Immunotherapy for SCCHN

Combination approach; rational and opportunities

Prof. Jean Bourhis

Lausanne University Hospital
Switzerland
Disclosures

Advisory Boards:

MERCK Serono, MSD, Astra Zeneca,
Bristol Myers Squibb
Immunotherapy in SCCHN ... 

EGFR-Inhibition
Cetuximab with radiotherapy in locally advanced SCCHN

1st line with platinum-based CT* in R/M SCCHN

checkpoint-inhibitors

Refractory/2nd line patients R/M SCCHN

CheckMate-141 (phase III, pivotal)
Keynote-012
“PD-1 inhibitors = the highest response rate of any single-agent immunotherapy,”

**Deactivated T cell**

- T-cell receptor
- Antigen
- PD-1
- PD-L1

**Activated T cell**

- T-cell receptor
- Antigen
- PD-1 inhibitor
- PD-L1

Release the Brake
Blocking PD1/PDL1 to restore anti-tumour T-cell responses in SCCHN

- **High response rates** in second line treatment *(compared to chemotherapy and cetuximab)*

- Approval by **FDA** *(Pembrolizumab and Nivolumab)*

- **Favorable safety** profile

- Effective both in **HPV+ and –**

- More activity if **PD-L1 high**.
Checkmate 141: OS benefit in R/M setting with nivolumab compared to investigator choice

Overall Survival (% of patients)

Months

1-year OS rate (95% CI)
36.0% (28.5–43.4)
16.6% (8.6–26.8)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Investigator's Choice</th>
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<tbody>
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Nivolumab in R/M: OS by PD-L1 Expression

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<tr>
<th>Months</th>
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<tr>
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Nivolumab in R/M: OS by p16 Status

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<th>Months</th>
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<td>Overall Survival (% of patients)</td>
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Keynote 012 study:
Decrease in tumor burden with pembrolizumab

51% (26/51) of patients had decreased tumor burden
PD1 PDL1 / Mab : a class of treatments active in R/M SCCHN ...

ORR : 11 to 20%
What are the strategies to integrated immunotherapy in SCCHN?

Outcome with existing SOC defining the medical need

Poor: «in addition to»

Intermediate: «instead of»

Good: «instead of»

+/- «Adjuvant»
Combination of immunotherapy with:

Radiotherapy
Chemotherapy
cetuximab
Other immunotherapy
Combination of immunotherapy with:

Radiotherapy

Chemotherapy
cetuximab

Other immunotherapy
Dual Effect of RT on the Immune Response:

**Suppression**
- Lymphocytes highly susceptible to RT induced apoptosis
- ↑ TGFβ (ECM remodeling)
- ↑ IL-10; in some experimental systems increases Treg

**Stimulation**
- ↑ Peptide production and surface MHC class I on tumor; tumor cells more susceptible to immune attack
- ↑ TNFα
- ↑ IL-6
- ↑ IL1β
- interferon gamma and type 1 interferons increase adhesion molecules
Innate and adaptive immune responses to radiation

1. Tumor cells dying
2. Antigen-presentation (Dendritic cells)
3. Priming and activation (DCs and CD8+ T cells)
4. CD8+ T cells trafficking
5. CD8+ T cells infiltration
6. CD8+ T cell recognition
7. CD8+ T cell killing

CD8$^+$ T Cells are Required for Combination Therapy with RT and PD-L1 Blockade

![Graph showing tumor volume over time with different treatment groups: Ctrl, αPD-L1, RT, RT+αPD-L1, RT+αPD-L1+αCD8.](image)

Days after tumor challenge

9 days post RT

Synergistic effects of RT when combined with immunotherapy

1) Enhancement **MHC class I, calreticulin**, and release of HMGB1;

2) Enhancement of **Fas** receptor

3) **Activation of dendritic cells** and enhancement of cross-presentation of tumor antigens;

4) **Increased density of TILs**

5) **Modulation of immune checkpoint** molecule expression: improved disease control in several pre-clinical studies.
PD-L1 Blockade Breaks the Equilibrium of Stable Disease to Favor Tumor Regression

Anti-PD-L1 blockade synergizes with Radiation

A

B

C

D

Days after tumor challenge

Tumor Volume (mm³)

Days after tumor challenge

Days after tumor challenge

Days post RT

Anti-PD-L1 blockade synergizes with Radiation
Many questions ...

