Combination of Immunotherapy & Radiotherapy

In CNS Metastases

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NO Conflict of Interest

Just a deep and sincere Thank to the Founder of all these 7 Meetings in Marseille

Pr Philippe METELLUS
More Patients with Brain Metastases
More *direct Deaths* from BM

- *Phase I – II trials of metastatic pts* ➔ Brain MRI
- Increasing *Incidence of Melanoma and Lung K*
- *More Targeted-drugs & Immunotherapies* ➔

Better Extra-CNS control: more ‘long survivors’

> 40% of *Direct Deaths* from Melanoma BM
BM & Radiotherapy (RT) / Surgery:
‘Historical’ local tts  ➔ Progress & Issues

- **RT**: Whole-brain  ➔ RS / SRT  ➔ up to 8-10 BM
- RS = 1 fract. / SRT = 1 - 5 fract. (> 20-35 mm Size)

‘Exclusive’ RT will NEVER increase Survival

- Known ‘post-RT’ Toxicities: ‘radionecrosis’ (RN)
- Also: edema, intra-BM hemorrhage ... seizures
- ‘Multiple’ RS (4-10): Neurocognition & Quality of Life?
Immunotherapies in Metastatic Cancer

Melanoma => \textit{Lung} => others!

- Metastatic \textbf{Melanoma} pts: longer Survivals!

\Rightarrow \textbf{Immune Checkpoint Inhib (ICI): 3 classes}

- \textbf{Anti-CTLA4}: \textit{Ipilimumab} (Ipi)
- \textbf{Anti-PD1}: \textit{Nivolumab} (Nivo), \textit{Pembrolizumab}
- \textbf{Anti-PDL-1}: Durvalumab, ...

- Metastatic \textbf{Melanoma}

- Now also \textbf{in NSCLC}!
Immunotherapies (IT) in BM’s from Metastatic Melanoma (MM) & Lung K

- **First Ph I-II IT trials** in MM: BM excluded!
- **Then:** ‘non active’ BM accepted → SRT before IT
- 2017: *retrospective* analysis, even if ‘prospective trial’

**ASCO 2017: ‘ABC’ & Checkmate 204**

- Pembro/ Ipi-Nivo → Intra-CNS Resp. Rates > 50%!
  → % of pts with ‘active BM’ treated by SRT ??

**IN THE REAL LIFE: IT + SRS regularly delivered!**
Immune Checkpoints Inhibitors + SRT: A ‘Real life’ question!

3 # situations: ICI + SRT ‘necessary’

- **1st line:** rapidly *progressing / symptomatic* BM’s

  *In parallel* to IT initiation, *but* long lasting effect (3-4 cycles)

- **Dissociated** resp: New/Progress. BM / *Extra-CNS OK*

- **Palliative:** Progress. Intra & *Extra-CNS + Neurol signs*

→ **1st line & Asymptomatic pts:** *Frontline SRT + IT?*
ICI + RT: a ‘Translational’ question
A new Paradigm opened for Research …

- **Combination** = Local Efficacy & Toxicity just added

- **In vivo / pre-clinical data**: more complex!
  - $3 \times 8$-10 Gy + IT ‘better’ than $1 \times 20$ Gy?
  - SRT before / after IT = # effects on Survival

- Extrapolation/ animals? Immunologic environment!

  About the ‘Abscopal effect’ / ‘Primer effect’ …

- ‘Extra-RT field’ by definition ... **and Intra-CNS**?

  ➔ Post SRT: prevention of potential new distant BM’s?
‘Combination’ of IT + SRS / SRT in BM

What are we talking about?

→ ‘Combined’: IT then SRT / SRT then IT

- SRT ‘within 6 mths’ / IT: 4-5 half-lifes (h-l)
- Ipi: 15 days h-l / Nivo: 1 month → Ipi + Nivo ??
- Pembro: 1 month h-l, Durvalumab ~ 12 days h-l

→ In Clinics: 3-4 cycles needed before ‘Response’

- 1st prosp. trials Ipi+RS: ‘Sandwich’ = Ipi°1-RS-Ipi°2

→ ‘Concurrent’: ‘1 mth’ / IT (1 h-l) Simultaneous: ‘1 Wk’
Combining IT with RT

What ‘**Risk** Benefit’ ratio *in the real life?* 1/2

- **‘Early-delayed’** Toxicities: definition?
  - < 3 mths: Pseudoprogressions ➔ seizures!
  - Intra-BM hemorrhage: but % before RS if Melanoma BM!
  - Radionecrosis: ‘surgical’ def? *Non invasive*: MR Perf / PET?

