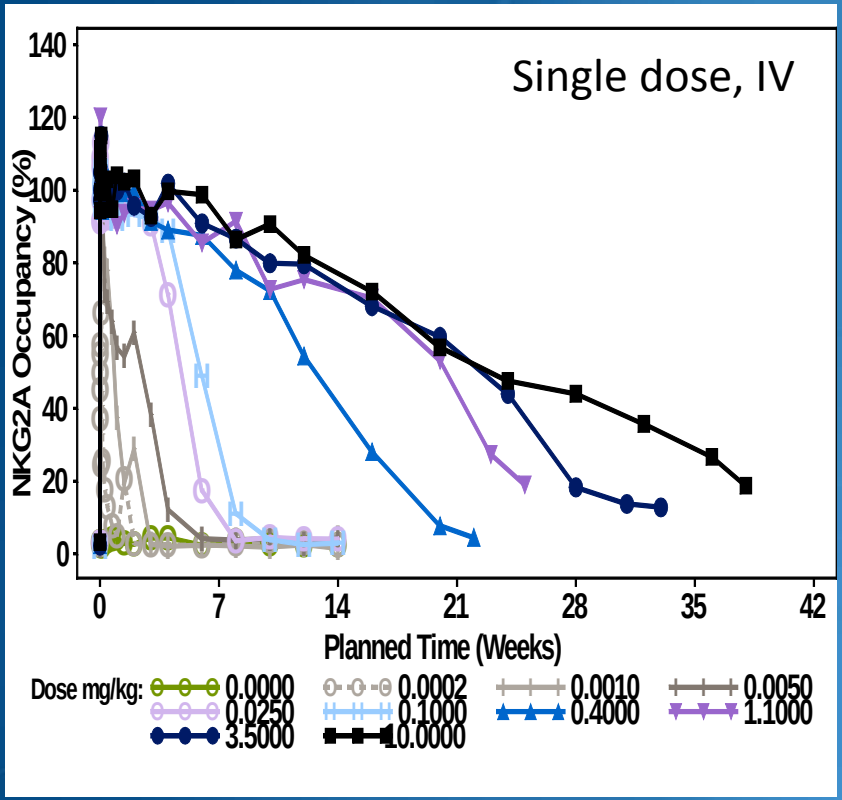
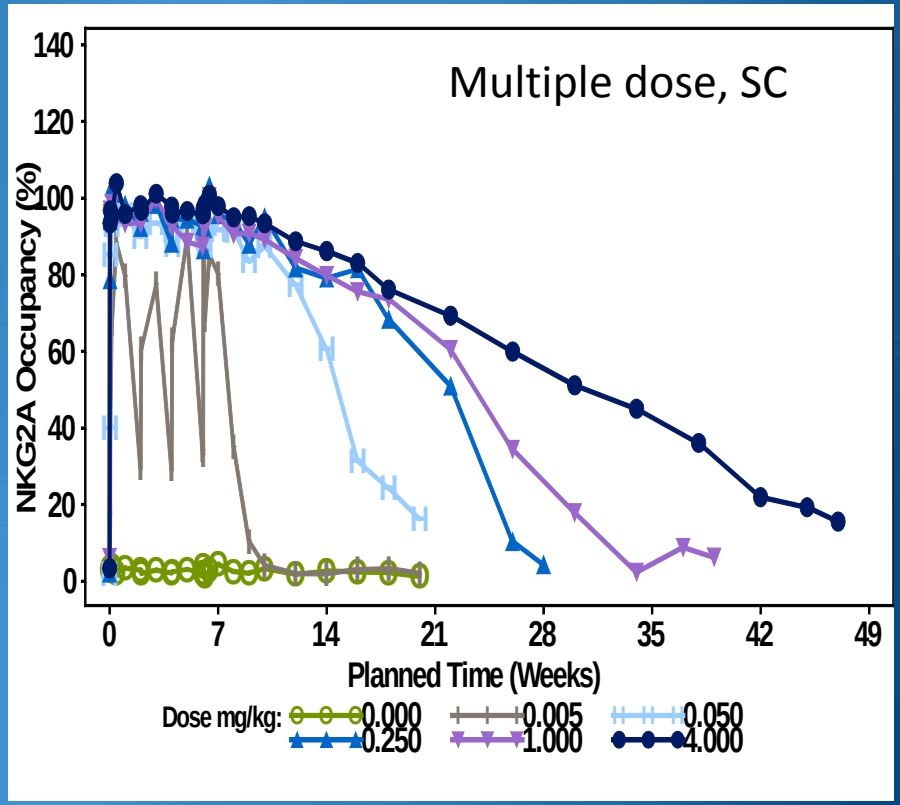
Receptor Occupancy over Time



Full occupancy at end-of-infusion for doses above 0.005 mg/kg



Full occupancy maintained within the 8 week dosing period for 0.05-4 mg/kg

IPH2201 Phase I Conclusion

- At least 12 week safety data available for all patients
  - No DLT - benign profile
    - Nasopharyngitis and headache most frequently reported AEs
    - Injection site reaction in ~ 22% of patients in MD SC cohort
- PK similar to other mAbs binding a membrane receptor
- Excellent NKG2A receptor occupancy
  - Dose-effect relationship
  - Dose dependent duration