◆ **Mechanism** behind the synergistic combination of PDL1/PD-1 blockade?

◆ Does radiation provide a window for anti-PD-L1/PD-1 axis inhibitors?

◆ What is the best sequence/timing for RT and Ab?

◆ **Does RT induce PD-L1 directly**? If so, mechanism?

◆ What changes in tumor microenvironment after the combination of radiation and anti-PD-L1/PD-1?

◆ Is anti-PDL-1 superior to anti-PD-1 when combined with radiation?
What are we actually modeling in the clinic?

- No T cell response
- Existing T cell response
- Generate Systemic cell Response
- Quantitatively Enhance Existing T cell Response
- Qualitatively Enhance Existing T cell Response

Vaccines:
- Anti-PD-1
- Anti-PD-L1
- Anti-CTLA4
- Anti-OX40
# Clinical Trials of PD-1 Checkpoint Blockade in Combination with Radiotherapy

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<th>PD-1 Inhibitors</th>
<th>Drug</th>
<th>Type of Cancer</th>
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<tr>
<td><strong>NCT01952769</strong>; 2014: Hadessah Medical Organization</td>
<td>Pidilizumab (MDV9300)</td>
<td>Diffuse intrinsic Pontine Glioma (pediatric study)</td>
<td>Phase 1: 6 (MDV9300 + RT); Phase 2: 15 (MDV9300 + CTX after RT); Safety/ Efficacy Study.</td>
<td>MDV9300: Phase 1: Cohort A: dose escalation (3 mg/m² + 6 mg/kg). Cohort B: if no toxicity &gt; grade 2 in Cohort A, dose will be 6 mg/kg. If toxicity &gt; grade 2 in ≥ 2 patients at 3 mg/kg, the dose in Cohort B will be 1 mg/kg during irradiation. Phase 2: biweekly MDV9300 + weekly CTX.</td>
<td>RT; no details provided.</td>
<td>CTX: Following RT, concurrent biweekly MDV9300 and weekly CTX 200mg/m².</td>
<td>No results posted. Estimated completion: April 2019.</td>
</tr>
<tr>
<td><strong>NCT02289209</strong>; 2014: University of Maryland, with Merck Sharp &amp; Dohme Corp.</td>
<td>Pembrolizumab (MK-3475)</td>
<td>Locoregional inoperable recurrence or second primary squamous cell carcinoma of the head and neck</td>
<td>48; Safety/ Efficacy Study.</td>
<td>MK-3475 (200mg): Day 1 and every 3 weeks until 3 months post completion of reirradiation. Further continuation of MK-3475 will be determined by response evaluation at 3 months post completion of reirradiation.</td>
<td>RT: 1.2 Gy 5 days a week for 5 weeks.</td>
<td>None</td>
<td>No results posted. Estimated completion: Dec. 2018.</td>
</tr>
<tr>
<td><strong>NCT02298946</strong>; 2014; NCI (USA)</td>
<td>AMP-224</td>
<td>Colorectal cancer metastatic to the liver.</td>
<td>17; Safety/ Efficacy Study.</td>
<td>Arm 1: AMP-224 10mg/kg on day 1 then q14 days. Arm 2: SBRT AMP-224 10mg/kg on day 1 then q14 days.</td>
<td>SBRT to liver. Arm 1: 8 Gy on day 0. Arm 2: 8 Gy on days -2, -1, 0.</td>
<td>CTX 200mg/m² IV on day 0.</td>
<td>No results posted. Estimated completion: Nov 2016.</td>
</tr>
<tr>
<td><strong>NCT02303366</strong>; 2014; Peter MacCallum Cancer Centre, Australia</td>
<td>Pembrolizumab (MK-3475)</td>
<td>Oligometastatic breast cancer</td>
<td>15; Safety Study.</td>
<td>MK-3475: 3 weekly treatments x 6 (200mg)</td>
<td>SABR: 20 Gy x 1 to at least one metastases (to a maximum of 5 metastases)</td>
<td>None.</td>
<td>No results posted. Estimated completion: Sept. 2020.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CTX: Cyclophosphamide; NCI (USA): National Cancer Institute, United States of America; RT: radiotherapy; SABR: Stereotactic ablative body radiosurgery; SBRT: Stereotactic body radiotherapy.
## Clinical Trials of PD-1 Checkpoint Blockade in Combination with Radiotherapy