- **‘Late’** Toxicities: Follow-up / expected Survival
  - RN = No plateau! 10% at 1 Yr ➔ 20% at 2 Yrs, etc...
  - The longest Survival, the highest post-TT complications
  - Microvascular complications: Stroke & Neurocognitive PB
Combining IT with RT

What ‘Risk Benefit’ ratio in the real life? 2/2

- **‘Efficacy’:** MR ‘Response Rates’ / ‘Non Progressing’
  - ‘Dynamic’ evolution *before* IT-RS: slowly / fastly growing ?
  - Timing? *RR often delayed* x *mths* after IT, *id.* for RS
- **Local / intra-cranial control** ... at 6 mths / at 1 yr?
- **Clinical benefit:** ‘symptoms’ improvement, QoL?
- **Better Survival:** optimistic *but* possible ➔ tbd!
  - The ‘Primer effect’: prevention of distant BM ?
IT + RT: a ‘pragmatic’ endpoint

‘Time to Neurological Deterioration’

As the EORTC Soffietti trial: changing practice!

‘Time to WHO PS deterioration > 2’

About 10 studies on IT + SRT ➔
<table>
<thead>
<tr>
<th>Study</th>
<th>primary</th>
<th>n</th>
<th>RT</th>
<th>drug</th>
<th>Brain Control</th>
<th>median Survival</th>
<th>toxicity</th>
<th>Median Follow-up (months)</th>
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<tbody>
<tr>
<td>Patel et al</td>
<td>melanoma</td>
<td>20</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>Not improved vs. SRS alone</td>
<td>Not improved vs.</td>
<td>No increased toxicity</td>
<td>7.3</td>
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<td>SRS alone</td>
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<td>(8 vs 9.1 mo)</td>
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<tr>
<td>Knisely et al</td>
<td>melanoma</td>
<td>77</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>Brain local 37% NR</td>
<td>21.3 mo</td>
<td>No neuro-toxicity (ipi)</td>
<td>NR</td>
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<td></td>
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<td>(vs. 4.9 mo without ipi)</td>
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<td>No before/after</td>
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<tr>
<td>Silk et al</td>
<td>melanoma</td>
<td>70</td>
<td>WBRT (16) SRS (17)</td>
<td>Ipilimumab</td>
<td>Not significantly increased in Ipi group</td>
<td>18.3 mo</td>
<td>No increased toxicity</td>
<td>10</td>
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<td>(vs. 5.3 mo without ipi)</td>
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<td>18.4 mo</td>
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<tr>
<td>Mathew et al</td>
<td>melanoma</td>
<td>58</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>Brain 65% (OS 6 mo)</td>
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<td>6</td>
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<tr>
<td>Kiess et al</td>
<td>melanoma</td>
<td>46</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>brain 31% Local 100%</td>
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<td>Grade 3-4</td>
<td>22</td>
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<td>(1-y OS)</td>
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<td>ITH 13%/0*</td>
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<td>Seizure 13%/0*</td>
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<td>Grade 6%/3%</td>
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<td>Seizure 0/0*</td>
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<tr>
<td>Study</td>
<td>primary</td>
<td>n</td>
<td>RT</td>
<td>drug</td>
<td>Brain Control</td>
<td>median Survival</td>
<td>toxicity</td>
<td>Median Follow-up (months)</td>
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<tr>
<td>Tazi et al</td>
<td>melanoma</td>
<td>10</td>
<td>SRS</td>
<td>Ipilimumab</td>
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<td>16.5 mo</td>
<td>No increased toxicity</td>
<td>NR</td>
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<td><em>During or after SRS</em></td>
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<tr>
<td>Gerber et al</td>
<td>melanoma</td>
<td>13</td>
<td>WBRT</td>
<td>Ipilimumab</td>
<td>56%</td>
<td>4 mo</td>
<td>1 grade 3 cognitive change</td>
<td>4</td>
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<td><em>4 before WBRT</em></td>
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<td>100% new or worsening ITH</td>
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<td><em>6 during WBRT</em></td>
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<td></td>
<td></td>
<td></td>
<td><em>3 after WBRT</em></td>
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<tr>
<td>Cohen-Inbar et al</td>
<td>melanoma</td>
<td>46</td>
<td>SRS</td>
<td>Ipilimumab</td>
<td>33.6%</td>
<td>6.4 mo</td>
<td>RN and post-SRS edema</td>
<td>7.9</td>
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<td></td>
<td><em>14 before SRS</em></td>
<td>16.5%</td>
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<td>increased when lpi was</td>
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<td></td>
<td><em>32 during/ after SRS</em></td>
<td>50.4%</td>
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<td>administered during or after</td>
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<td></td>
<td>72.6%</td>
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<td>SRS</td>
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<td>Alomari et al [91]</td>
<td>NSCLC</td>
<td>2</td>
<td>SRS</td>
<td>Pembrolizumab</td>
<td>100%</td>
<td>NA</td>
<td>pseudo clinical and</td>
<td>6</td>
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<td></td>
<td>+ Nivolumab +</td>
<td></td>
<td></td>
<td>radiological progression</td>
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<tr>
<td>Ahmed et al</td>
<td>melanoma</td>
<td>26</td>
<td>SRS</td>
<td>Nivolumab</td>
<td>(1-y)</td>
<td></td>
<td>ITH : 5%</td>
<td>9.4</td>
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<td></td>
<td><em>During (washout 6d)/ before/after</em></td>
<td>(1-y)</td>
<td></td>
<td>Grade 3 oedema : 10%</td>
<td></td>
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<tr>
<td>Nardin*</td>
<td>melanoma</td>
<td>25</td>
<td>SRS</td>
<td>Pembrolizumab</td>
<td>46%</td>
<td>15.3 mo</td>
<td>3 RN (including 1 ITH)</td>
<td>14</td>
</tr>
</tbody>
</table>