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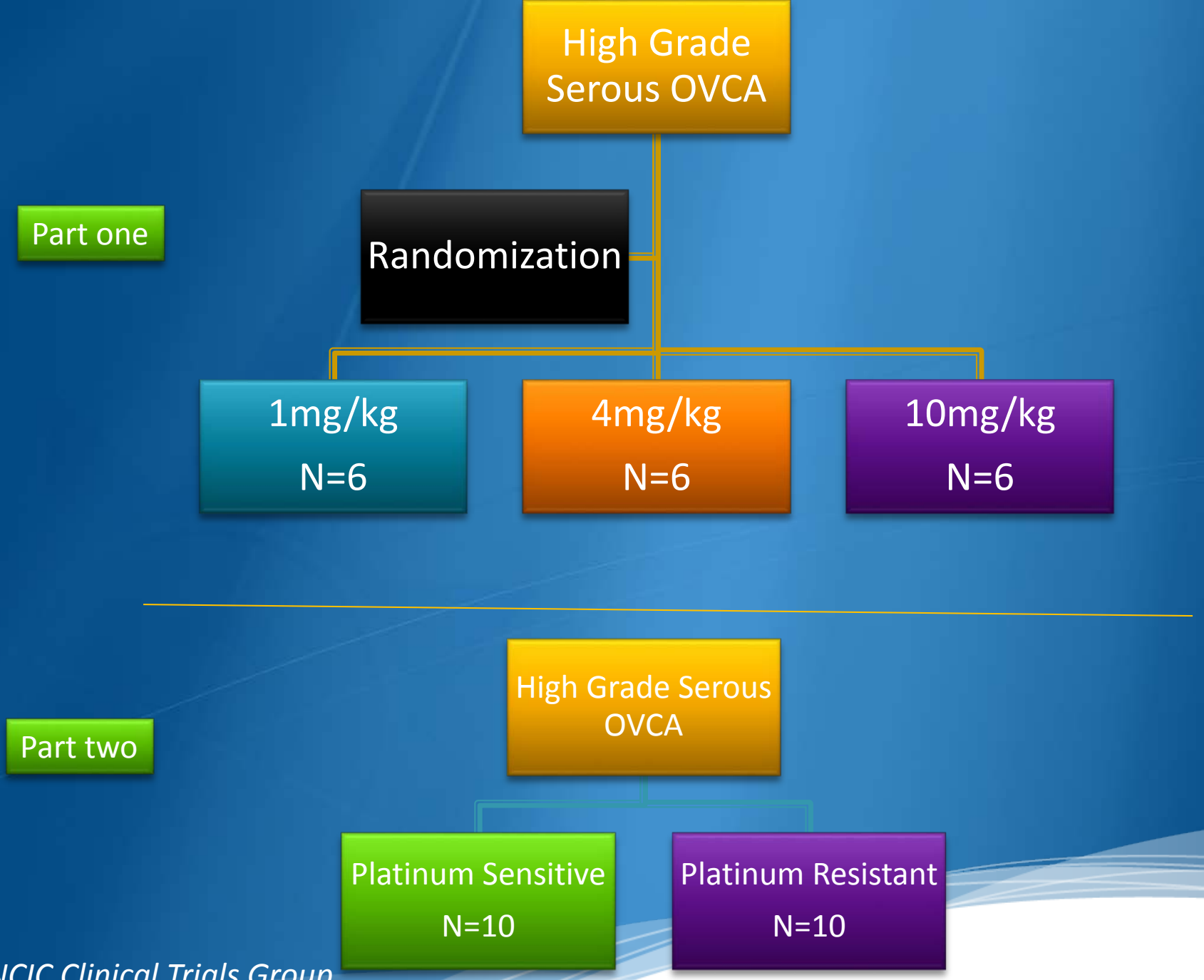
A DOSE-RANGING STUDY OF IPH2201 IN PATIENTS WITH HIGH GRADE SEROUS CARCINOMA OF OVARIAN, FALLOPIAN TUBE OR PERITONEAL ORIGIN



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Objectives

- **Primary:**
  - confirm RP2D in cancer patients
- **Secondary:**
  - safety, toxicity and pharmacokinetics
  - pharmacodynamic effects (pre & post Rx)
    - TIL, HLA-E and CD94/NKG2A expression (FFPE, biopsy, ascites)
    - Receptor occupancy studies (flow cytometry)
    - ctDNA, cytokines
  - anti-drug antibodies
  - explore the efficacy of IPH2201 as a single agent in platinum resistant or sensitive HGSC

Timelines

- Protocol and CTA being finalized
- Starting soon……

NCT02331875

"Efficacy Study of Pre-operative IPH2201 in Patients With Squamous Cell Carcinoma of the Oral Cavity"

- Patients: Treatment-naïve pre-operative patients with resectable intermediate or high risk SCC
- Sponsor: Innate Pharma
- Site: Charité University Medicine Berlin

Conclusions

- Exciting and active area of investigation
- IPH2201 is first-in-class monoclonal antibody
  - Non-clinical evidence of activity
  - Good PK profile
  - Benign toxicity profile
  - PD effects at achievable exposure
- Clinical trials in cancer have just started
  - Confirm PK/PD
  - Explore evidence clinical effects