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<tr>
<td>NCT02383212; 2015; Regeneron Pharmaceuticals</td>
<td>REGN2810</td>
<td>Advanced malignancies</td>
<td>30; Safety Study.</td>
<td>No details provided. Arm 1: REGN2810 alone; Arm 2a: REGN2810 with hypofractionated RT; Arm 2b: REGN2810 with CTX; Arm 3: REGN2810 with hypofractionated RT and CTX.</td>
<td>Hypofractionated RT; No details provided.</td>
<td>CTX: No details provided.</td>
<td>No results posted. Estimated completion: Oct. 2018.</td>
</tr>
<tr>
<td>NCT02407171; 2015; Yale</td>
<td>Pembrolizumab (MK-3475)</td>
<td>Metastatic melanoma, NSCLC</td>
<td>30; Safety/ Efficacy Study.</td>
<td>Pembrolizumab (200 mg): every 2 weeks</td>
<td>SBRT: The starting dose will be 3000 cGy in 5 fractions; there will be one dose escalation cohort (3000 cGy in 3 fractions), and if necessary one dose de-escalation cohort (1000 cGy in a single fraction).</td>
<td>None</td>
<td>No results posted. Estimated completion: Dec. 2018</td>
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<tr>
<td>NCT02434081; 2015; European Thoracic Oncology Platform, with Bristol-Myers Squibb and Frontier Science Foundation, Hellas.</td>
<td>Nivolumab</td>
<td>Stage III NSCLC, amenable to concomitant or sequential chemoradiotherapy</td>
<td>43; Safety/ Efficacy Study.</td>
<td>Nivolumab (3mg/kg): after standard chemoradiotherapy for as long as 1 year.</td>
<td>No details provided.</td>
<td>No details provided.</td>
<td>This study is not yet open for participant recruitment. Estimated completion: Aug. 2019.</td>
</tr>
<tr>
<td>NCT02580638; 2015; Royal Marsden NHS Foundation, with Merck Sharp &amp; Dohme Corp., Institute of Cancer Research, NIHR (UK)</td>
<td>Pembrolizumab</td>
<td>Invasive/Metastatic bladder cancer: Group A: Locally advanced disease; Group B: Metastatic disease</td>
<td>34; Safety Study.</td>
<td>Pembrolizumab, starting at 100mg and increasing to 200mg for the next cohort of patients, if the first dose is well tolerated.</td>
<td>Hypofractionated RT; No details provided.</td>
<td>None</td>
<td>This study is not yet open for participant recruitment. Estimated completion: Jan. 2019.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CTX: Cyclophosphamide; NCI (USA): National Cancer Institute, United States of America; NIHR (UK): National Institute for Health Research, United Kingdom; NSCLC: Non-small cell lung cancer; RT: radiotherapy; SBRT: Stereotactic body radiotherapy.
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<tr>
<td>NCT02586610; 2015; Hoosier Cancer Research Network, and Merck Sharp &amp; Dohme Corp.</td>
<td>Pembrolizumab</td>
<td>Rectal cancer</td>
<td>53; Safety/ Efficacy Study</td>
<td>Pembrolizumab (200 mg): days 1, 22 and 43</td>
<td>Daily fractions of 1.8 Gy over a 6 week interval; total dose of 50.4 Gy.</td>
<td>Capecitabine 525 mg/m² PO in twice daily doses (total 1650 mg/m²) on 5 consecutive days / week M-F given on the radiation days for 28 days</td>
<td>This study is not yet open for participant recruitment. Estimated completion: Dec. 2020.</td>
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<td>NCT02587455; 2015; Royal Marsden NHS Foundation, with Merck Sharp &amp; Dohme Corp., Institute of Cancer Research, NIHR (UK)</td>