* Tolerance and outcomes of stereotactic radiosurgery combined with anti-PD1 (pembrolizumab) for melanoma brain metastases. *Melanoma Res* Accept
a 2017 CUREUS ‘meta-analysis’
Only 4 publications selected / 37: why?

Retrospective studies + limited number of pts

→ HETEROGENEITY of

- Population: 1st line / salvage, previous WBRT
- TTs: Anti-CTLA4, -PD(L)1, RS vs SRT (1-5 fract)
- IT / RT Timing: concurrent, 1 mth, 3 or 6 mths?
- Endpoints: ‘Brain’ control, Clinical benefit, Survival
- Follow-up < 1 Yr: not enough for delayed Toxicities
Cureus 2017 ➔ 4 ‘selected’ publ / 37
On IPI + SRS vs SRS Alone in MBM

‘Possible’ Better Survival  **but low** quality of data’
No ‘significant’ Toxicities  **but very low** quality of data’
Last Publications
Still a ‘hot’ debate!

Improved survival and complete response rates in patients with advanced melanoma treated with concurrent ipilimumab and radiotherapy versus ipilimumab alone.
Koller KM¹, Mackley HB², Liu J³, Wagner H², Talamo G¹, Schell TD¹, Pameijer C⁵, Neves RT², Anderson B⁶, Kokotis KM⁴, Mallon CA¹, Drabick JJ¹.

Stereotactic radiosurgery of early melanoma brain metastases after initiation of anti-CTLA-4 treatment is associated with improved intracranial control.
An Y¹, Jiang W², Kim BYS³, Qian JM¹, Tang C², Fang P⁴, Logan J², D’Souza NM², Haydu LE⁴, Wang Xia², Hess KR², Kluger H¹, Glitza IC⁴, Mahajan A², Welsh JW², Lin SH², Yu JB¹, Davies MA⁴, Hwu P⁴, Sulman EP², Brown PD², Chiang VLS⁵, Li J⁶.

Does immunotherapy increase the rate of radiation necrosis after radiosurgical treatment of brain metastases?
Colaco RJ¹, Martin P², Kluger HM³, Yu JB¹, Chiang VL².