<td>Pembrolizumab (MK-3475)</td>
<td>Lung cancer</td>
<td>48; Safety Study</td>
<td>Pembrolizumab (dose escalation).</td>
<td>Standard palliative radiotherapy. Arm 1: Low dose; Arm 2: High dose. No further details provided.</td>
<td>None</td>
<td>This study is not yet open for participant recruitment. Estimated completion: Jan 2018.</td>
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<td>NCT02599779; 2015; Sunnybrook Health Sciences Centre, with Merck Sharp &amp; Dohme Corp., and Ozymosis Research Inc.</td>
<td>Pembrolizumab (MK-3475)</td>
<td>Metastatic renal cell cancer</td>
<td>35; Safety/ Efficacy Study</td>
<td>Pembrolizumab (200mg): day 1 of every 3 week cycle until progression</td>
<td>Arm 1: SBRT given at the time of progression. Arm 2: SBRT given before the 2nd course of pembrolizumab.</td>
<td>None [patients refractory to the approved first line therapy with a targeted drug (Sunitinib or Pazopanib) will be enrolled on study].</td>
<td>This study is not yet open for participant recruitment. Estimated completion: Jan. 2019.</td>
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<tr>
<td>NCT02608385; 2015; University of Chicago</td>
<td>Pembrolizumab</td>
<td>NSCLC; Advanced Solid Tumor</td>
<td>138; Safety Study</td>
<td>Pembrolizumab (no dosage): every 3 weeks.</td>
<td>SSRT to metastases. Patients will receive 3 or 5 fractions of RT as determined by metastases location.</td>
<td>None</td>
<td>No results posted. Estimated completion: Dec. 2017.</td>
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**Abbreviations:** NCI (USA): National Cancer Institute, United States of America; NHS: National Health Service; NIHR (UK): National Institute for Health Research, United Kingdom; NSCLC: Non-small cell lung cancer; RT: radiotherapy; SSRT: Stereotactic body radiotherapy.
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<td>NCT02621398; 2015; Rutgers, with NCI, and Rutgers Cancer Institute of New Jersey</td>
<td>Pembrolizumab</td>
<td>NSCLC</td>
<td>30; Safety Study</td>
<td>Pembrolizumab (no dosage): day 1, and every 21 days for up to 18 courses. Arm 1: 2-6 weeks after the start of chemotherapy and RT; Arm 2: 2 weeks before the end; Arm 3: At the start of therapy.</td>
<td>3D CRT or IMRT QD 5 days a week for 6 weeks.</td>
<td>Paclitaxel and carboplatin on days 1, 8, 15, 22, 29, and 36.</td>
<td>This study is not yet open for participant recruitment. Estimated completion: Sept. 2019.</td>
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<td>NCT02642809; 2015; Washington University School of Medicine, with Merck Sharp &amp; Dohme Corp.</td>
<td>Pembrolizumab</td>
<td>Metastatic esophageal cancers (initial treatment)</td>
<td>15; Safety/Efficacy Study.</td>
<td>Pembrolizumab (no dosage): started within 1 week (± 3 days) after brachytherapy, every 3 weeks.</td>
<td>Brachytherapy: 8 Gy x 2, with 7-10 days between fractions.</td>
<td>None.</td>
<td>This study is not yet open for participant recruitment. Estimated completion: Jan. 2019.</td>
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</table>

Abbreviations: 3D CRT: 3-Dimensional Conformal Radiation Therapy; IMRT: Intensity-Modulated Radiation Therapy; NCI (USA): National Cancer Institute, United States of America; NSCLC: Non-small cell lung cancer.
### Clinical Trials of PD-L1 Checkpoint Blockade in Combination with Radiotherapy

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<tr>
<td>NCT02400814; 2015; University of California, Davis, with NCI (USA) and Genetech, Inc.</td>
<td>MPDL3280A (RG7446)</td>
<td>Stage IV NSCLC</td>
<td>45; Safety/ Efficacy Study.</td>
<td>MPDL3280A (no dosage): Day 1, and every 3 weeks in the absence of disease progression or unacceptable toxicity.</td>
<td>SBRT: 2-3 times per week (with 40 - 96 hours between fractions) over 1.5-2 weeks for a total of 5 fractions. Arm 1: beginning on day 1 of MPDL3280A. Arm 2: beginning on day 1 of course 3 of MPDL3280A.</td>
<td>None.</td>
<td>This study is not yet open for participant recruitment. Estimated completion: Jan. 2019</td>
</tr>
<tr>
<td>NCT02584829; 2015; Fred Hutchinson Cancer Research Center, with EMD Serono and NCI (USA)</td>
<td>Avelumab</td>
<td>Metastatic Merkel Cell Carcinoma</td>
<td>20; Safety/ Efficacy Study.</td>
<td>Avelumab (no dosage): Day 1, and every 2 weeks for 6 months. Arm 1: avelumab + RT or IFNbeta. Arm 2: avelumab + RT or IFNbeta + adoptive T-cell therapy.</td>
<td>RT (no dosage): Within 7-10 days after completion of 1-3 doses of Avelumab.</td>
<td>IFNbeta: Within 7-10 days after completion of 1-3 doses of Avelumab. Adoptive T-cell therapy: 2-5 days after RT or IFNbeta.</td>
<td>No results posted. Estimated completion: Jan. 2019</td>
</tr>
<tr>
<td>NCT02463994; 2015; University of Michigan Cancer Center, with the University of Washington</td>
<td>MPDL3280A (RG7446)</td>
<td>Metastatic NSCLC</td>
<td>12; Treatment Study.</td>
<td>MPDL3280A (1,200 mg): Day 1 and every 3 weeks until progression</td>
<td>Hypofractionated image-guided RT (no dosage)</td>
<td>None.</td>
<td>No results posted. Estimated completion: July 2020</td>
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</tbody>
</table>

**Abbreviations:** IFN: Interferon; NCI (USA): National Cancer Institute, United States of America; NSCLC: Non-small cell lung cancer; RT: radiotherapy; SBRT: Stereotactic body radiotherapy.
Is there a need for phase I with dose escalation for the combination with PD1/PDL1 inhibition?

Several PD1/PD-L1 inhibitors are initially tested at a fixed dose when combined with RT, CT-RT or chemotherapy.

phase III with initial run in safety cohort / IDSMC
PembroRad randomized study

Locally advanced HNSCC
Non suitable for CT-RT

Pembrolizumab 200 mg x 3 + RT
(no maintenance)

Cetuximab + RT

In field RT Tolerance for the 15 first patients was good
Combination of immunotherapy with:

- Radiotherapy
- Chemotherapy
- cetuximab
- Other immunotherapy
Chemotherapy and radiotherapy can mediate the immunogenic cell death


Early clinical data regarding safety and efficacy already support such combination in various cancer types for both chemotherapy and radiotherapy [Antonia et al, ASCO 2014 (Checkmate-012 trial); Papadimitrakopoulou et al, ASCO 2014 (KEYNOTE-021 trial); Postaw et al, NEJM 2012].
First line R/M: durvalumab

- Phase III
- R/M HNSCC
- All PD – L1 status

N = 628

1:1:1

MEDI 4736

MEDI 4736 + TREMELIMUMAB

EXTREME

NCT02551159
Avelumab randomized study  
*(Pfizer-MERCK Alliance)*

Locally advanced HNSCC  

- **RT + cisplatin + avelumab**  
  (+ maintenance)

- **RT + cisplatin + placebo**  
  (+ maintenance)

*Status: about to start*
Combination of immunotherapy with:

- Radiotherapy
- Chemotherapy
- cetuximab
- Other immunotherapy
SCCHN: Cetuximab and PD-1/PD-L1 Antibodies

Figure 1. Comparison of the effects of anti-EGFR mAb and anti-PD-L1 mAb. 1.1.