The incidence of radiation necrosis following stereotactic radiotherapy for melanoma brain metastases: the potential impact of immunotherapy.
Kaidar-Person O¹, Zagar TM, Deal A, Moschos SJ, Ewend MG, Sasaki-Adams D, Lee CB, Collichio FA, Fried D, Marks LB, Chera BS.
<table>
<thead>
<tr>
<th>Pharmaceutic class</th>
<th>Study reference</th>
<th>RT scheme and drug</th>
<th>Description</th>
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<tr>
<td>Anti-CTLA4</td>
<td>NCT02097732</td>
<td>SRS, Ipilimumab</td>
<td>Ipilimumab Induction in Patients With Melanoma Brain Metastases Receiving Stereotactic Radiosurgery</td>
<td>Active, not recruiting</td>
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<tr>
<td></td>
<td>NCT02662725</td>
<td>SRS, Ipilimumab</td>
<td>Ipilimumab Combined With a Stereotactic Radiosurgery in Melanoma Patients With Brain Metastases</td>
<td>completed</td>
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<tr>
<td></td>
<td>NCT01703507</td>
<td>SRS, Ipilimumab</td>
<td>Phase I Study of Ipilimumab Combined With Whole Brain Radiation Therapy or Radiosurgery for Melanoma</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td></td>
<td>NCT01950195</td>
<td>SRS, Ipilimumab</td>
<td>A Pilot Study of Stereotactic Radiosurgery Combined With Ipilimumab in Patients With Newly Diagnosed Melanoma Metastases in the Brain and Spine</td>
<td>terminated</td>
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<tr>
<td></td>
<td>NCT02107755</td>
<td>SRS, Ipilimumab</td>
<td>Stereotactic Radiation Therapy and Ipilimumab in Treating Patients With Metastatic Melanoma</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>NCT02716948</td>
<td>SRS, Nivolumab</td>
<td>A Pilot Study of Stereotactic Radiosurgery Combined With Nivolumab in Patients With Newly Diagnosed Melanoma Metastases in the Brain and Spine</td>
<td>recruiting</td>
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<tr>
<td></td>
<td>NCT02696993</td>
<td>SRS/WBRT, Nivolumab/Ipilimumab</td>
<td>Trial of Nivolumab With Radiation or Nivolumab and Ipilimumab With Radiation for the Treatment of Intracranial Metastases From Non-Small Cell Lung Cancer</td>
<td>recruiting</td>
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<tr>
<td></td>
<td>NCT02978404</td>
<td>SRS, Nivolumab</td>
<td>Combining Radiosurgery and Nivolumab in the Treatment of Brain Metastases</td>
<td>Not yet recruiting</td>
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<tr>
<td></td>
<td>NCT02858869</td>
<td>SRS, pembrolizumab</td>
<td>Pembrolizumab and Stereotactic Radiosurgery for Melanoma or Non-Small Cell Lung Cancer Brain Metastases</td>
<td>recruiting</td>
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<td>NCT02886585</td>
<td>SRS, pembrolizumab</td>
<td>Pembrolizumab In Central Nervous System Metastases</td>
<td>recruiting</td>
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<td>Anti-PD-L1</td>
<td>NCT02669914</td>
<td>WBRT/SRS, Durvalumab</td>
<td>MEDI4736 (Durvalumab) in Patients With Brain Metastasis From Epithelial-derived</td>
<td>recruiting</td>
</tr>
</tbody>
</table>
‘SO WHAT’ ??

Consider 3 Items: **Drug**, ‘D-V-F’ & Timing

- **Ipalimumab**: more Pseudo-Progr *(anti-CTLA4)*
- **Nivolumab**: optimal Benefit / Risk?
- **Ipi/Nivo** + RS combination: too early
- **Pembro**: too early, comparable / Nivo?
- **Anti PDL-1**: too early, possible good ratio...
3 Key Parameters (2/3)

‘D-V-F’: Dose-Volume & Fractionation

- Consider **Dose** per fraction / Total Dose
- **Volume** irradiated: ‘PTV’ > or < 1 cm³
- **Fractionation**: in terms of Efficacy & Toxicity
  - 1 x 20 – 24 Gy  # from
  - 3 x 10 Gy  # from
  - 5 x 7 Gy

➤ **Machine**: LINAC / CKN / GKN: dose-gradient #
3 Key Parameters (3/3)
Drug, DVF & **Timing**

- **Combined:** IT ‘within 6 months’ / SRS
- **Concurrent:** ‘within 1 month’
  - possible more Toxicity, more radionecrosis ➔ more Efficacy?
- **Simultaneous:** ‘within a week’
- **Sequential:** ‘not concurrent’ ...
Place for a Randomized Trial?  
A unique Opportunity… or ‘too late’?

- Asymptomatic pts with non threatening BM’s
- First line, No previous RT
- Melanoma / Lung

**Frontline ICI alone vs Combined SRS + ICI**

- 1st Endpoint: Intra-CNS control ➔ Survival !?
- An International - EORTC Trial!
- Issues: funding, inter-groups ‘cooperation’…
… and / or a ‘Pragmatic’ option

an International Registration Platform

Pts from the ‘real life’ ➔ +80% outside trials!

- Pre-defined items prospectively registered
- ALL Toxicities: early (3 mths) ➔ late (6 – 12 mths)
- Efficacy: Intra-CNS control / Symptoms / Survival
  Pseudo-progression / Abscopal effects?
- Results regularly updated & shared

NEW QUESTIONS RAISED!
Optimistic!

Take Home Message

- **Asymptomatic** BM: a ‘case by case’ Staff decision
  - *Combination*: if ‘progressing’ BM under TT (switch drug?)
  - *IT ➔ SRS ‘as Salvage’*: if main Prognostic is extra-CNS
  - Melanoma BM > 10 mm ➔ RS # Lung BM: no RS

- **Symptomatic** / neurologically *threatening* BM
  - Arguments favoring ‘Concurrent’ SRS + IT’ (within 1 mth)
  - *Concurrent IT + SRS ‘possibly’ more toxic ...*
  - ‘probably’ *more effective*: still tbd!
Thank you for your attention