Cetuximab: A chimeric IgG1 monoclonal antibody blocking EGFR

Cetuximab
Antibody-dependent cell mediated cytotoxicity (ADCC)

1. Recruitment of effector cells

2. Destruction of tumor cell
Cetuximab: monoclonal antibody activating anti-tumoral immune response

«Although panitumumab effectively inhibits EGFR signaling to a similar extent as cetuximab, it is less effective at triggering anti-tumor, cellular immune mechanisms which maybe crucial for effective therapy of HNSCC.»

Detection of EGFR-specific CD8\(^+\) T-Lymphocytes from blood samples collected in two prospectives clinical CRT-studies, combined either with Cetuximab (UPCI # 08-013, NCT 01218048) or Panitumumab (UPCI 06-120, NCT00798655).

1. Trivedi S, Clinical Cancer Research 2016; 22; 13
PD1/PD11 inhibition + EGFr targeting?

- **avelumab** (MSB0010718C) fully human **anti-PD-L1** IgG1 Mab inhibits PD1/PD-L1 interactions,

- Retains a native Fc-region that can induce antibody-dependent cell-mediated cytotoxicity (**ADCC**).

- Of particular interest to synergize with **cetuximab**

- **Grade 3-4** treatment-related AEs: **3.2%**; **OR 18%** in R/M SCCHN
REACH randomized study in LA SCCHN
(Radiotherapy plus Erbitux and Avelumab for Cancer of the Head and neck)

SCCHN
Stage III-IVa-Ivb
Non-operated
N=688 pts

FIT for cisplatin

RT cisplatin

RT – cetuximab - avelumab
'avelumab maintenance

RT – cetuximab - avelumab
'avelumab maintenance

SOC : RT - cetuximab

UNFIT for cisplatin
Combination of immunotherapy with:

Radiotherapy
Chemotherapy
cetuximab

Other immunotherapy
Other immune check-point inhibitors

Mellman I et al., Science, 2011
Example: Ipilimumab + Nivolumab

Melanoma / 53% OR

More rapid and deeper clinical tumor responses

More side effects
MEDI 4736 (durvalumab) + Tremelizumab in R/M

HAWK
PD - L1 positive
N = 112

CONDOR
PD - L1 negative
N = 240
1:1:2
1:1:1

EAGLE
PD - L1 positive and negative
N = 720

Main endpoint: RR

Main endpoint: RR

Main endpoint: RR

MEDI 4736
MEDI 4736
MEDI 4736

TREMELIMIMUMAB
MEDI 4736 + TREMELIMIMUMAB
MEDI 4736 + TREMELIMIMUMAB

Investig. Choice

1:1:2
1:1:1
First-line R/M: pembrolizumab

- Phase III
- R/M HNSCC
- All PD–L1 status

N = 825

1:1:1

Pembrolizumab

Platin 5FU + Pembrolizumab

EXTREME

NCT02358031
Other combinations; ex: Reovirus (Type 3 Dearing) and Anti-PD-1

- The combination of intratumoral reovirus with an anti-PD-1 antibody results in prolonged survival of mice with melanomas.
Immunotherapy for SCCHN: Combination approach; rational and opportunities

Conclusions

- New PD-1/PD-L1 immunotherapy: a real benefit in SCCHN

- How to integrate them “in stead of” or “in addition to” +/- adjuvant to the existing SOC

- Numerous randomized studies ongoing in R/M and LA SCCHN

- Numerous questions on … mechanisms / sequencing / timing / which type of combination / which tumors do benefit ?? etc …